Original Article

The Length of Peri-Neural Spreading in Clinically Mandibular Invaded Oral Cavity Squamous Cell Carcinoma

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Background: The objective of surgical management of oral squamous cell carcinoma (OSCC) is adequate resection with a clear margin. However, there is still a debate as to the optimal length for a mandibular resected margin.

Objective: To examine the length of peri-neural spreading in T4 mandibular invaded oral cavity squamous cell carcinoma.

Materials and Methods: Twenty-eight T4 pathological OSCC specimens that involved mandible and serial slices were studied and the length of tumor spreading along the inferior alveolar nerve (IAN) was determined. Tumor characteristics, risk factors, and survival were analyzed.

Results: The incidence of peri-neural invasion was 11.11%, and IAN invasion was found in 14.29% of the tumor-invaded mandibular marrow. The length of tumor spreading along IAN was 3 to 12 mm. Poor prognostic factors of T4 OSCC were it being located on the tongue (HR 14.16), was pathological N2-3 (HR 31.05), and had high-risk features such as peri-neural invasion, lymphovascular invasion, and extra-nodal extension.

Conclusion: A mandibular resected margin of at least 18 mm is recommended as a clear surgical margin in cases of T4 mandibular invasion OSCC.

Keywords: Oral cancer, Perineural invasion, Inferior alveolar nerve, Squamous cell carcinoma, Mandibulectomy

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In 2012, there were an estimated 300,000 new cases of the oral squamous cell carcinoma (OSCC) and more than 145,000 deaths worldwide, 77% of these were in underdeveloped countries. The incidence rate of OSCC is relatively high in Asia[1]. The prevalence of OSCC is also higher in the South and the Southeast Asia[2]. In Thailand, the age-standardized incidence rate of OSCC between 2001 and 2003 was 4.5 per 100,000 in males and 3.7 per 100,000 in females, with the highest incidence in the northeast[3]. For the present study, data were collected from 1,472 patients with squamous cell carcinoma of the oral cavity at Khon Kaen University's Srinagarind Hospital in Thailand between January 2000 and December 2010. A high proportion of patients were in stage IV (39.5%) when diagnosed. The overall five-year survival rate was low at 31.9%, and for stage IV was 19.5%. In Asia, betel nut chewing, tobacco smoking, alcohol use, poor oral hygiene, and low socioeconomic conditions are the predisposing factors for OSCC[4].

In Thailand, OSCC patients are often diagnosed in the later stages of the disease, as early-stage OSCC is difficult to diagnose, and patients with little formal education are not aware of the disease. They also have faith in alternative medicine and herbal treatment[5,6]. When patients present with stage IV OSCC, it has often invaded into the mandible and nerve. In such cases, en-bloc resection of the tumor and clinically invaded mandible is performed with a gross margin of 1.5 to 2 cm by visibility and palpation[7,8]. An

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inadequate surgical margin (especially the mandibular margin) can lead to the recurrence of OSCC[9,10]. By contrast, having an adequate surgical margin can lead to a lower rate of recurrence. However, this can lead to more morbidities related to swallowing, chewing, speaking, breathing, and cosmetic. However, less resection of mandible makes less morbidities and is easier to reconstruction[11,12].

Perhaps, adequate bony margin did not represent the soft tissue margin. A study by Brown et al in 100 resected mandibles with OSCC found 94 free bone margins and 62 free soft tissue margins[13]. There is currently no method for evaluating intraoperative margins, although, intraoperative frozen section is widely used, nevertheless, it has a discrepancy of 50%[10,14].

Another important factor is peri-neural infiltration, especially of the inferior alveolar nerve (IAN), which could be representing aggressive tumor behavior and has a high recurrence rate, a low disease-free survival rate, and a low overall survival rate[15,16]. The clinical of peri-neural infiltration is difficult to evaluate clinically or radiologically. A pathological study of resected OSCC mandibles conducted by Agni et al found that 25 of 26 specimens showed peri-neural infiltration that could not to be diagnosed by clinical or radiological[17]. Pandey et al studied the patterns of mandibular invasion in OSCC, and found that in 20% of the cases, the OSCC had spread through the inferior alveolar canal, and in approximately 6.3% of the cases had peri-neural infiltration of the IAN[18]. When tumors involve mandible marrow space, the inferior alveolar canal and nerve can be a route of tumor spread, so extirpation must be conducted with an adequate bone margin and extension along the IAN.

