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Original Article

A retrospective investigation of minor risk factors as prognostic predictors and treatment indications in oral squamous cell carcinoma

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KEYWORDS
Oral squamous cell carcinoma;
Minor risk factor;
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Pattern of invasion

Abstract
Background/purpose: The clinical significance of minor risk factors remins uncertain in oral squamous cell carcinoma (OSCC) patients. The purpose of this study was to investigate the clinical impact of minor risk factors in OSCC patients.
Materials and methods: The cases of OSCC patients that underwent surgery were retrospectively analyzed. Patients with major risk factors for recurrence, such as positive surgical margins or extracapsular spread, were excluded. The impact of possible minor risk factors on treatment outcomes was analyzed. One hundred and seventy-five patients with primary OSCC that underwent surgery were included in this study.
Results: The 5-year overall survival (OS), cancer-specific survival (CSS), and relapse-free survival (RFS) rates were 81.2%, 91.0%, and 72.4%, respectively. In multivariate analyses, RFS exhibited a significant association with the pattern of invasion (grade 4 vs. grades 1—3: hazard ratio: 3.096, 95% confidence interval: 1.367—6.884, $p < 0.01$), OS exhibited a tendency towards associations with the pattern of invasion and perineural invasion, and CSS displayed a tendency towards an association with perineural invasion. The prognosis of the patients with $\geq$2 minor

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risk factors was significantly worse than that of the patients with 0 or 1 minor risk factor(s) (OS: 91.6% vs. 64.5%, respectively, $p < 0.01$; CSS: 98.9% vs. 78.9%, respectively, $p < 0.001$; and RFS: 81.2% vs. 58.5%, respectively $p < 0.05$).
Conclusion: Grade 4 invasion and perineural invasion might be significant minor risk factors in OSCC patients. The presence of $\geq$2 minor risk factors might be a predictor of a poor prognosis in OSCC patients.

Introduction

Oral squamous cell carcinoma (OSCC), which is the most common malignant neoplasm among head and neck malignancies, was reported to account for >90% of oral cancers.[1] The primary treatment strategy for OSCC is surgical resection of the tumor with adequate surgical margins, and recent advances in the treatment of OSCC have improved the outcomes of OSCC patients. However, standard radical therapy, including the wide resection of lesions, often results in functional decline and a reduction in quality of life in OSCC patients.[2]

Various prognostic factors for OSCC have been reported, including the TNM classification, disease stage, the degree of histological differentiation, the pattern of invasion, the depth of invasion, lymphatic invasion, perineural invasion, vascular invasion, the number and location of lymph node metastases, and the extracapsular spread (ECS) of lymph node metastasis.[3–5]

In the current standard treatment strategy for OSCC, patients that are considered to be at high risk of recurrence undergo concurrent chemoradiotherapy (CCRT) with cisplatin (CDDP) as an adjuvant therapy. The National Comprehensive Cancer Network (NCCN) guidelines for OSCC recommend CCRT with high-dose CDDP for patients with adverse features, such as positive surgical margins or ECS.[6] Originally, CCRT with high-dose CDDP was recommended by the European Organization for Research and Treatment of Cancer (EORTG) and the Radiation Therapy Oncology Group (RTOG) based on the results of two randomized trials (EORTG trial ♯22931 and RTOG trial ♯9501), in which CCRT with high-dose CDDP was employed in the postoperative setting for head and neck SCC patients that were at high risk of recurrence or metastasis.[7,8] Although postoperative adjuvant chemotherapy-enhanced radiotherapy (RT) produced significant improvements in locoregional control and disease-free survival compared with those seen after postoperative radiation alone in these 2 trials, the trial employed different indication criteria.[7,8] In EORTG trial ♯22931, a high risk of recurrence was defined as the presence of tumor cells at the surgical margins (within $\leq$5 mm), ECS, lymph node metastasis from carcinomas arising at level 4 or 5 of the oral cavity or oropharynx, perineural disease, and/or vascular emboli.[7] On the other hand, in RTOG trial ♯9501, a high risk of recurrence was defined as the presence of tumor cells at the surgical margins, the involvement of $\geq$2 lymph nodes, and/or ECS.[8] Based on a comparative pooled analysis of the selection criteria for these trials, since patients with $\geq$2 histopathologically involved lymph nodes without ECS did not seem to benefit from the addition of chemotherapy, ECS and/or microscopically involved surgical margins were the only risk factors for which chemotherapy-enhanced RT had a significant impact in both trials.[9]

