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Original Article

Surgical treatment and prognosis of posteriorly invading oral cancer: Potential clinical significance of pterygomandibular raphe

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Abstract *Background/purpose:* The prognosis of oral squamous cell carcinoma (OSCC) with posterior invasion is poor. We examined whether the pterygomandibular raphe (PMR) is useful for the diagnosis of invasion and determination of surgical methods.
Materials and methods: Of 390 patients with OSCC treated surgically at our hospital between June 2009 and June 2020, 80 patients with posterior invasion were included in the study. Preoperative magnetic resonance imaging was used to classify the lesions into three types: non-contact with PMR (non-contact type), contact with PMR (contact type), and invasion beyond PMR (invasion type). We compared the local control, recurrence, and survival rates of each of the three types.
Results: The invasion type showed a significantly higher recurrence rate than the non-contact type ($P < 0.001$) and contact type ($P = 0.018$). Overall survival rate comparisons showed that the invasion type had significantly worse prognosis than the non-contact ($P = 0.004$) and contact types ($P = 0.041$).
Conclusion: OSCCs with posterior invasion beyond the PMR showed a poor treatment outcome and, therefore, should be treated with caution. The initial surgery is especially important and

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must ensure local control. This study indicates that the PMR is an important criterion for surgical method determination and that invasion beyond the PMR is a predictor of local recurrence and poor prognosis.

Introduction

The buccinator muscle is posteriorly continuous with the superior pharyngeal constrictor muscle. The border between the two is the pterygomandibular raphe (PMR), with tendon-like structures.[1,2] The PMR exists between the pterygoid hamulus and the inner surface of the mandible in the lamina medialis. The PMR is in contact with the pterygoid process, internal and external pterygoid muscles, levator and tensor veli palatini muscles, retromolar triangle, and neurovasculature of the skull base.[1,2] The fascia of the buccinatopharyngeus muscle (BPM), which is a combination of the buccinator and superior pharyngeal constrictor muscles, is a loose connective tissue, and if oral squamous cell carcinoma (OSCC) invades this fascia, it may spread using the PMR as a hub. The PMR also borders the masticator space. In general, posterior extension of OSCC has a poor prognosis[3,4] because it is difficult to operate on OSCC located in the masticator space.[5] The PMR is considered one of the entry points for OSCC to invade the masticator space. Therefore, we examined the outcomes of OSCC and PMR that extended posteriorly beyond the line connecting the maxillary second molar and mandibular second molar.

Materials and methods

Of the 390 patients with OSCC treated surgically at the Department of Clinical Oral Oncology, Nagasaki University Hospital, between June 2009 and June 2020, 80 patients with posteriorly advanced OSCC (patients with OSCC extending posteriorly beyond the line connecting the maxillary and mandibular second molars) were included in the study. Preoperative contrast-enhanced magnetic resonance imaging was used to classify the lesions into three types: non-contact type (no PMR contact), contact type (PMR contact), and invasion type (PMR obscuration) (Fig. 1). Age, sex, performance status, primary site, clinical T stage (T4b), pathological lymph node metastasis, preoperative treatment, postoperative treatment, surgical margin, histological grade, and pattern of invasion were recorded and examined for each type. The pattern of invasion was assessed using the Yamamoto-Kohama classification system.[6] We also compared the local control rate (LCR), overall survival (OS) rate, disease-specific survival (DSS) rate, and recurrence site between each type. Contrast-enhanced magnetic resonance imaging (short TI inversion recovery, weighted image) was used to evaluate the PMR invasion of OSCC. The BPM was identified on the axial image, and the PMR was defined as the area from the pterygoid process to the mandibular molar on the superior and inferior sides and the area from the anterior border of the mandibular branch to the pterygoid process on the anterior and posterior sides. The diagnosis was reached by a consensus of radiologists and oral surgeons using magnetic resonance images.

All statistical analyses were performed using the Statistical Package for the SPSS software (version 26.0; IBM Japan Co., Ltd.,Tokyo, Japan), and a two-tailed P-value <0.05 was considered significant. The survival curve was calculated using the Kaplan—Meier method and analyzed by the log-rank test. Factors related to prognosis were analyzed using the chi-square test or Fisher's exact test according to sample size and multivariate Cox regression.

