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Risk factors and treatment of contralateral neck recurrence for unilateral oral squamous cell carcinoma: A retrospective study of 1482 cases

Zhien Feng, Li Xuan Niu, Yuan Yuan, Xin Peng, Chuan Bin Guo *

Department of Oral and Maxillofacial Surgery, School of Stomatology, Peking University, Beijing 100081, China

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SUMMARY

Background: The aim of this study was to describe risk factors of contralateral neck recurrence (CLNR) and to identify its high-risk population after treatment for unilateral oral squamous cell carcinoma.
Methods: Between June 1991 and June 2012, a total of 1482 eligible patients who were treated with radical surgery with or without adjuvant therapy were retrospectively reviewed.
Results: The outcome assessment parameters were the rate of 5-year CLNR and the rate of disease-specific survival (DSS). In the entire study cohort, the 5-year CLNR rate was 4.1%. In a multivariate analysis, only extracapsular spread (ECS) status (hazard ratio [HR]: 12.978, 95% confidence interval [CI]: 1.328–126.829, $P = 0.028$) was an independent risk factor for 5-year CLNR. In addition, 5-year CLNR (HR: 36.410, 95% CI: 7.093–186.914, $P < 0.001$), T stage (HR: 3.475, 95% CI: 1.151–10.488, $P = 0.027$) and growth pattern (HR: 4.831, 95% CI: 1.776–13.140, $P = 0.002$) were independent risk factors for 5-year DSS. Patients with at least two risk factors were identified as a high-risk population for CLNR; these patients also had a poor prognosis. Elective contralateral neck dissection (ND) plus concurrent chemoradiotherapy (CCRT) can improve the 5-year DSS in these high-risk patients, but it does not decrease the 5-year CLNR rate.
Conclusion: For low- and moderate-risk patients, contralateral neck observation should be considered sufficient if strict compliance with a cancer surveillance protocol is followed. However, whether high-risk patients benefit from contralateral ND plus adjuvant CCRT can only be answered in a prospective trial.

Introduction

Contralateral neck metastases are uncommon in patients with oral squamous cell carcinoma (OSCC) at the time of diagnosis. Currently, few large studies on the association between clinicopathologic factors and the development of contralateral neck recurrence (CLNR) after surgical resection of primary OSCC are available [1]. However, the prognosis of patients with OSCC and neck lymph node recurrence remains dismal, especially in cases of contralateral recurrence [1–3]. Several clinical and pathologic risk factors have been proposed in OSCC, including primary site, extension, clinical stage, pathologic grade, tumour thickness, and perineural invasion [4–6]. A recent study, performed in an area with high rates of betel quid chewing and based on a treatment design that did not account for the possibility of lymphatic drainage crossing the midline, showed that patients with local recurrence have a higher incidence of CLNR than those without [7]. In terms of treatment decision-making, the use of elective contralateral neck dissection (ND) remains controversial for patients with OSCC that does not cross the midline [7].There have been no comprehensive studies on the rate of CLNR or on the risk factors and principles of combined treatment for unilateral OSCC in patients from a non-betel quid chewing area.

The aim of this retrospective investigation was to identify significant predictors for CLNR in a large cohort of patients with OSCC who were recruited in an area of Northern China where betel nut is not commonly chewed. All patients in this study were treated with radical surgery, either with or without radiotherapy (RT) or concurrent chemoradiotherapy (CCRT). This study can first clarify the rate of CLNR in patients with OSCC in Northern China, which has a population of more than 600 million people, accounting for approximately half of the Chinese population. Second, it may show whether contralateral ND and adjuvant treatment can improve the clinical outcome of patients with OSCC by reducing the risk of CLNR. Finally, the prognostic scoring of risk factors in the whole cohort may allow the identification of high-risk OSCC patients who may require more intensive therapy.

* Corresponding author. Address: Department of Oral and Maxillofacial Surgery, School of Stomatology Peking University, No. 22 Zhong-Guan-Cun South Road, Hai-Dian District, Beijing 100081, China. Tel.: +86 10 62179977; fax: +86 10 62179977.
E-mail address: guodazuo@sina.com (C.B. Guo).

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Patients and methods

Patients

The Institutional Review Board (IRB) of the Stomatological Hospital of Peking University approved this study. Due to the retrospective nature of this study, it was granted an exemption by the IRB. The eligibility criteria were as follows: (1) histological diagnosis of OSCC; (2) no previous treatment; (3) no evidence of preoperative contralateral nodal metastasis; and (4) a primary tumour without evidence of distant metastasis. Exclusion criteria included the presence of midline lesions, bilateral lesions, second metachronous malignancies, and/or refusal or inability to receive definitive treatment for the disease.

