

Indications for postoperative adjuvant therapy in patients with other risk features in oral squamous cell carcinoma

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Received January 15, 2026; Accepted July 22, 2026

DOI: 10.3892/ol.2026.15935

Abstract. Postoperative adjuvant therapy (radiotherapy or consideration of concomitant chemoradiotherapy) is recommended for patients with oral squamous cell carcinoma (OSCC) who have other risk features identified on histopathological examination. However, categorizing all patients with other risk features into a single group may not be appropriate. The present study aimed to clarify the indications for postoperative adjuvant therapy in patients with other risk features. This single-center retrospective study enrolled patients with OSCC who underwent primary surgery with simultaneous radical or elective neck dissection between April 2001 and March 2024. Predictor variables included surgical margin, pathological (p) T and pN stages, metastatic level, perineural invasion, vascular invasion and lymphatic invasion (LI). The main outcome variables included disease-specific survival (DSS), overall survival (OS) and recurrence-free survival (RFS). Survival outcomes were analyzed using the Kaplan-Meier method and compared using the log-rank test. Multivariate analyses were performed using Cox regression. The final sample comprised 194 patients [median age, 70 years; age range, 23-93 years; 108 (55.7%) male patients]. No significant differences in 5-year DSS, OS or RFS were observed between patients with and without

other risk features. Multivariate analysis identified pT3 or pT4 primary tumors and LI as significant independent prognostic factors for poorer DSS and OS. pN2 or pN3 nodal disease and vascular invasion were identified as significant independent prognostic factors for poorer RFS. Postoperative adjuvant therapy was not associated with improved DSS in patients with pT3 or pT4 primary tumors or LI. In conclusion, pT3 or pT4 primary tumors and LI were identified as independent prognostic factors for DSS and OS. These findings may help refine the selection of patients with other risk features who are most likely to benefit from postoperative adjuvant therapy.

Introduction

According to the National Comprehensive Cancer Network (NCCN) guidelines (1), the recommended initial treatment for oral squamous cell carcinoma (OSCC) is surgical resection, followed by postoperative radiotherapy (RT) or cisplatin-based concomitant chemoradiotherapy (CCRT) when histopathological examination identifies adverse pathologic features such as extranodal extension (ENE) involving the cervical lymph nodes or a positive resection margin of the primary tumor. Other adverse pathologic features, classified by the NCCN guidelines as other risk features, include close margins, pathological (p)T3 or pT4 primary tumors, pN2 or pN3 nodal disease, nodal disease at levels IV or V, perineural invasion (PNI), vascular invasion (VI), and lymphatic invasion (LI). When these features are identified, RT or consideration of CCRT is recommended as postoperative adjuvant therapy. A multicenter study comprising Japanese patients with OSCC and high-risk features (positive margin and ENE) showed that surgery followed by RT alone or high-dose cisplatin-based CCRT improved overall survival (OS) compared with surgery alone (2,3). However, evidence regarding the benefit of postoperative adjuvant therapy in patients with OSCC who present with other risk features is limited. Regarding late adverse events of RT, osteoradionecrosis (ORN), which develops in 13.4% of patients with head and neck cancer (4), is rarely cured with conservative treatment and impairs oral function and quality of life (QOL). Therefore, considering QOL and adverse events, categorizing all patients with other risk features into a single group may not be appropriate.

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Abbreviations: CCRT, concomitant chemoradiotherapy; DM, distant metastasis; DSS, disease-specific survival; ENE, extranodal extension; LI, lymphatic invasion; LR, local recurrence; NCCN, National Comprehensive Cancer Network; ORN, osteoradionecrosis; OS, overall survival; OSCC, oral squamous cell carcinoma; p, pathological; PNI, perineural invasion; QOL, quality of life; RFS, recurrence-free survival; RR, regional recurrence; RT, radiotherapy; VI, vascular invasion

Key words: OSCC, postoperative adjuvant therapy, other risk features, prognostic factor, adverse pathologic features

Regarding the presence of other risk features, postoperative adjuvant therapy (RT or CCRT) may have additional benefits for disease-free survival or OS (5,6). Conversely, other studies have shown no survival benefit for postoperative RT in patients with intermediate risk factors (7,8). A systematic review also revealed no evidence to support the application of postoperative RT based solely on histological risk factors (9). Thus, the indications for postoperative RT in patients with other risk features remain controversial, with treatment decisions left to the discretion of clinicians.