This study was approved by the Institutional Review Board (#21031503) of Nagasaki University Hospital. The research protocol and guaranteed opportunity to opt-out were posted on the hospital's official website.

Results

Patient characteristics

The demographic and clinical characteristics of the 80 patients included in this study are shown in Table 1. A total of 44 patients were men, and 36 were women, with an average age of 72 years. Preoperative treatment was administered to six patients using chemotherapy and one using chemoradiotherapy. Postoperative treatment included radiotherapy in 7 patients, chemotherapy in 2, and chemoradiotherapy in 10. In total, 49 patients were non-contact type, 15 were contact type, and 16 were invasion type based on the PMR. Patients with the invasion type were significantly more likely to have a T4b stage and pathologically positive lymph node metastasis.

LCR and OS by PMR type

The LCRs in patients with non-contact, contact, and invasion types were 81.6%, 80.0%, and 43.8%, respectively. The patients with the invasion type had a significantly higher recurrence rate than those with non-contact ($P < 0.001$) and contact types ($P = 0.018$). The OS rates in patients with the non-contact, contact, and invasion types were 65.3%, 66.7%, and 31.3%, respectively, which indicated that patients with the invasion type had a significantly worse prognosis than those with non-contact ($P = 0.004$) and contact types ($P = 0.041$). The DSS rates of the three types were 83.7%, 66.7%, and 37.5%, respectively, and the prognosis of the invasion type was significantly worse than that of the non-contact type ($p < 0.001$) (Table 2) (Fig. 2).

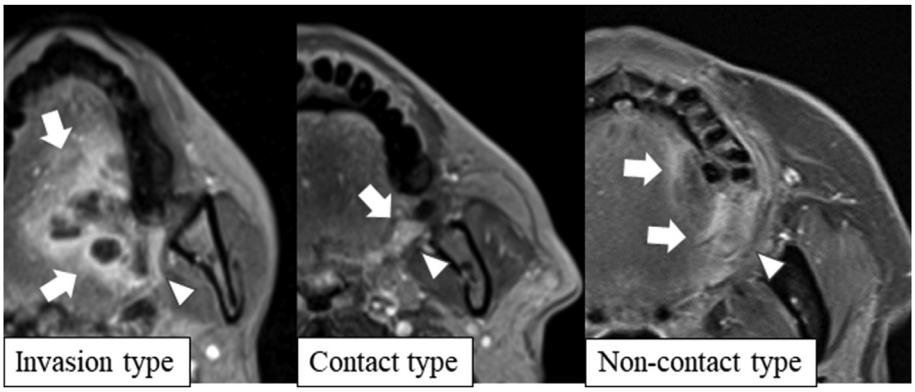

Figure 1 Type of pterygomandibular raphe (shown in enhanced magnetic resonance images). Non-contact type: 54-year-old female; maxillary gingival cancer (T4aN0M0) (right). Contact type: 70-year-old male; mandibular gingival cancer (T2N0M0) (center). Invasion type: 23-year-old male; tongue cancer (T4aN2bM0) (left). White arrow: Tumor; white triangle: pterygomandibular raphe.

Table 1 Clinico-pathological parameters of the 80 oral cancer patients.

Variable		Total	PMR type			P-value
			Non-contact type	Contact type	Invasion type	
Sex	Male	44	23	10	11	0.189
	Female	36	26	5	5	
Age	<75	45	24	11	10	0.214
	≧75	35	25	4	6	
Performance status	0–1	71	42	15	14	0.304
	2	9	7	0	2	
Primary site	Maxillary gingiva and palate	25	15	7	3	0.238
	Mandibular gingiva	38	24	7	7	
	Tongue and buccal mucosa	17	10	1	6	
Clinical T stage	1	3	3	0	0	0.023
	2	10	8	2	0	
	3	4	3	0	1	
	4a	60	35	13	12	
	4b	3	0	0	3	
T4b	+	3	0	0	3	0.002
	–	77	49	15	13	
Pathological lymph node metastasis	+	38	18	6	14	0.002
	–	42	31	9	2	
Preoperative treatment	+	7	6	1	0	0.420
	–	73	43	14	16	
Postoperative treatment	+	19	8	6	5	0.137
	–	61	41	9	11	
Surgical margin	Positive	16	8	4	4	0.137
	Negative	64	41	11	12	
Histological grade	Well and moderately	77	49	13	15	0.050
	Poorly	3	0	2	1	
Pattern of invasion	1, 2	53	36	9	8	0.193
	3, 4	27	13	6	8	
Total		80	49	15	16	

PMR: pterygomandibular raphe.
Analyzed by chi-square test or Fisher exact tests.