All study participants underwent an extensive preoperative evaluation, including preoperative CT, MRI, and/or positron emission tomography (PET) scans to determine the extent of the tumour; baseline chest X-ray, complete blood count, and blood chemistries were also obtained. Clinical staging was based on the clinical and imaging findings according to the 2009 Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC), 7th edition staging criteria.

Treatment

All the patients were initially treated with surgery. The surgical procedure was selected by the surgeons according to tumour site and local practice. Standardised surgery, including radical tumour resection, neck dissection and the reconstruction of tissue defects (as necessary), was performed. Local excision of the primary tumour was performed with margins of at least 15 mm. Tumour margins were cryosectioned. If a margin was positive, additional tissue was excised and cryosectioned to ensure that the margin was free of tumour. Patients were treated with bilateral NDs if the primary tumour was less than 1 cm away from the midline of the oral cavity. Postoperative RT was advised for patients with positive lymph nodes. RT was scheduled within 4–8 weeks after the operation. The prescribed dose was 1.8–2 Gy per fraction per day, given 5 days per week. The total radiation dose was 66 Gy for patients with multiple positive neck lymph nodes and 60 Gy for the remaining patients. In principle, contralateral RT was not routinely performed unless the presence of contralateral pathological nodal metastases was detected. Concomitant chemoradiotherapy (CCRT) with cisplatin (30 mg/m^2 weekly) was recommended for patients with multiple pathologically proven multiple nodal metastases and/or ECS.

For routine histopathological analysis of the neck dissection specimens, we put each levels of node in different pots. Sides and different node levels were delineated with the help of orienting stitches that were placed just after the removal of the specimens. Standard H&E staining was performed.

Follow-up strategy

Following surgery, patients were advised to return regularly at 2-month intervals during the first year, 3 months in the second year, 6 months in the third, fourth and fifth years, and every 6 months to 1 year thereafter. For surviving patients who did not comply with the recommended schedule of return visits, telephone interviews were conducted every 6 months. The above policy for follow-up has been a routine practice in our hospitals.

Statistical analysis

The cut-off date for all follow-ups among surviving patients was May 1, 2014. All patients had follow-up examinations for at least 24 months after surgical treatment or until death. Descriptive statistics are summarised using frequencies, percentages, and mean ± standard deviation. The primary outcome assessment parameter was 5-year CLNR. This was defined as the percentage of patients whose CLNR was not associated with a local recurrence. The secondary endpoint was the 5-year disease-specific survival (DSS) rate, which was calculated from the time of the first operation to the time of death or last follow-up. The Kaplan–Meier method was used to provide estimates of the rates of both the 5-year CLNR and DSS and only included patients who underwent their first treatment five years ago. Statistical significance was determined by the log-rank test. Univariate and multivariate analyses were used to identify independent predictors for CLNR and DSS. Independent prognostic factors were identified by multivariate Cox regression analysis using the forward selection method. All tests were two-sided, and P values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS for Windows, version 17.0 (SPSS, Chicago, USA).

Results

Patients

Between May 1991 and May 2012, a total of 2180 consecutive patients with previously untreated OSCC were scheduled for radical surgery in our hospital. A total of 698 patients were excluded due to the presence of midline lesions, bilateral lesions, or second metachronous malignancies. A total of 1482 patients were eligible for the final analysis. The final cohort included 822 (55.5%) males and 660 (45.5%) females. The median age was 60 years (range, 5–90 years). The primary tumour sites were the tongue in 636 patients (42.9%), the lower gingiva in 265 patients (17.9%), the buccal mucosa in 233 patients (15.7%), the floor of the mouth in 123 patients (8.3%), the upper gingiva in 169 patients (11.4%), and the hard palate in 56 patients (3.8%).The tumours were primarily unilateral, with a distance from the midline of more than 1 cm in 1,350 (91.1%) patients. These patients underwent ipsilateral ND. In 132 patients (8.9%), the primary tumour was located less than 1 cm from the midline; these patients underwent bilateral ND (elective contralateral ND). The clinical staging was as follows: T1 (n = 381,25.7%), T2 (n = 575,38.8%), T3 (n = 159,10.7%), T4a (n = 354,23.9%), and T4b (n = 13,0.9%). With regard to pathologic grade, 764 patients (51.6%) had grade I tumours, 608 (41.0%) had grade II tumours, 68 (4.6%) had grade III tumours, and tumour grade data were missing for 42 (2.8%) patients. The pathological nodal status was as follows: pNx (no ND, n = 315,21.3%), pN0 (n = 681,46.0%), pN1 (n = 229,15.5%), pN2b (n = 236,15.9%), and pN2c (n = 21,1.4%).