In the present study, we investigated the clinical outcome of other risk features in patients with OSCC treated with standardized therapy to assess whether all patients with other risk features are appropriate candidates for postoperative adjuvant therapy. The specific aims of this study were to determine which other risk features were independently associated with disease-specific survival (DSS), OS, and recurrence-free survival (RFS), and to clarify the indications for postoperative adjuvant therapy based on survival and salvage outcomes.

Materials and methods

Study design. The study population comprised all patients presenting to the Department of Oral and Maxillofacial Surgery at Nagasaki University Hospital to undergo management of histologically confirmed OSCC between April 2001 and March 2024. A total of 194 patients (108 males and 86 females) were enrolled. The median age was 70 years (range, 23–93 years). The inclusion criteria were as follows: i) Patients who underwent primary surgery with simultaneous radical or elective neck dissection and ii) had a minimum follow-up of more than 18 months. The exclusion criteria were i) patients who had received neoadjuvant chemotherapy, RT, or CCRT, ii) those with a history of previous OSCC, and iii) those with missing/insufficient information.

Electronic or paper medical records were used to identify the demographic, tumor, and treatment variables. The final follow-up was conducted on July 30, 2025. At our institute, the standard treatment for OSCC is surgery, and patients with positive margins and/or ENE routinely receive postoperative adjuvant therapy. In contrast, postoperative adjuvant therapy was not routinely administered to patients with other risk features. In these cases, the decision to administer postoperative adjuvant therapy was made at the physician's discretion after considering the pathological findings, the patient's general condition, comorbidities, and overall clinical status. Postoperative RT/CCRT with a dose of 60–66 Gy and a high dose of cisplatin (100 mg/m² tri-weekly or 40 mg/m² weekly) was administered. Elective neck dissection was not routinely performed; when indicated, either a supraomohyoid or conventional neck dissection was performed.

Study variables

Predictor variables. Adverse pathologic features were defined in accordance with the NCCN clinical practice guidelines as histological evidence of ENE, positive margins, close margins, pT3 or pT4 primary tumors, pN2 or pN3 nodal disease, nodal disease at levels IV or V, PNI, VI, and LI (1). ENE and positive margins were considered high-risk features, while the remaining adverse pathologic features were classified as other

risk features. The predictor variables comprised these other risk features. In this study, ENE was defined as complete rupture of the lymph node capsule; tumor involvement close to the lymph node capsule or the surrounding adipose tissue was not considered ENE in the absence of capsular rupture. A positive margin was defined as the presence of tumor cells at the surgical margin. A close margin was defined as tumor cells located within 0–5 mm of the surgical margin on microscopy. Classification of pT and pN was performed according to the TNM system (8th edition) of the International Union Against Cancer (10). The American Academy of Otolaryngology-Head and Neck Surgery criteria were used to delineate the location of lymph node disease in the neck. PNI, VI, and LI were determined based on the presence or absence of tumor cell invasion on microscopy (11). Patients with one or more other risk features were classified as patients with other risk (+) features and divided into two groups: those who underwent surgery alone and those who underwent surgery followed by postoperative adjuvant therapy. Comparison groups comprised patients without other risk features and those with high-risk features.

Outcome variables. The main outcome variables were DSS, OS, and RFS. The secondary outcome variable was the salvage rate, which was assessed by comparing the surgery-alone group with the group that received surgery followed by postoperative adjuvant therapy. Similarly, local recurrence (LR), regional recurrence (RR), and distant metastasis (DM) were also assessed. Covariates included demographic (age, sex, and performance status) and tumor characteristics (primary site, pT, pN, surgical margin, metastatic level, PNI, VI, LI, and the number of positive nodes).