According to the NCCN guidelines, the presence of other adverse risk factors, including multiple positive lymph nodes without ECS, perineural invasion, vascular invasion, lymphatic invasion, a pT3 or pT4 primary tumor, and oral cancer with positive level 4 or 5 lymph nodes, is an indication for postoperative RT. However, since EORTG trial ♯22931 revealed that CDDP with concurrent postoperative RT conveyed a survival advantage on patients with these adverse features, compared with RT alone, the NCCN Panel recommended that CCRT should be considered for patients with these features.[6,7]

However, few studies have examined the indications for adjuvant therapy in patients with these other adverse features.[10–12] Therefore, the purpose of this study was to investigate the clinical impact of these other adverse features in OSCC patients, based on a monoinstitutional retrospective analysis.

Materials and methods

The protocol for the present study was approved by the ethics committee of Shinshu University School of Medicine (No.4075). A research plan and a guaranteed opt-out opportunity were published on the hospital's homepage.

The medical records of all patients who underwent surgery with curative intent for OSCC at the Department of Dentistry and Oral Surgery, Shinshu University Hospital, between January 2008 and December 2018 were retrospectively reviewed. Among these OSCC patients, those with major risk factors for recurrence, such as positive surgical margins or ECS, were excluded from the study. Data regarding the following factors were collected: age, sex, demographic information, histological differentiation, the pathological TNM stage, surgical margin status, the pattern of invasion, perineural invasion, lymphatic invasion, vascular invasion, adjuvant therapy, and outcomes. The pathological tumor stage was classified according to the 7th TNM classification of the International Union against Cancer.[13] The pattern of invasion was assessed using the Yamamoto-Kohama (YK) classification.[14]

Treatment strategies were selected based on the tumor stage and the patient's comorbidities, performance status

(PS), G8 score, ability to perform activities of daily living, and wishes. At our institution, surgery is the preferred treatment for patients with OSCC. Patients that were in relatively good health (PS: $\leq$2) underwent radical surgery with/without chemotherapy/RT according to the NCCN guidelines.[6] Patients who did not agree to undergo radical surgery or did not undergo radical surgery because of the presence of advanced tumors or other physical conditions underwent limited surgery, which, after considering the potential postoperative dysfunctions it might cause, was performed with/without the recommended adjuvant therapy or chemotherapy/RT with curative intent. The use of chemotherapy mainly depended on the patient's physical condition rather than the status of their tumor. Patients with very advanced tumors, distant metastasis, or that were in a bad physical condition received palliative RT or best supportive care. In the standard treatment, the primary tumors were excised with 1.0-cm safety margins (superficial and deep margins). Surgery included the removal of the primary tumor, and radical neck dissection was performed in patients who were clinically positive for cervical lymph node metastasis. Elective neck dissection was not routinely performed.

Postoperative CCRT/RT with a dose field of >60 Gy triweekly and a high dose of CDDP was administered to patients with positive margins or ECS, according to the NCCN guidelines.[6] Patients that suffered potentially curable/operable recurrence underwent salvage surgery and RT, if applicable. Patients that developed incurable recurrence were treated with palliative chemotherapy. All patients were followed up on a regular basis: every 2 weeks for the first year, every month for the second year, every 3 months for the third and fourth years, and then biannually for life.

The clinical significance of each adverse feature (minor risk factor) in terms of the overall survival (OS), cancer-specific survival (CSS), and relapse-free survival (RFS) times was analyzed. OS, CSS, and RFS rates were calculated with the Kaplan–Meier method, and the statistical significance of associations was examined with log-rank test. Univariate analyses were performed with the log-rank test and Fisher's exact test. Multivariate analyses were performed with Cox's proportional hazards model. All statistical analyses were conducted using JMP® 13.0 (SAS Institute Inc., Cary, NC, USA). P-values of <0.05 were considered to indicate significance.

Table 1 The characteristics of the patients (n = 175).