Pathologic data regarding histologic risk factors (e.g., perineural invasion, vascular emboli, diffuse infiltration) and ECS status were obtained from our previous retrospective studies. A total of 335 consecutive cases were available for the analysis of histologic signs of severity, and 272 consecutive cases were available for the analysis of ECS status. Specifically, perineural invasion was present in 39 cases, absent in 274 cases, and missing in 22 cases. Vascular emboli were present in 3 cases, absent in 308 cases, and missing in 24 cases. Diffuse infiltration was present in 66 cases, absent in 245 cases, and missing in 24 cases. The ECS status was positive in 57 cases, negative in 195 cases, and missing in 20 cases.

Treatment results

Of the 1482 patients, 1167 (78.7%) underwent NDs. A total of 1035 (88.7%) patients underwent ipsilateral ND, and 132 (11.3%) underwent bilateral ND. Of the 1035 patients who underwent

ipsilateral ND, 448 (43.3%) had elective level I–III ND, 51 (4.9%) had elective level I–IV ND, 241 (23.3%) had elective level I–V ND, 107 (10.3%) had therapeutic level I–III ND, 21 (2.1%) had therapeutic level I–IV ND, and 167 (16.1%) had therapeutic I–V ND. Of the 132 patients who underwent contralateral ND, 111 (84.1%) had elective level I–III ND, 6 (4.5%) had elective level I–IV ND, and 15 (11.4%) had elective level I–V ND. Of the 1,482 patients, 910 (61.4%) underwent surgery alone, 398 (26.9%) had surgery plus RT, and 174 (11.7%) had surgery plus CCRT.

Follow-up results

At the time of this analysis, 899 (60.7%) patients were alive, 473 (31.9%) were dead, and 110 (7.4%) were lost to follow-up. Thirty-five patients died as a result of causes unrelated to cancer including cardiac failure and stroke (15 patients), multiple organ failure (7 patients), respiratory failure (7 patients), acute gastrointestinal haemorrhage (2 patients), suicide (2 patients), and uncertain causes (2 patients). The first relapse of the primary tumour was as follows: 273 (18.4%) developed local recurrence (coupled with neck recurrence in 47), 162 (10.9%) had neck recurrences alone, 187 (12.6%) had a second primary carcinoma (SPM) (coupled with neck recurrence in 42), and 68 (5.0%) had distant metastases. Out of a total of 251 patients with neck recurrence, 188 had ipsilateral neck recurrence, and 63 had contralateral or bilateral neck recurrence. CLNR as the first relapse was found after a median follow-up of 9.5 months (range, 1–97 months).

Eight hundred forty-four of 1482 patients underwent treatment for the first time five years ago. Of these patients, 35 of 844 patients experienced contralateral neck recurrence, yielding a 5-year CLNR rate of 4.1%. The overall 5-year CLNR rate was 2.5% for patients who experienced local recurrence and 6.0% for those with SPM. Specifically, the 5-year CLNR rate was 18.5% in patients with local recurrence coupled with neck recurrence, 24.2% in those with SPM coupled with neck recurrence, and 21.4% in those with neck recurrence alone ($P = 0.857$).The distribution of the primary neck treatment and sites of the first relapse for 35 patients with 5-year CLNR were significantly different ($P = 0.016$, Table 1). Compared with neck observation or bilateral ND, ipsilateral ND was associated with a higher risk of CLNR alone (76.0%). However, CLNR in patients who underwent neck observation alone often occurred secondary to a local recurrence or SPM (77.8%). For the salvage treatment of patients with 5-year CLNR, 5 patients had no ND (3 underwent CCRT and 2 quit therapy), 21 patients had ipsilateral ND (12 underwent postoperative RT or CCRT), and 9 had bilateral ND (4 underwent postoperative RT and 1 underwent postoperative CCRT).

Univariate and multivariate analyses of the 5-year CLNR rate

According to the univariate analyses, the following factors were found to be associated with the 5-year CLNR rate: pathological lymph node status of unilateral ND ($P = 0.005$), ECS status ($P = 0.009$), and combined treatment ($P = 0.002$), (Table 2). In the multivariate analyses, ECS status (HR: 12.978, 95% CI: 1.328–126.829, $P = 0.028$) was an independent risk factor for 5-year CLNR.