Statistical analysis. All statistical analyses were conducted using SPSS version 29.0 (Japan IBM Co., Tokyo, Japan). Continuous variables are presented as the median (range) and were compared using the Kruskal-Wallis test, followed by the Steel-Dwass post hoc test when the overall comparison was statistically significant. Categorical variables were compared using Fisher's exact test. Survival analysis was performed using the Kaplan-Meier method and compared using the log-rank test. Pairwise comparisons were adjusted using the Bonferroni correction. Multivariate Cox proportional hazards regression analyses were performed in the combined cohort of patients with other risk (+) features and those with high-risk features, as well as in the subgroup of patients with other risk (+) features who did not receive postoperative adjuvant therapy. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics and clinical outcomes. The demographic and clinicopathological characteristics of patients with other risk (+) features ($n=112$), patients without other risk features ($n=17$), and patients with high-risk features ($n=65$) are summarized in Table I. In patients with other risk (+) features, the mandibular gingiva was the most common site, followed by the tongue and the floor of the mouth. Nine patients had close margins, 87 had pT3 or pT4 primary tumors, and 21 had pN2 or pN3 nodal disease. Additionally, one patient had level IV

Table I. Patient characteristics.

Variable	Total (n=194)	Other risk (+) (n=112)	Other risk (-) (n=17)	High-risk (n=65)	P-value
Sex, n (%)					0.3
Male	108 (55.7)	61 (54.5)	7 (41.2)	40 (61.5)	
Female	86 (44.3)	51 (45.5)	10 (58.8)	25 (38.5)	
Median age, years (range)	70 (23-93)	70 (23-93)	77 (39-88)	68 (32-91)	0.4
ECOG PS, n (%)					0.4
0 and 1	171 (88.1)	96 (85.7)	16 (94.1)	59 (90.8)	
2 and 3	23 (11.9)	16 (14.3)	1 (5.9)	6 (9.1)	
Primary site, n (%)					0.4
Tongue	51 (26.3)	26 (23.2)	3 (17.6)	22 (33.8)	
Mandibular gingiva	76 (39.2)	50 (44.6)	5 (29.4)	21 (32.3)	
Maxillary gingiva	20 (10.3)	9 (8.0)	1 (5.9)	10 (15.4)	
Floor of the mouth	23 (11.9)	13 (11.6)	6 (35.3)	4 (6.2)	
Buccal mucosa	13 (6.7)	7 (6.3)	1 (5.9)	5 (7.7)	
Hard palate	2 (1.0)	1 (0.9)	0 (0)	1 (1.5)	
Lip	1 (0.5)	0 (0)	1 (5.9)	0 (0)	
Intraosseous	8 (4.1)	6 (5.4)	0 (0)	2 (3.1)	
Surgical margin, n (%)					<0.001 ^a
Clear	153 (78.9)	103 (92.0)	17 (100)	33 (50.7)	
Close	13 (6.7)	9 (8.0)	0 (0)	4 (6.2)	
Positive	28 (14.4)	0 (0)	0 (0)	28 (43.1)	
pT stage, n (%)					<0.001 ^a
T1	17 (8.8)	6 (5.4)	8 (47.1)	3 (4.6)	
T2	35 (18.0)	19 (17.0)	9 (52.9)	7 (10.8)	
T3	37 (19.1)	26 (23.2)	0 (0)	11 (16.9)	
T4a	102 (52.6)	60 (53.5)	0 (0)	42 (64.6)	
T4b	3 (1.5)	1 (0.9)	0 (0)	2 (3.1)	
pN stage, n (%)					<0.001 ^a
N0	94 (48.5)	69 (61.6)	12 (70.6)	13 (20.0)	
N1	31 (16.0)	22 (19.6)	5 (29.4)	4 (6.2)	
N2a	9 (4.6)	1 (0.9)	0 (0)	8 (12.3)	
N2b	22 (11.3)	20 (17.9)	0 (0)	2 (3.1)	
N2c	1 (0.5)	0 (0)	0 (0)	1 (1.5)	
N3b	37 (19.1)	0 (0)	0 (0)	37 (56.9)	
Metastasis level, n (%)					<0.001 ^a
None	93 (47.9)	68 (60.7)	12 (70.6)	13 (20.0)	
Level 1/2/3	94 (48.5)	43 (38.4)	5 (29.4)	46 (70.8)	
Level 4/5	7 (3.6)	1 (0.9)	0 (0)	6 (9.2)	
Perineural invasion, n (%)					<0.001 ^a
(-)	102 (52.6)	62 (55.4)	17 (100)	23 (35.4)	
(+)	92 (47.4)	50 (44.6)	0 (0)	42 (64.6)	
Vascular invasion, n (%)					<0.001 ^a
(-)	86 (44.3)	49 (43.8)	17 (100)	20 (30.8)	
(+)	108 (55.7)	63 (56.2)	0 (0)	45 (69.2)	
Lymphatic invasion, n (%)					0.001 ^a
(-)	152 (78.4)	93 (83.0)	17 (100)	42 (64.6)	
(+)	42 (21.6)	19 (17.0)	0 (0)	23 (35.4)	
Adjuvant therapy, n (%)					<0.001 ^a
(-)	152 (78.4)	104 (92.9)	17 (100)	31 (47.7)	
(+)	42 (21.6)	8 (7.1)	0 (0)	34 (52.3)	

Table I. Continued.