The authors prioritized the adequate margin of resection, rate of recurrence, disease-free, and survival. Thus, the aim of study was to investigate the incidence of peri-neural infiltration of the IAN and the length of OSCC spreading along IAN. The study has been reviewed and approved by the Khon Kaen University Ethics Committee for Human Research based on the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Practice Guidelines (HE601263).

Materials and Methods

The 28 patients examined in the present study were clinically diagnosed with mandibular invaded OSCC (T4 lesions) at Khon Kaen University's Srinagarind Hospital between January 2015 and December 2017. All patients underwent wide en-bloc tumor resection, which included segmental mandibulectomy with clinical clear margins of 1.5 to 2 cm under general anesthesia. The cervical lymph nodes were dissected depending on tumor staging. One of the patients was excluded due to a pathological report, which did not find any trace of the tumor in the specimen after induction with pre-operative chemotherapy, with a complete pathological response. All patients were informed and consents to use data and tissue specimens for the present study.

The specimens were fixed in 10% neutral buffer formalin for 24 hours, and then, underwent gross examination. The mandibular bone with attached neoplasm, mucosa, and soft tissue was sectioned to grossly identify tumor invasion and location in the IAN. Afterward, the bone was serially sliced at a thickness of 1 millimeter per level and submitted for further tissue processing including decalcification. Conventional dehydration and paraffin embedding were performed. The 4 μm-thick serial sections of the paraffin-embedded tissue were oven baked. They were stained using Haematoxylin & Eosin autostainer (Sakura®) and the completely-stained slides were removed and rinsed with tap water, then dehydrated, cleared, and mounted.

A single pathologist (Sangkhamanon S) examined each specimen under a light microscope at both high and low power (40x and 10x) to evaluate the tumor cells' infiltration in the IAN. The length of nerve involvement was measured by the number of slides in which the tumor was present.

Statistical analyses were performed with descriptive statistics and expressed as number and percentages. The normal distributions of numerical variables were analyzed using a Shapiro-Wilk test. The results are expressed as mean, standard deviation or median, interquartile range as appropriate. The 2-year disease-free survival and 2-year overall survival rates were calculated using the Kaplan-Meier survival curve, and the log rank test was used to calculate differences between actuarial curves. Multivariate analysis was carried out using the multiple Cox proportional hazards model. A p-value of less than 0.05 was considered as statistically significant. All statistical analyses were carried out using Stata, version 10.1 (StataCorp LP, College Station, TX, USA).

Results

Twenty-seven patients were recruited, 13 (48.15%) were male and 14 (51.85%) were female. The average age was 68 (55 to 73) years and the

Table 1. Demographic data (n=27)

	n (%)
Sex: male/female	13/14 (48.15/51.85)
Age (years); mean (range)	68 (55 to 73)
BMI (kg/m^2); mean (range)	18.77 (16 to 20.69)
Occupation	
Farmer	21 (77.78)
Housekeeper	4 (14.81)
Wage laborer	1 (3.70)
Public servant	1 (3.70)
Underlying disease	
Hypertension	5 (18.52)
Diabetic type 2	2 (7.41)
Chronic kidney disease	1 (3.70)
Risk factors	
Betel nut chewing	14 (51.85)
Smoking	11 (40.74)
Alcohol consumption	4 (14.81)
Clinical T4 staging	27 (100)
Clinical N staging	
N0	19 (70.37)
N1	3 (11.11)
N2	5 (18.52)
Location of tumor	
Gums	12 (44.44)
Floor of mouth	7 (25.93)
Buccal	4 (14.81)
Tongue	3 (11.11)
Lower lip	2 (7.41)
Pre-operative induction chemotherapy	6 (22.22)