Multivariate Cox regression showed that the PMR ($P = 0.004$) in LCR, PMR ($P = 0.024$) and pattern of invasion ($P = 0.022$) in OS rate, and PMR ($P = 0.004$) and pattern of invasion ($P = 0.008$) in DSS rate were significant prognostic factors (Table 3).

Site of local recurrence

Local recurrences occurred in 21 of 80 patients (26.3%). The most frequent recurrence site was the internal or external pterygoid muscle (7 patients), followed by the BPM (6

Table 2 Univariate analysis of prognostic factors for local control rate (LCR), overall survival rate (OS), and disease specific survival rate (DSS).

Variable		5-year LCR (%)	P-value	5-year OS (%)	P-value	5-year DSS (%)	P-value
Sex	Male	70.5	0.491	52.3	0.372	68.2	0.634
	Female	77.8		66.7		75.0	
Age	<75 years	71.1	0.846	60.0	0.609	66.7	0.544
	≧75 years	77.1		57.1		77.1	
Performance status	0.1	73.2	0.973	59.2	0.292	70.4	0.791
	2	77.8		55.6		77.8	
Primary site	Maxillary gingiva and palate	72.0	0.491	72.0	0.072	80.0	0.282
	Mandibular gingiva	78.9		60.5		71.1	
	Tongue and buccal mucosa	64.7		35.3		58.8	
Clinical T stage	1	100.0	0.167	33.3	0.949	100.0	0.695
	2	80.0		60.0		80.0	
	3	75.0		50.0		50.0	
	4a	73.3		60.0		70.0	
	4b	33.3		66.7		66.7	
T4b	+	75.3	0.020	58.4	0.935	71.4	0.802
	−	33.3		66.7		66.7	
Pathological lymph node metastasis	+	73.8	0.681	64.3	0.114	83.3	0.005
	−	73.7		52.6		57.9	
Preoperative treatment	+	71.8	0.363	59.2	0.482	71.8	0.424
	−	83.3		66.7		83.3	
Postoperative treatment	+	76.7	0.534	63.3	0.164	78.3	0.027
	−	68.4		47.4		52.6	
Surgical margin	Positive	76.7	0.760	59.4	0.445	71.9	0.480
	Negative	62.5		56.3		68.8	
Histological grade	Well and moderately	66.7	0.786	59.7	0.419	72.7	0.195
	Poorly	74.0		33.3		33.3	
Pattern of invasion	1, 2	79.2	0.055	69.8	0.007	84.9	0.000
	3, 4	63.0		37.0		44.4	
PMR type	Non-contact type	81.6	0.000	65.3	0.011	83.7	0.000
	Contact type	80.0		66.7		66.7	
	Invasion type	43.8		31.3		37.5	

PMR: pterygomandibular raphe.
Analyzed by Kaplan—Meier method and analyzed by the log-rank test.

patients). There was no apparent association between the PMR type and recurrence site (Table 4) (Fig. 3).

Discussion

OSCCs with posterior invasion beyond the PMR showed a poor treatment outcome and, therefore, should be treated with caution. This study indicates that the PMR is an important criterion for surgical method and that invasion beyond the PMR is a predictor of local recurrence and poor prognosis.

The prognosis of OSCC is generally poor if it invades posteriorly,[3,4] because the masticator space is anatomically present in the posterior part of the oral cavity, wherein invasion of this space makes treatment especially difficult. In general, T4b patients with masticator space invasion are considered unresectable.[5] However, in recent years, if surgery is available for T4b patients, the outcome is comparable to that of T4a patients.[7–9] Therefore, it is expected that a surgical method for posteriorly advanced OSCC will soon be established. In this study, the type of PMR invasion was a significant prognostic factor for posteriorly advanced OSCC. In particular, patients with the invasion type had an extremely poor prognosis and, therefore, may require careful attention in treatment.