Variable	Total (n=194)	Other risk (+) (n=112)	Other risk (-) (n=17)	High-risk (n=65)	P-value
Differentiation, n (%)					0.6
Well	156 (80.4)	90 (80.4)	15 (88.2)	51 (78.5)	
Moderately	28 (14.5)	16 (14.3)	2 (11.8)	10 (15.4)	
Poorly	7 (3.6)	3 (1.5)	0 (0)	4 (6.1)	
Others	3 (1.5)	3 (1.5)	0 (0)	0 (0)	
Number of positive lymph nodes, median (range)	1 (0-12)	0 (0-5)	0 (0-1)	2 (0-12)	<0.001 ^a
ENE (patients with pN+), n (%)					<0.001 ^a
(-)	69 (60.5)	44 (100)	5 (100)	20 (30.8)	
(+)	45 (39.5)	0 (0)	0 (0)	45 (69.2)	

^aP<0.05. ENE, extranodal extension; p, pathological; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table II. Multivariate Cox regression analyses of OS, DSS and RFS in patients with other risk (+) features and high-risk features.

Variable	OS			DSS			RFS		
	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI
Sex									
Female vs. male	0.1	1.5	0.9-2.5	0.2	1.5	0.8-2.7	0.09	1.5	0.9-2.4
Age, years									
<70 vs. ≥70	0.004	2.2	1.3-3.8	0.07	1.8	0.96-3.3	0.09	1.5	0.9-2.5
ECOG PS									
0-1 vs. 2-3	0.045	2.1	1.01-4.2	0.09	2.1	0.9-4.8	0.75	1.1	0.5-2.4
Primary site									
Other site vs. tongue	0.2	1.5	0.8-2.6	0.4	1.3	0.7-2.5	0.07	1.6	0.96-2.6
Group									
Other risk (+) vs. high-risk	<0.001	2.3	1.4-3.6	<0.001	3	1.7-5.3	<0.001	2.2	1.4-3.5

DSS, disease-specific survival; OS, overall survival; RFS, recurrence-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

lymph node metastasis. Fifty patients had PNI, 63 had VI, and 19 had LI. Only eight patients received postoperative adjuvant therapy. Compared with patients with other risk (+) features and those without other risk features, patients with high-risk features showed significantly worse 5-year DSS, OS, and RFS rates ($P<0.001$, $P=0.005$, and $P<0.001$, respectively). No significant differences were observed between patients with other risk (+) features and those without other risk features ($P=0.65$, $P=1.0$, and $P=0.24$, respectively) (Fig. 1A-C). Multivariate Cox proportional hazards regression analysis comparing patients with other risk (+) features and those with high-risk features showed that high-risk status was an independent prognostic factor for DSS, OS, and RFS (Table II).

Characteristics of patients with other risk (+) features are presented in Table III. Patients who underwent surgery followed by postoperative adjuvant therapy ($n=8$) had significantly younger age, pN2 or pN3 nodal disease, LI, and a higher number of metastatic lymph nodes than those who

underwent surgery alone ($n=104$). No other significant factors were found to influence decisions regarding postoperative adjuvant therapy. Clinical outcomes of LR, RR, and DM were not significantly different between the two subgroups. Of the 36 patients who underwent surgery alone and experienced recurrence, 23 underwent salvage surgery. In comparison, two of four patients who underwent surgery followed by postoperative adjuvant therapy and then experienced recurrence underwent salvage surgery. The salvage rates were 41.7 and 25%, respectively. The two subgroups showed no significant difference (Table IV).