BMI=body mass index

Table 2. Pathological findings (n=27)

	n (%)
Pathological result	
Invaded cortical bone of mandible	6 (22.22)
Invaded marrow	21 (77.78)
Peri-neural invasion	3 (11.11)
IAN invasion	3 (14.29)
Length of tumor spreading along IAN	
3 mm	1 (3.70)
6 mm	1 (3.70)
12 mm	1 (3.70)
Lymphovascular invasion	4 (14.81)
Nodal status	
Pathological N0	18 (66.67)
Pathological N1	4 (14.81)
Pathological N2	4 (14.81)
Pathological N3	1 (3.70)
Extra-nodal extension	1 (3.70)
Tumor differentiation	
Well	19 (70.37)
Moderate	5 (18.52)
Poor	2 (7.41)
Undifferentiated	1 (3.70)
Pathological margin	
Free margin (≥5 mm)	12 (44.44)
Close margin (<5 mm)	10 (37.04)
Positive margin	5 (18.52)

IAN=inferior alveolar nerve

average body mass index (BMI) was 18.77 (16 to 20.69 kg/m²). Most participants were farmers (21 cases, 77.78%) while others were housekeepers (four cases, 14.81%), wage laborers (1 case, 3.7%), and public servants (1 case, 3.7%). Five patients had hypertensive disorder (18.52%), two were diabetic (7.41%), and one had end stage chronic kidney disease (3.7%). The most common risk factors were betel nut chewing (14 cases, 51.85%), smoking (11 cases, 40.74%), and heavy alcohol consumption (four cases, 14.81%) (Table 1).

The most frequent site was the lower gums (12 cases, 44.44%), followed by the floor of mouth (seven cases, 25.93%), the buccal mucosal area (four cases, 14.81%), the tongue (three cases, 11.11%), the lower lip (two cases).

The tumors were staged according to the TNM clinical staging system proposed by the International Union Against Cancer. No patient had evidence of distant metastasis at the time of initial examination. All 27 patients (100%) had T4 lesions. The clinical N stages were N0 in 19 (70.37%) patients, N1 in three (11.11%) patients, and N2 in five (18.52%) patients. Radical or modified radical neck dissections were performed in all 27 patients. Six patients received pre-operative inductive chemotherapy (5-fluorouracil plus cisplatinum regimen) due to the tumors being large and difficult to control intra-operatively.

The pathological report showed that tumors had invaded the cortical bone of the mandible in six cases (22.22%) and the marrow in 21 cases (77.78%). Tumors invaded the IAN in three of the 21 cases of marrow invasion (14.29%), in which the length of

Table 3. Cox's proportion hazard model

	HR	95% CI	p-value
Tongue lesions	14.16	2.03 to 98.53	<0.01
Pathological N2 to N3	31.05	4.90 to 196.57	<0.01
High-risk features*	8.30	2.00 to 34.39	<0.01

HR=hazard ratio; CI=confidence interval

* High-risk features: peri-neural invasion, lymphovascular invasion, and extra-nodal extension

tumor spreading along the IAN was 3 mm, 6 mm, and 12 mm. Four cases had lymphovascular invasion (14.81%) and three had peri-neural invasion (11.11%). The pathological N stages were N0 in 18 (66.67%) patients, N1 in four (14.81%) patients, N2 in four (14.81%) patients, and N3 in one (3.7%) patient. Only one (3.7%) case exhibited extra-nodal extension. The tumor was well differentiated in 19 patients (70.37%), moderately differentiated in five (18.52%), poorly differentiated in two (7.41%), and undifferentiated in one patient (3.7%) (Table 2).

After resection of the bony margin 1.5 to 2.0 cm from the gross tumors showed free margin (pathological margin 5 mm or more) in only 12 patients (44.44%), closed margin (pathological margin less than 5 mm) in ten (37.04%), and positive margin in five patients (18.52%).

The Kaplan-Meier survival curve showed that the median survival time of 27 patients with stage IV oral cavity carcinoma was 51 weeks (Figure 1). The results of analysis using Cox's proportional hazard model are shown in Table 3. The tumor being located on the tongue, pathological N2 to N3, and presence of high-risk features (peri-neural invasion, lymphovascular invasion, and extra-nodal extension) had a significant impact on overall survival. After controlling for confounding variables, the factors that increased the risk of death were tongue lesions (HR 14.16), pathological N2 to N3 (HR 31.05), and presence of high-risk features (HR 8.30).