The PMR is a tendon-like structure in the area where the buccinator muscle meets the superior pharyngeal constrictor muscle. The PMR is in contact with the pterygoid process, internal and external pterygoid muscles, levator and tensor veli palatini muscles, retromolar triangle, and neurovasculature of the skull base.[1,2] In the case of posterior invasion of tongue cancer, the PMR may be directly invaded via the internal pterygoid muscle inferior to the PMR, wherein the PMR is the entrance to the masticator space where OSCC invades posteriorly and plays the role of a hub. Trotta et al. indicated that oropharyngeal carcinoma can extend into the PMR via the superior pharyngeal constrictor muscle on the front side and invade the buccinator muscle, retromolar triangle, and skull base. It can also invade the buccinator muscle, retromolar triangle, and skull base.[10] Therefore, surgical methods for treating posterior advanced OSCC require knowledge and consideration of the PMR as a hub for cancer invasion.

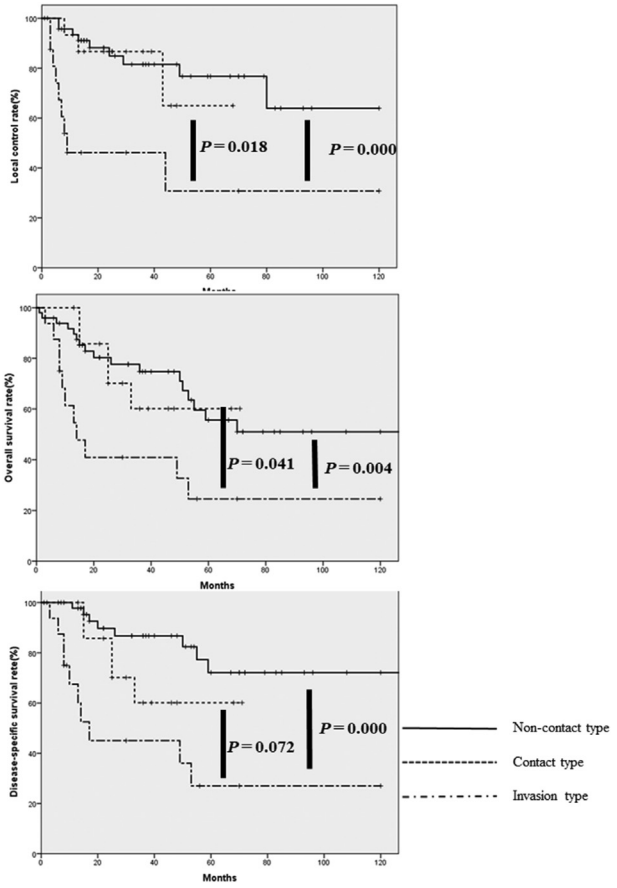

Figure 2 Kaplan–Meier analysis of local control, overall survival, and disease-specific survival rates. LCR: local control rate (upper); OS: overall survival (center); DSS: disease-specific survival (lower).

Trotta et al. reported that OSCC arising in the oral cavity and oropharynx has three different diffusion pathways: 1) direct extension to the mucosal surface, muscle, and bone; 2) diffusion via lymphatic flow; and 3) extension along the neurovascular system. Staging requires evaluation of all three diffusion pathways.[10] Therefore, the assessment of local recurrence needs to be evaluated in a similar manner. Bone and mucosal surface recurrence can usually be diagnosed accurately by visual inspection and imaging. However, it is difficult to clearly assess recurrence along the muscles and neurovascular system. Therefore, a council of oral surgeons and radiologists identified the recurrence site along the muscles and neurovascular system. The most frequent site of recurrence for contact and invasive types was around the PMR in 10 of 12 patients (5 in the internal and external pterygoid muscles, 4 in the BPM, and 1 in the neurovascular structures of the skull base). These sites exist around the PMR, which suggests that the PMR may become a hub for cancer invasion. In addition, no patient with recurrence around the PMR was salvageable in this study. Therefore, the initial surgery is crucial in posteriorly advanced OSCC, and local control must be ensured.