Association of individual risk features with survival among patients with other risk (+) features who did not receive postoperative adjuvant therapy. Multivariate Cox proportional hazards regression analysis (Table V) identified LI as an independent prognostic factor for poorer DSS (HR, 8.8; $P<0.001$), OS (HR, 5.82; $P<0.001$), and RFS (HR, 6.0; $P<0.001$). In

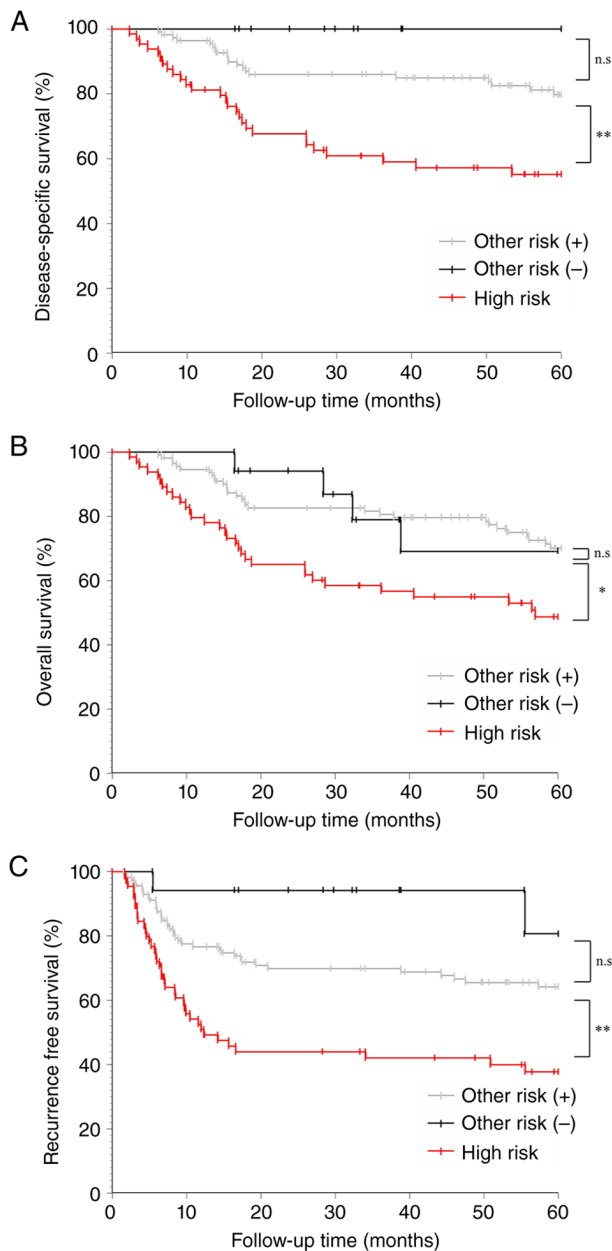


Figure 1. Kaplan-Meier survival curves comparing patients with other risk (+) features, patients without other risk features, and patients with high-risk features. (A) Disease-specific survival, (B) overall survival and (C) recurrence-free survival. Survival was compared using the log-rank test. * $P<0.05$, ** $P<0.01$. n.s., not significant.

addition, pT3 or pT4 primary tumors were an independent prognostic factor for poorer DSS (HR, 9.5; $P=0.03$) and OS (HR, 4.45; $P=0.007$). Furthermore, pN2 or pN3 nodal disease and VI were independent prognostic factors for poorer RFS (HR, 3.2; $P=0.003$ and HR, 2.45; $P=0.03$, respectively). Metastatic nodal disease at levels IV or V was excluded from the multivariate analysis because of the small number of cases.

The association between postoperative adjuvant therapy and survival was further evaluated according to pT stage and LI status. Among patients with pT3 or pT4 primary tumors, the 5-year DSS rates were 75.9% in the surgery-alone group and 66.7% in the surgery plus postoperative adjuvant therapy group, with no significant difference between groups. Similarly, among patients with LI, the corresponding 5-year