A 5-year CLNR was closely associated with long-term survival

In the entire cohort, 272 of 844 patients who underwent treatment for the first time five years ago had died, and the 5-year DSS rate was 67.8%. Univariate analysis suggested that 5-year CLNR ($P = 0.006$), gender ($P = 0.009$), T stage ($P < 0.001$), pathological node status ($P < 0.001$), pathological grade ($P = 0.001$), growth pattern ($P = 0.001$), perineural invasion ($P = 0.008$), diffuse infiltration ($P = 0.001$), ECS status ($P = 0.001$), tobacco use ($P = 0.036$), neck treatment ($P = 0.013$), combined treatment ($P < 0.001$) and tumours that reached the midline ($P = 0.001$) were significantly related to 5-year DSS. Subsequently, multivariate survival analysis showed that 5-year CLNR (HR: 36.410, 95% CI: 7.093–186.914, $P < 0.001$), T stage (HR: 3.475, 95% CI: 1.151–10.488, $P = 0.027$) and growth pattern (HR: 4.831, 95% CI: 1.776–13.140, $P = 0.002$) were independent predictive factors for 5-year DSS; details are shown in Table 3.

Contralateral lymph nodal metastasis was not associated with CLNR

As mentioned in Table 2, elective contralateral ND (1.5%) compared with bilateral neck observation (4.7%)and ipsilateral ND (4.3%) can significantly decrease the 5-year CLNR rate, though no statistically significant difference was observed (Log rank, $P = 0.558$, Fig. 1). In addition, of the patients who underwent elective contralateral ND, none of the patients with pN2c neck disease subsequently developed CLNR. The results showed that contralateral lymph nodal metastasis was not associated with CLNR.

Prognostic scoring of risk factors and screening of a high-risk population

Prognostic scoring of risk factors for DSS included the parameters of 5-year CLNR, T stage and growth pattern. However, the 5-year CLNR is an outcome assessment index and its guideline value for prognosis is not prospective. In this study, we chose ECS—an independent predictive factor of 5-year CLNR—as a substitution parameter of risk in this scoring system. Therefore, each risk factor (i.e., T3–4, presence of ECS and infiltrative growth) identified as an independent prognosticator in the survival analysis was given a score of 1. The 5-year CLNR rate differed significantly in patients with a score of 0 (1.3%) compared with those with a score of 1 (4.2%) or $\geqslant 2$ (16.5%) ($P < 0.001$, Fig. 2). The 5-year DSS was 78.6% for patients with a score of 0, 67.2% for those with a score of 1, and 21.4% for those with a score of $\geqslant 2$ ($P < 0.001$, Fig. 3). Therefore, patients with a score of $\geqslant 2$ were identified as the high-risk population for 5-year CLNR and DSS; a score of 1 indicated a moderate-risk population, while a score of 0 indicated a low-risk population.

Formulation of a tailored treatment schedule according to the prognostic scoring of risk factors

After further analysis of the relationship between prognosis and different treatment approaches in the high-risk population (score of $\geqslant 2$), we found that the patients who received surgery + RT

Table 1
The distribution of the primary neck treatment and sites of the first relapse for 35 patients with 5-year CLNR.

Relapse sites	Ipsilateral ND ($n = 25$)		Bilateral ND ($n = 1$)		Neck observation ($n = 9$)	
	No.	%	No.	%	No.	%
Local + neck	3	12.0	0	0	2	22.2
SPM + neck	3	12.0	0	0	5	55.6
Neck alone	19	76.0	1	100	2	22.2
P	0.016					

Note: ND: neck dissection; SPM: second primary malignancy.

Table 2
Univariate analysis and multivariate analysis for the estimation of risk factors for the 5-year CLNR rate in patients with OSCC.