Resection of OSCC is often performed through an extraoral approach. This makes it difficult to obtain a clear field of view when resecting the posterior OSCC and makes the surgery difficult. If the resection proceeds with tension of the OSCC toward the outside of the mouth, the resection margin may be reduced by pulling the BPM. During resection, it is necessary to ensure not only a mucosal margin, but also a sufficient resection margin for BPM when the PMR is included. In oropharyngeal cancer, transoral robotic surgery and transoral robotic surgery using endoscopes and robots are widely used and can be performed without tension on the

Table 4 Site of local recurrence by PMR type.

Recurrent site	PMR type		
	Non-contact type	Contact type	Invasion type
Internal or external pterygoid muscle	2	2	3
BPM	2	1	3
Mucosal surface	1	—	—
Neurovascular of skull base	—	—	1
Others rowhead	4	—	2
Local recurrence rate	9/49 (18.4%)	3/15 (20.0%)	9/16 (56.3%)

BPM: buccinatopharyngeus muscle.
PMR: pterygomandibular raphe.

Table 3 Multivariate analysis of prognostic factors for local control rate (LCR), overall survival rate (OS), and disease specific survival rate (DSS).

Variable	LCR			OS			DSS		
	HR	95%CI	P-value	HR	95%CI	P-value	HR	95%CI	P-value
T4b (+/−)	1.712	0.351–8.36	0.506						
Pathological lymph node metastasis (+/−)							1.78	0.638–4.965	0.271
Postoperative treatment (+/−)							2.081	0.847–5.11	0.110
Pattern of invasion (1–2/3-4)				2.258	1.125–4.533	0.022	3.476	1.391–8.687	0.008
PMR type (Non-contact type/ Contact type/Invasion type)	2.185	1.287–3.707	0.004	1.588	1.062–2.374	0.024	2.234	1.299–3.84	0.004

CI, confidence interval; HR, hazard ratio; PMR, pterygomandibular raphe.

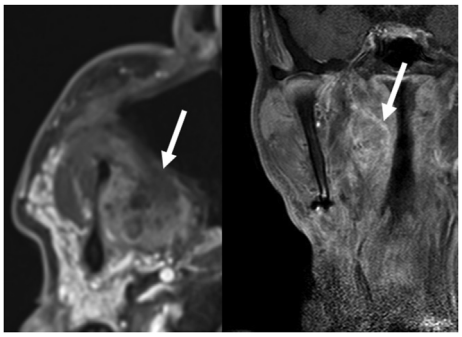

Figure 3 Type of recurrence (shown in enhanced magnetic resonance images). Buccinatopharyngeus muscle recurrence: 69-year-old male; mandibular gingival cancer (T4aN0M0) (right). Internal or external pterygoid muscle recurrence: 48-year old, male; maxillary gingival cancer (T4aN0M0) (left). White arrow: Tumor.

BPM.[11–13] This is a pitfall in OSCC surgery. Conversely, adequate resection of the BPM at the PMR may improve the outcome of posterior advanced OSCC. To avoid tension on the BPM during posterior advanced OSCC surgery, we suggest the use of Weber-Ferguson incision, mandibular swing method, endoscopic surgery, and robotic surgery.[14,15] However, for T4b, more extensive surgery is needed.

Furthermore, considering lymph node metastasis, there is a well-developed lymphoid network in the submucosa from the posterior oropharynx to the oropharynx, which penetrates the BPM and flows into the parapharyngeal space.[16] Although pathological lymph node metastasis was not a prognostic factor in this study, dissection of the parapharyngeal space should be considered for lymphatic flow when performing surgery around the PMR.

To the best of our knowledge, this is the first study to focus on the PMR and to investigate its association with local recurrence in patients with posteriorly advanced OSCC. In the future, we would like to increase the number of cases and to reexamine this association to establish an appropriate surgical method for posteriorly advanced OSCC with PMR invasion.

This study has some limitations. First, this is a retrospective study with a small number of patients. Second, it is sometimes difficult to identify the site of local recurrence by magnetic resonance imaging.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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