Variables	Number (%)	Variables	Number (%)
Gender		status of surgical margin	
Male	106 (60.6)	Free ($\geqq$5 mm)	77 (44.0)
Female	69 (39.4)	Closed (<5 mm)	98 (56.0)
Age		Pattern of invasion	
Average $\pm$ SD (years)	64.9 $\pm$ 12.8 (23–92)	Grade 1	7 (4.0)
Primary site		Grade 2	32 (18.3)
Tongue	95 (54.3)	Grade 3	100 (57.1)
Lower gingiva	36 (20.6)	Grade 4	36 (20.6)
Oral floor	19 (10.9)	Perineural invasion	
Buccal mucosa	16 (9.1)	None	147 (84.0)
Upper gingiva	9 (5.1)	Presence	28 (16.0)
Histological differentiation		Lymphatic invasion	
Well	130 (74.3)	None	150 (85.7)
Moderate	37 (21.1)	Presence	25 (14.3)
Poor	8 (4.6)	Vessel invasion	
pT classification		None	140 (80.0)
T1	56 (32.0)	Presence	35 (20.0)
T2	76 (43.4)	Postoperative adjuvant therapy	
T3	11 (6.3)	None	124 (70.9)
T4	32 (18.3)	Done	51 (29.1)
pN classification		Observation period	
N0	129 (73.7)	Average $\pm$ SD (Months)	56.1 $\pm$ 39.1
N1	24 (13.7)		
N2a	2 (1.1)		
N2b	15 (8.6)		
N2c	5 (2.9)		
pStage classification			
stageI	50 (28.6)		
stageII	54 (30.9)		
stageIII	26 (14.9)		
stageIV	45 (25.7)		

SD: standard deviation.

Table 2 Univariate analysis of effects of minor risk factors on prognosis in OSCC patients.

Variables	5-year OS (%)	P value*	5-year CSS (%)	P value*	5-year RFS (%)	P value*
Gender						
Male	79.3	NS	87.8	NS	72.5	NS
Female	84.9	P = 0.672	96.6	P = 0.072	72.5	P = 0.868
Age						
<65	76.8	NS	89.3	NS	72.7	NS
≧65	86.4	P = 0.676	92.7	P = 0.497	72.1	P = 0.937
Histological differentiation						
Poor	90	NS	90	NS	50	NS
Well/Moderate	80.8	P = 0.857	91.1	P = 0.780	73.4	P = 0.988
pT classification						
pT1-3	86.9	P < 0.001	93.8	P < 0.05	76.6	P < 0.05
pT4	47.6		76.7		51	
pN classification						
None	82.9	NS	92.7	NS	76.2	P < 0.05
Presence	63.8	P = 0.099	80	P = 0.081	63.8	
pStage classification						
p Stage I-III	86.4	NS	94	P < 0.05	75.7	NS
pStage IV	64.9	P = 0.074	82		63.3	P = 0.271
Status of surgical margin						
Free (≧5 mm)	79.4	NS	90.5	NS	75.1	NS
Closed (<5 mm)	82.6	P = 0.806	91.2	P = 0.929	70.4	P = 0.196
Pattern of invasion						
Grade 1-3	87	P < 0.001	95.2	P < 0.001	80.5	P < 0.001
Grade 4	55.3		71.6		34	
Perineural invasion						
None	86.1	P < 0.001	95.5	P < 0.001	76.5	P < 0.05
Presence	56.5		68.6		49.7	
Vessel invasion						
None	82.7	NS	92.8	NS	73.3	NS
Presence	75.9	P = 0.658	83.9	P = 0.129	69.1	P = 0.414
Lymphatic invasion						
None	85.6	P < 0.01	94	P < 0.001	74.1	NS
Presence	55.1		71.8		63.3	P = 0.258
Postoperative adjuvant therapy						
None	86.1	NS	92.7	NS	72.6	NS
Done	69.8	P = 0.059	86.7	P = 0.230	72.1	P = 0.884

OSCC: oral squamous cell carcinoma.
OS: overall survival.
CSS: cancer-specific survival.
RFS: relaps-free survival.