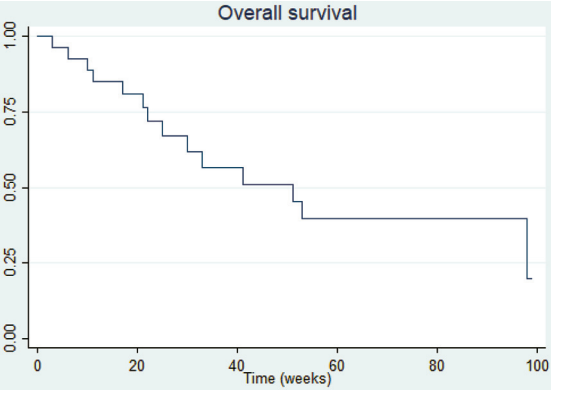

Figure 1. The median time survival of 27 patients with stage IV oral cavity carcinoma was 51 weeks.

Discussion

Most of the patients with oral cancer in the authors' hospital presented with stage IV[4] and almost all had at least one risk factor, especially betel nut chewing and smoking. Ninety percent of them were of low socioeconomic status, which may have been the reason for their being late in seeking treatment.

In the cases of tumor with mandibular invasion, this increased the local recurrent rate[19]. Lin et al showed that a margin of 1 mm or less was a predictor of loco-regional recurrence[20]. The incidence of local recurrence in patients with positive surgical margins was twice as much as in those with negative margins (36% versus 18%)[21], and risk of death[9].

After serial resection of the mandibles in which OSCC was involved, the authors found the incidence of peri-neural invasion to be 11.11%. There was bone marrow invasion in 14.29% of the cases in which peri-neural spreading originated from the tumor. Wide en-bloc tumor resection including segmental mandibulectomy was performed in all cases with a clinical clear margin of 1.5 to 2 cm, the authors could get the free margin in only 44.44% and closed margin (margin less than 5 mm) in 37.04%. The maximal length of tumor spread along the IAN was 12 mm. This suggested that a surgical mandibular margin greater than 18 mm is required as a free surgical margin in cases of tumor invasion into the mandibular marrow.

Kerdpon et al[22] reported that the tumor being located at the floor of mouth was associated with a lower risk of advanced stage disease. However, in the present series, the tumors located at floor of mouth were in 25% of cases. The tumor being located on the tongue was a poor prognostic factor in the present study (HR 14.16, 95% CI 2.03 to 98.53). After investigating the prognostic values of several histopathological features in oral T4 squamous cell carcinoma, the authors found pathological N2-3 (HR 31.05, 95% CI 4.90 to 196.57) and high-risk features such as peri-neural invasion, lymphovascular invasion and extra-nodal extension (HR 8.30, 95% CI 2.00 to 34.39) were poor prognostic features. Those results were similar to those found in previous studies conducted by Brown et al[23] and Jones[24].

The pathological margin had a similar impact

on the incidence of local recurrence and survival rate as that of the involved margins. Many investigators consider closed and tumor at the inked resected margins together in their analysis of the impact of status on outcome[9,21]. As the present study analyzed only a small number of T4 lesions, it was unable to demonstrate that surgical margin was a statistically significant prognostic factor for the outcomes.

Conclusion

The prognosis of patients with OSCC in the tongue is very serious. Certain pathological features, such as peri-neural invasion, lymphovascular invasion, and extra-nodal extension, are indicators of tumor aggressiveness to the same extent as pathological N2 to N3. The peri-neural spreading can be up to 12 mm in length, meaning that a surgical mandibular resection margin of at least 18 mm is recommended.

What is already known on this topic?

The maximal length of peri-neural spreading along IAN in case of T4 mandibular invasion of OSCC is 12 mm.

What this study adds?

This study was able to determine that the adequate bony margin resection of mandible of at least 18 mm is recommended for pathological clear margin (pathological margin >5 mm).

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Conflicts of interest

The authors declare no conflict of interest.

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