Variable	Patients (*n*)	5-year CLNR *n* (%)	Hazard ratio	95% Confidence interval	*P*
Univariate analysis					
Age					
⩾50	657	28 (4.3%)	1.122	0.490–2.568	0.786
<50	187	7 (3.7%)			
Gender					
Male	467	18 (3.9%)	1.160	0.598–2.251	0.660
Female	377	17 (4.5%)			
Sites					
Tongue	356	19 (5.3%)	0.946	0.779–1.149	0.575
Lower gingiva	144	6 (4.2%)			
Buccal mucosa	141	3 (2.1%)			
Floor of mouth	70	1 (1.4%)			
Upper gingiva	101	4 (4.0%)			
Hard palate	32	2 (6.3%)			
T stage					
T1–2	639	25 (3.9%)	1.486	0.713–3.098	0.291
T3–4	205	10 (4.9%)			
pN status (non-bilateral ND)					
pN0	352	9 (2.6%)	3.273	1.443–7.424	0.005
pN1-2b	231	16 (6.9%)			
pNx	193	9 (4.7%)			
pN2c (bilateral ND)					
No	58	1 (1.7%)	0.040	0.000–2.979E9	0.801
Yes	10	0 (0.0%)			
Pathologic grade					
I	433	17 (3.9%)	0.971	0.538–1.750	0.921
II	349	16 (4.6%)			
III	43	0 (0.0%)			
Missing	19	2 (10.5%)			
Growth pattern					
Exophytic	282	13 (4.6%)	1.207	0.810–1.799	0.356
Ulcerative	221	9 (4.1%)			
Infiltrative	200	13 (6.5%)			
Missing	141	0 (0.0%)			
Perineural invasion					
Absent	236	4 (1.7%)	2.228	0.249–19.939	0.474
Present	27	1 (3.7%)			
Vascular emboli					
Absent	260	5 (1.9%)	0.049	0.000–2.744E19	0.902
Present	2	0 (0.0%)			
Diffuse infiltration					
Absent	211	3 (1.4%)	3.069	0.512–18.417	0.220
Present	51	2 (3.9%)			
ECS					
Absent	170	1 (0.6%)	20.735	2.145–200.476	0.009
Present	28	3 (10.7%)			
Tobacco use					
Non-smoker	485	23 (4.7%)	0.766	0.381–1.539	0.453
Smoker	329	12 (3.6%)			
Missing	30	0 (0.0)			
Alcohol habit					
Non-drinker	575	27 (4.7%)	0.690	0.313–1.519	0.356
Drinker	239	8 (3.3%)			
Missing	30	0 (0.0%)			
Combined treatment					
Surgery	517	11 (2.1%)	1.920	1.271–2.899	0.002
Surgery + RT	221	19 (8.6%)			
Surgery + CCRT	106	5 (4.7%)			
Neck dissection					
Neck observation	193	9 (4.7%)	0.743	0.399–1.385	0.350
Ipsilateral ND	583	25 (4.3%)			
Bilateral ND	68	1 (1.5%)			
Tumour reaching the midline					
No	772	30 (3.9%)	1.917	0.743–4.945	0.178
Yes	72	5 (6.9%)			
Total local recurrence*					
No	642	30 (4.7%)	0.804	0.308–2.099	0.656
Yes	202	5 (2.5%)			
Total SPM*					
No	710	27 (3.8%)	1.393	0.633–3.067	0.411
Yes	134	8 (6.0%)			
Multivariate analysis (forward method)					
ECS (presence vs. absence)			12.978	1.328–126.829	0.028

Note: ECS: extracapsular spread; RT: radiotherapy; CCRT: concurrent chemoradiotherapy; ND: neck dissection; Total local recurrence*: including local recurrence with and without neck recurrence; Total SPM*: including second primary malignancy with and without neck recurrence.

Table 3
Cox proportional hazards regression models estimating the 5-year DSS.

Variable	Hazard ratio	95% Confidence interval	*P*
Univariate analysis			
Five-year CLNR (presence vs. absence)	1.961	1.215–3.164	0.006
Gender (male vs. female)	0.723	0.566–0.923	0.009
T stage (T1–2 vs. T3–4)	2.666	2.089–3.402	<0.001
pN status (positive vs. negative)	2.861	2.168–3.776	<0.001
Pathologic grade (I, II, III)	1.747	1.447–2.109	<0.001
Growth pattern (infiltrative vs. non-infiltrative)	1.441	1.085–1.915	0.012
Perineural invasion(presence vs. absence)	2.025	1.205–3.404	0.008
Diffuse infiltration (presence vs. absence)	2.000	1.317–3.037	0.001
ECS (presence vs. absence)	2.367	1.407–3.980	0.001
Tobacco use (smoker vs. non-smoker)	1.299	1.017–1.659	0.036
Neck treatment (observation, ipsilateral ND, bilateral ND)	1.329	1.061–1.665	0.013
Combined treatment (S, S + RT, S + CCRT)	1.897	1.632–2.206	<0.001
Tumour reaching/crossing the midline (yes vs. no)	1.844	1.293–2.631	0.001
Multivariate survival analysis (forward method)			
Five-year CLNR (presence vs. absence)	36.410	7.093–186.914	<0.001
Growth pattern (infiltrative vs. non-infiltrative)	4.831	1.776–13.140	0.002
T stage (T1–2 vs. T3–4)	3.475	1.151–10.488	0.027