Results

Among 215 OSCC patients that were surgically treated with curative intent between 2008 and 2018, 40 patients with positive surgical margins and/or ECS were excluded from this study. Therefore, 175 patients with primary OSCC that were surgically treated were included in the study population. The characteristics of these patients are shown in Table 1. The mean age at diagnosis was 64.9 ± 12.8 years (range: 23–92 years). The most common primary site was the tongue (95 patients, 54.3%). In addition, the primary site was located in the lower gingiva, oral floor, buccal mucosa, and upper gingiva in 36 (20.6%), 19 (10.9%), 16 (9.1%), and 9 (5.1%) patients, respectively. As for the histological grade, well-differentiated, moderately differentiated, and poorly differentiated SCC was seen in 130 (74.3%), 37 (21.1%), and 8 (4.6%) patients, respectively. Regarding the TNM stage, as defined by the Union for International Cancer Control 7th edition,[13] stage II was the most common stage (54 patients, 30.9%), and stage I, IV, and III disease were seen in 50 (28.6%), 45 (25.7%), and 26 (14.9%) patients, respectively. Concerning surgical margin status, the primary tumor was resected with close margins (<5 mm) in 98 (56.0%) patients and with tumor-free margins (≥5 mm) in 77 (44.0%) patients. As for the pattern of invasion, grade 3 (according to the YK classification) invasion was observed in 100 patients (57.1%). Grade 4, including grade 4c and 4 d, invasion was seen in 36 patients (20.6%). Perineural, lymphatic, and vascular invasion were observed in 28 (16.0%), 25 (14.3%), and 35 (20.0%) patients,

respectively. Postoperative adjuvant therapy was administered to 51 patients (29.1%) (see Table 1).

The median duration of the follow-up period was 56.1 ± 39.1 months. The 5-year OS, CSS, and RFS rates for all patients were 81.2%, 91.0%, and 72.4%, respectively. In the univariate analyses, OS was found to be significantly associated with the pT classification (pT1−3 vs. pT4: 86.9% vs. 47.6%, respectively; $p < 0.001$), the pattern of invasion (YK grade 1−3 vs. YK grade 4: 87.0% vs. 55.3%, respectively; $p < 0.001$), perineural invasion (absent vs. present: 86.1% vs. 56.5%, respectively; $p < 0.001$), and lymphatic invasion (absent vs. present: 85.6% vs. 55.1%, respectively; $p < 0.01$) (Table 2). OS exhibited a tendency towards associations with positive lymph node metastasis, the pathological stage, and postoperative adjuvant therapy. CSS was found to be significantly associated with the pT classification (pT1−3 vs. pT4: 93.8% vs. 76.7%, respectively; $p < 0.05$), the pathological stage (pT1−3 vs. pT4: 94.0% vs. 82.0%,

Table 4 The impact of number of minor risk factors on prognosis in OSCC patients.

Number of minor risk factors	5-year OS	P value*	5-year CSS	P value*	5-year RFS	P value*
<1	87.1	NS	96.6	NS	83.5	NS
≧1	79.8	P = 0.173	89.6	P = 0.220	69.6	P = 0.074
<2	91.6	P < 0.01	98.9	P < 0.001	81.2	P < 0.05
≧2	64.5		78.9		58.5	
<3	86.9	P < 0.001	95.1	P < 0.001	78.7	P < 0.01
≧3	57.6		74.2		44.5	

*Log-rank test.
OSCC: oral squamous cell carcinoma.
OS: overall survival.
CSS: cancer-specific survival.
RFS: relaps-free survival.
NS: not significance.

Table 3 Multivariate analysis of effects of minor risk factors on prognosis in OSCC patients.

Variables	OS			CSS			RFS		
	HR	95%CI	P value*	HR	95%CI	P value*	HR	95%CI	P value*
Gender (Male/Female)	—	—	—	0.402	0.060−1.630	NS(P = 0.219)	—	—	—
Age (<66/≧66)	—	—	—	—	—	—	—	—	—
pT classification (pT4/pT1-3)	1.746	0.676−4.392	NS(P = 0.246)	1.38	0.297−8.421	NS(P = 0.694)	0.933	0.376−2.219	NS(P = 0.878)
pStage classification (pStage IV/pStage I-III)	—	—	—	0.714	0.139−3.525	NS(P = 0.676)	—	—	—
Positive lymph node metastasis (Positive/Negative)	1.921	0.865−4.364	NS(P = 0.109)	2.296	0.554−10.235	NS(P = 0.249)	1.816	0.872−3.921	NS(P = 0.111)
Pattern of invasion (Grade 4/Grade 1−3)	2.164	0.948−4.758	NS(P = 0.066)	2.01	0.541−7.397	NS(P = 0.291)	3.096	1.367−6.884	P < 0.01
Perineural invasion (Presence/None)	2.679	0.953−7.268	NS(P = 0.061)	4.463	0.987−19.762	NS(P = 0.052)	1.854	0.752−4.351	NS(P = 0.175)
Lymphatic invasion (Presence/None)	0.989	0.355−2.652	NS(P = 0.983)	1.326	0.284−6.122	NS(P = 0.717)	—	—	—
Postoperative adjuvant therapy (Done/None)	0.844	0.365−2.000	NS(P = 0.695)	—	—	—	—	—	—

*Cox proportional hazard model.
OSCC: oral squamous cell carcinoma.
OS: overall survival.
CSS: cancer-specific survival.
RFS: relaps-free survival.
HR: hazard ratio.
CI: confidence interval.
NS: not significance.

respectively; $p < 0.05$), the pattern of invasion (YK grade 1–3 vs. YK grade 4: 95.2% vs. 71.6%, respectively; $p < 0.001$), perineural invasion (absent vs. present: 95.5% vs. 68.6%, respectively; $p < 0.001$), and lymphatic invasion (absent vs. present: 94.0% vs. 71.8%, respectively; $p < 0.001$). CSS displayed a tendency towards associations with sex and positive lymph node metastasis. RFS was found to be significantly associated with the pT classification (pT1–3 vs. pT4: 76.6% vs. 51.0%, respectively; $p < 0.05$), positive lymph node metastasis (absent vs. present: 76.2% vs. 63.8%, respectively; $p < 0.05$), the pattern of invasion (YK grade 1–3 vs. YK grade 4: 80.5% vs. 34.0%, respectively; $p < 0.001$), and perineural invasion (absent vs. present: 76.5% vs. 49.7%, respectively; $p < 0.05$).

Based on the variables that exhibited significant associations or tendencies towards significant associations with OS, CSS, or RFS, multivariate analyses were performed to identify significant minor risk factors for OSCC patients. The multivariate analyses revealed that there were no significant independent risk factors for OS or CSS. However, OS exhibited a tendency towards associations with the pattern of invasion and perineural invasion, and CSS displayed a tendency towards an association with perineural invasion. On the other hand, the pattern of invasion was identified as a significant independent risk factor in terms of RFS (pattern of invasion: hazard ratio (HR): 3.096, 95% confidence interval (CI): 1.367–6.884, $p < 0.01$) (Table 3). These results suggested that grade 4 invasion and the presence of perineural invasion might be significant minor risk factors in OSCC.

The prognostic impact of the number of minor risk factors a patient possesses was investigated in univariate analyses focusing on adverse pathological features according to the NCCN guidelines [6] (Table 4). As a result, it was found that OS, CSS, and RFS were significantly affected by the presence of $\geq$2 minor risk factors. While the 5-year OS rate in patients with $<$2 minor risk factors was 91.6%, the patients with $\geq$2 minor risk factors exhibited a significantly worse prognosis (OS rate: 64.5%) ($p < 0.01$). Similar results were obtained for the 5-year CSS and RFS rates (CSS: 98.9% vs. 78.9%, respectively, $p < 0.001$; RFS: 81.2% vs. 58.5%, respectively, $p < 0.05$).

Discussion

The prognostic factors for OSCC were reported to be the TNM classification, disease stage, histological differentiation, the pattern of invasion, the depth of invasion, lymphatic invasion, perineural invasion, vascular invasion, the number and location of lymph node metastases, and ECS.[3–5] Among these factors, the NCCN guidelines for OSCC recognize positive surgical margins and ECS as major risk factors for recurrence and recommend postoperative adjuvant therapy for patients with such factors.[6] However, the clinical significance of other adverse factors is disputed. The purpose of this study was to investigate the clinical impact of minor risk factors on the prognosis of OSCC patients. Among the adverse features other than positive surgical margins and ECS, the pattern of invasion and perineural invasion were identified as possible independent prognostic factors for OSCC. Regarding the prognostic impact of the number of minor risk factors a patient possesses, patients with $\geq$2 minor risk factors might have worse prognoses than those with $<$2 minor risk factors.