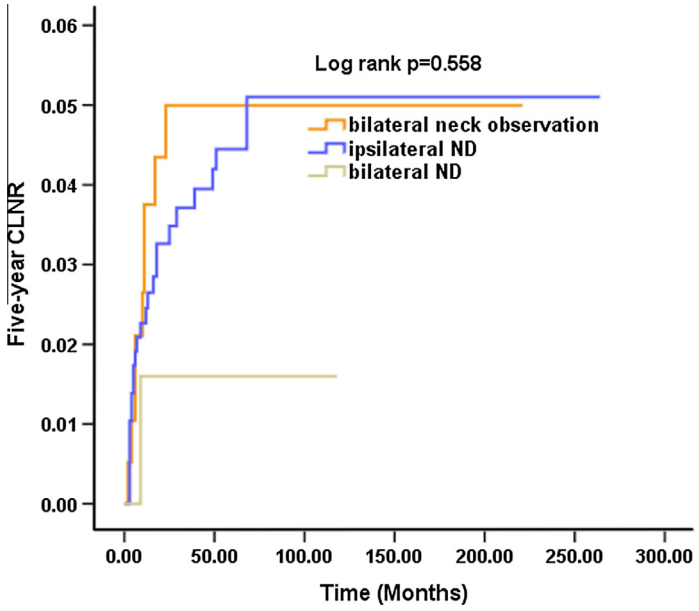

Fig. 1. Kaplan–Meier survival curve for the 5-year CLNR according to the different modalities of neck treatment.

(85.7%) or surgery + CCRT (86.2%) experienced a similar 5-year CLNR compared with those who underwent surgery alone (79.5%) ($P = 0.844$). Importantly, we found that the patients who underwent surgery + CCRT experienced a better 5-year DSS (30.8%) than those who had surgery + RT (24.1%) or surgery alone (8.6%) (surgery alone vs. surgery + RT: $P = 0.144$; surgery alone vs. surgery + CCRT: $P = 0.044$; surgery + RT vs. surgery + CCRT: $P = 0.587$; interblock analysis: $P = 0.105$, Fig. 4).

In contrast, in the low- and moderate-risk population (scores of 0 and 1), patients who underwent surgery alone (76.0%) experienced a better 5-year DSS compared with those who had surgery + RT (72.9%) and surgery + CCRT (65.8%) (surgery alone vs. surgery + RT: $P = 0.378$; surgery alone vs. surgery + CCRT: $P = 0.034$; surgery + RT vs. surgery + CCRT: $P = 0.213$; interblock analysis: $P = 0.100$, Fig. 5).

Discussion

Contralateral neck lymph nodes are occasionally involved in OSCC, but such cases have an extremely poor prognosis [3,8]. Traditionally, elective contralateral ND is generally recommended only when the tumour crosses the midline [9,10]. To our knowledge, there have been few large studies on the prognostic factors specific for CLNR in relation to carcinoma that originates in the lateral aspect of the oral cavity. González-García et al. [11] reported an incidence rate of 5.7% for CLNR, which is similar to our 5-year CLNR rate of 4.1%, while another large cohort study by Huang et al. [7] showed a 7.1% higher 5-year CLNR rate than our results.

Several authors have analysed factors associated with an increased risk for CLNR in patients with OSCC. Patients with tumours of the tongue and floor of the mouth, as well as those with tumours involving the retromolar region or the lower gingiva, have also been reported to have a higher risk for contralateral metastasis [3]. In the present study, however, the site of the primary tumour was not a significant predictor for CLNR risk by univariate analysis.

Recently, anatomical studies have shown the presence of rich lymphatic connections in the submucosal plexus within 1 cm of the midline of the oral cavity [12]. The importance of midline involvement has already been identified, with a reported 16–46% CLNR rate in tumours that cross the midline [13,14]. However, in this study, tumours that reach the midline in cases of elective