Among the minor risk factors for OSCC,[6] the pattern of invasion and the presence of perineural invasion were identified as significant independent prognostic factors in the current study. In this study, the pattern of invasion was evaluated based on the YK classification, which is based on the Jakobsson classification and focuses on histological findings obtained at the border between a tumor mass and normal tissue.[14] It was reported that the survival rate decreased as the disease progressed from grade 1 to 4 according to the YK classification,[14] and there were significant differences in prognosis between grades 4C and 4D.[15] In esophageal SCC, the YK classification was also reported to be helpful for predicting lymph node metastasis along with decreased E-cadherin expression.[16] In addition, the presence of grade 4C/4D disease was shown to be a powerful predictor of regional metastasis in clinically node-negative OSCC patients.[17] On the other hand, in recent studies although 5-year disease-free survival was significantly lower in patients that exhibited grade 4C invasion than in those that displayed grade 1, 2, or 3 invasion, there was no significant difference in the survival rate between grades 4C and 4D.[18] Our results are consistent with those of previous studies.[14,18] However, the criteria used to determine a tumor's YK classification, and especially grade 4C/4D invasion, vary markedly among pathologists, which might have affected our results.[19]

In previous studies, perineural invasion was detected in 30% of OSCC patients.[20,21] In a systematic review of perineural invasion in OSCC, perineural invasion was reported to be a predictor of a poor prognosis, and strong associations with aggressive tumor behavior, such as disease recurrence, and increased morbidity and mortality, were detected.[22] In another study, oral tongue cancer patients with a high number of perineural invasion foci exhibited a significantly lower disease-specific survival rate, mainly due to distant recurrence, which was the most common pattern of failure. Therefore, perineural invasion was not found to be a predictor of locoregional recurrence-free survival or regional recurrence-free survival.[21] In perineural invasion-positive patients, although postoperative adjuvant RT might not significantly improve prognosis, elective neck dissection might improve local control in the neck.[22] In the present study, perineural invasion was found in 16.0% of patients, and tendencies towards associations between perineural invasion and OS or CSS were detected in the multivariate analyses. In addition, the prevalence of distant metastasis in patients with perineural invasion was 17.9% (5 of 28 patients with perineural invasion). Although there was no significant difference in the frequency of distant metastasis between the patients with perineural invasion and those without it, a tendency towards an association between perineural invasion and distant failure was detected in this study ($p = 0.052$, Fisher's exact test). Since these results were consistent with those of previous studies, perineural invasion might have a significant adverse clinical impact on OSCC patients.

The number of minor risk factors possessed by a patient was reported to be a predictor of a poor prognosis and an indication for postoperative adjuvant therapy in OSCC patients.[10–12] The 3-year OS rate was reported to be 82% in patients with no risk factors, 76% in those with 1 or 2 risk factors, and 45% in those with ≥3 risk factors.[10] The number of minor risk factors possessed was identified as a significant prognostic factor in a multivariate analysis, and possessing 1 or 2 risk factors for recurrence was found to be an indication for postoperative RT.[10] In another study, possessing 2 minor risk factors was shown to be an indication for postoperative RT, and possessing major risk factors or >2 minor risk factors was identified as an indication for postoperative CCRT.[11] In addition, postoperative CCRT was reported to significantly improve RFS and OS in patients with ≥3 minor risk factors.[12] In the current study, patients with >2 minor risk factors exhibited significantly worse prognoses than those with no or 1 minor risk factor(s). This result supports the findings of previous investigations, including those regarding the indications for postoperative adjuvant RT.[10–12]

This study had some limitations. Although it investigated the clinical significance of minor risk factors in OSCC patients, it was a retrospective study, involving a small number of cases, and was conducted at a single institution. In this study, the 5-year OS and CSS rates for all patients were 81.2%, and 91.0%. This difference might be due to the fact that 14 cases of death from other causes were included. In addition, the depth of invasion was incorporated into the pT stage in the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual.[23] The depth of invasion was reported to be significantly associated with lymph node metastasis; local recurrence; and poor prognosis, such as OS and disease-specific survival.[24,25] The date on which the depth of invasion was measured could not be obtained in this study, which might have affected the study's results. Further studies are needed to clarify the clinical impact of the depth of invasion.

In conclusion, this retrospective study investigated the clinical impact of minor risk factors on the prognosis of OSCC patients. OS exhibited a tendency towards associations with the pattern of invasion and perineural invasion, and CSS displayed a tendency towards an association with perineural invasion. On the other hand, the pattern of invasion was identified as a significant independent predictor of RFS. Grade 4 invasion according to the YK classification and the presence of perineural invasion might be significant minor risk factors in OSCC patients. OS, CSS, and RFS were affected significantly by the presence of ≥2 minor risk factors.

Conflicts of interest

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

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