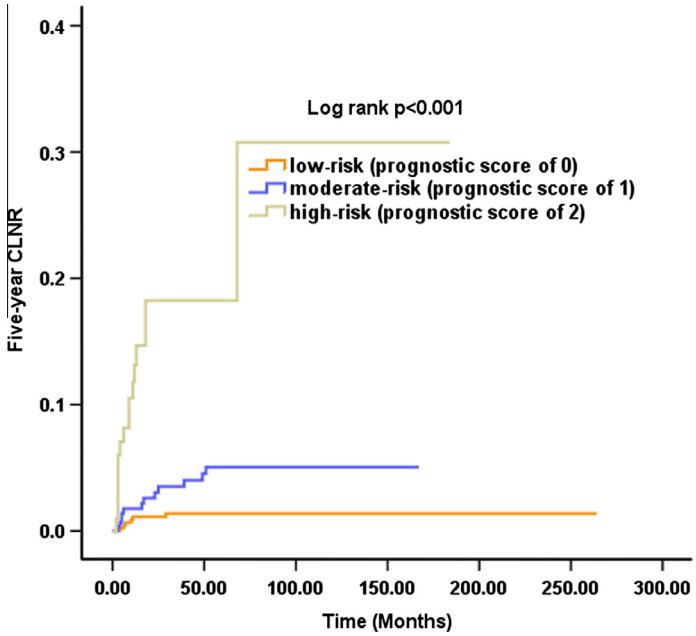

Fig. 2. Kaplan–Meier survival curve for the 5-year CLNR according to risk score.

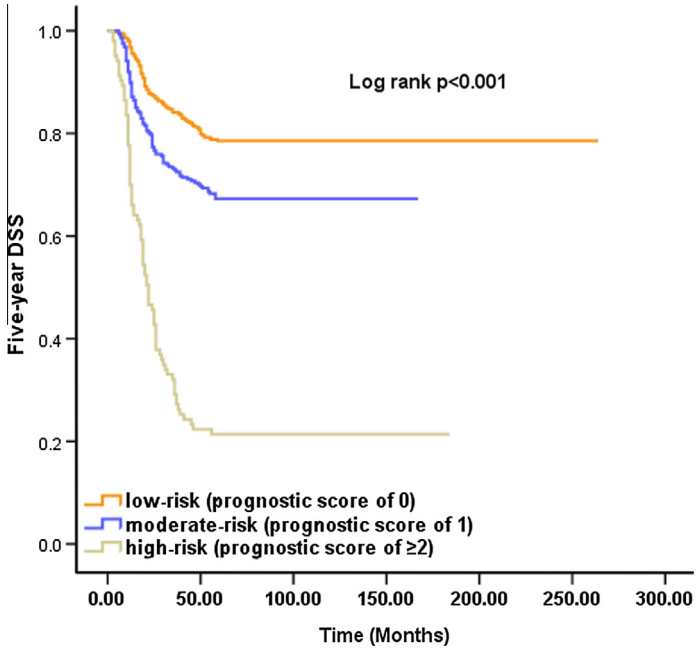

Fig. 3. Kaplan–Meier survival curve for the 5-year DSS according to prognostic score.

contralateral ND that was performed were not a significant predictor for CLNR. Additionally, this factor was also not an independent predictor for DSS according to the multivariate analysis.

Some previous studies have shown that patients with local recurrence have a higher incidence of CLNR than those without [7]. In this study, we divided the sites of the first relapse into local recurrence, neck recurrence alone and SPM to analyse in detail the weight of different forms of tumour relapse for CLNR. Interestingly, in this study, the 5-year CLNR rate was similar in patients with local recurrence coupled with neck recurrence (18.5%), SPM coupled with neck recurrence (24.2%), and in those with neck recurrence alone (21.4%, $P = 0.857$).

In this retrospective study, we demonstrated that ECS status was correlated with 5-year CLNR. However, the 5-year CLNR rate in patients with ECS was only 3/28 (10.7%); therefore, elective contralateral ND for these patients is not strongly recommended. Further analyses showed that 5-year CLNR, T stage and growth pattern were three prognostic factors associated with 5-year DSS. A prognostic scoring system was therefore formulated by a summation of the significant factors (T3–4, presence of ECS and infiltrative growth) and divided by the patients in the low-risk group (score of 0, CLNR rate: 1.3%), moderate-risk group (score of 1, CLNR rate: 4.2%) and high-risk group (score $\geqslant$ 2, CLNR rate: 16.5%). Elective treatment of the cervical nodes is only accepted in such patients when the risk of metastases exceeds 15–20% [15–19]. Elective contralateral ND is also not strongly recommended in high-risk patients (score $\geqslant$ 2). In this study, postoperative CCRT compared with surgery alone can improve the 5-year DSS in these high-risk

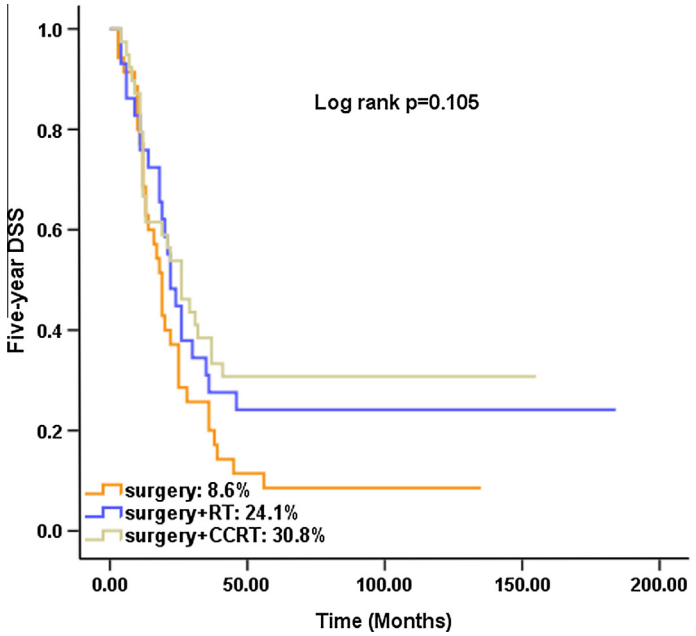

Fig. 4. Kaplan–Meier survival curve for the 5-year DSS according to the modality of combined treatment for the high-risk population (score of $\geqslant 2$).

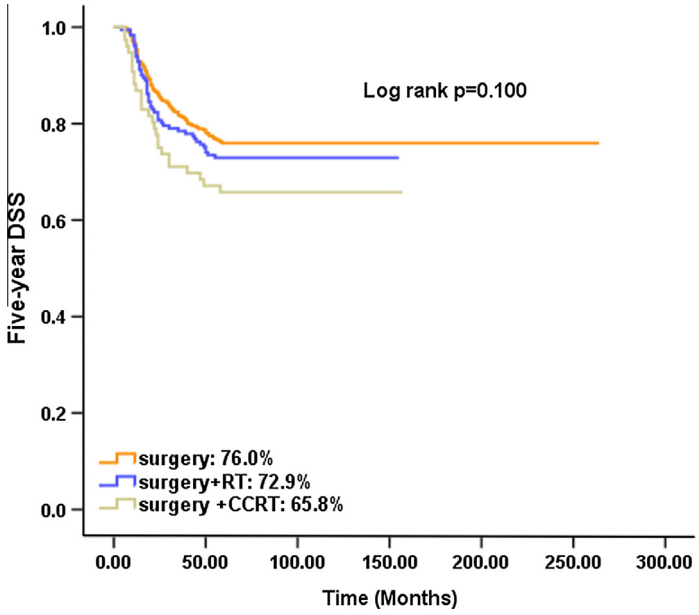

Fig. 5. Kaplan–Meier survival curve for the 5-year DSS according to the modality of combined treatment for the low- and moderate-risk populations (score of 0, 1).

patients but does not decrease the 5-year CLNR rate. However, postoperative RT compared with surgery alone did not exhibit an obvious advantage in terms of neck control rate and prognosis. The above conclusion is in accordance with recent results showing that postoperative CCRT is more effective than RT alone in high-risk patients [20,21]. However, it is apparent that the use of CCRT in the adjuvant setting, which is highly toxic, may cause immune suppression. Moreover, CCRT may also be inappropriate for low-risk patients with multiple comorbidities [22]. In comparison, our results also show that contralateral neck observation in low-risk and moderate-risk patients (scores of 0 or 1) should be considered sufficient if strict compliance with a cancer surveillance protocol is followed.

This study was retrospective and thus has inherent limitations. It may also be criticised for a lack of data on some important baseline factors, including depth of invasion and thickness of the tumour. The above limitations will be given further consideration in future studies. No clear conclusion can be drawn from the present study with regard to the best treatment approach for improving the contralateral neck control rate. Whether high-risk patients benefit or not from postoperative CCRT can only be determined in a prospective trial.

Conclusion

CLNR is an independent predictor for the long-term survival of patients with OSCC. In low- and moderate-risk patients (score 0 or 1), contralateral neck observation should be considered sufficient if strict compliance with a cancer surveillance protocol is followed. However, whether high-risk patients (score $\geqslant$ 2) benefit from contralateral ND prior to adjuvant CCRT can only be determined in a prospective trial.

Conflict of interest statement

None declared.

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