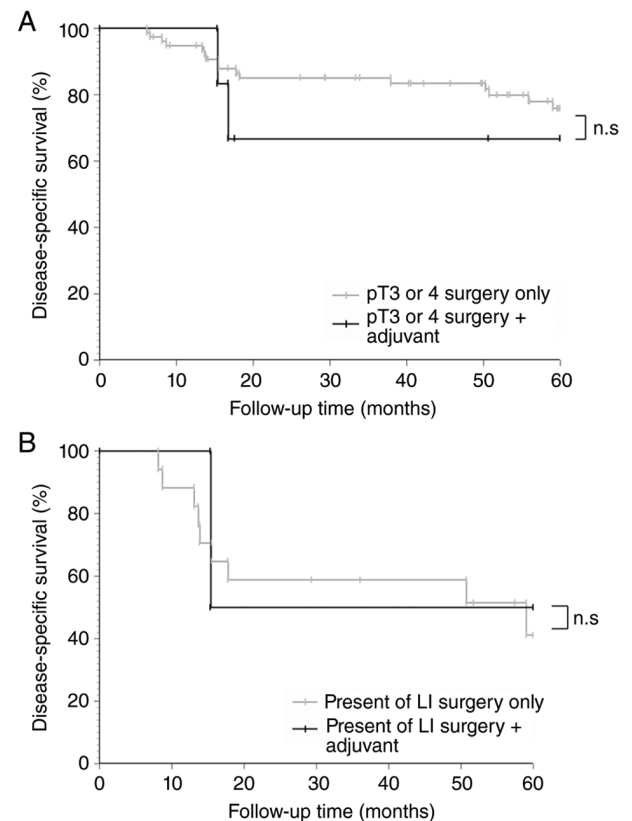


Figure 2. Kaplan-Meier disease-specific survival curves in patients with (A) pT3 or pT4 primary tumors and (B) LI, according to treatment modality (surgery alone vs. surgery followed by postoperative adjuvant therapy). Survival was compared using the log-rank test. LI, lymphatic invasion; p, pathological.

DSS rates were 41.2 and 50.0%, respectively, with no significant difference between groups (Fig. 2A and B).

Discussion

Currently, postoperative adjuvant therapy is recommended for patients with OSCC when other risk features are identified on histopathological examination. However, categorizing all patients with other risk features into a single group may not be appropriate, and clarifying the indications for postoperative adjuvant therapy is considered useful for clinical practice. Previously, some authors reported that categorizing all patients with ENE into a single group may not be appropriate; ENE minor (tumor extension <2 mm beyond the capsule) may not require postoperative adjuvant therapy (12,13). Similarly, all patients with other risk features should not be classified into a single group, but rather analyzed using more detailed data. In the present study, we compared DSS, OS, and RFS between patients with other risk features, without other risk features, and with high-risk features, and found that patients with high-risk features had significantly poorer survival. In contrast, no significant differences in DSS, OS, or RFS were observed between patients with and without other risk features. These findings suggest that the prognostic impact of individual other risk features may differ. Multivariate analysis comparing patients with other risk (+) features and those with high-risk features showed that high-risk status was independently

Table III. Association between postoperative adjuvant therapy and clinicopathological variables.

Variable	Other risk (+) (n=112)		P-value
	Surgery-only (n=104)	Surgery + adjuvant (n=8)	
Sex, n (%)			1
Female	47 (45.2)	4 (50.0)	
Male	57 (54.8)	4 (50.0)	
Median age, years (range)	70 (23-93)	61.5 (40-76)	0.047 ^a
ECOG PS, n (%)			0.6
0 and 1	88 (84.6)	8 (100)	
2 and 3	16 (15.4)	0 (0)	
Primary site, n (%)			0.08
Tongue	22 (21.2)	4 (50.0)	
Others	82 (79.8)	4 (50.0)	
Surgical margin, n (%)			0.1
Clear	97 (93.3)	6 (75.0)	
Close	7 (6.7)	2 (25.0)	
pT stage, n (%)			1
1 and 2	27 (26.0)	2 (25.0)	
3 and 4	77 (74.0)	6 (75.0)	
pN stage, n (%)			<0.001 ^a
0 and 1	89 (85.6)	2 (25.0)	
≥2	15 (14.4)	6 (75.0)	
Metastasis level, n (%)			1
I-III	103 (99.0)	8 (100)	
IV and V	1 (1.0)	0 (0)	
Perineural invasion, n (%)			0.5
(-)	59 (56.7)	3 (37.5)	
(+)	45 (43.3)	5 (62.5)	
Vascular invasion, n (%)			1
(-)	46 (44.2)	3 (37.5)	
(+)	58 (55.8)	5 (62.5)	
Lymphatic invasion, n (%)			<0.001 ^a
(-)	87 (83.7)	2 (25.0)	
(+)	17 (16.3)	6 (75.0)	
Number of positive nodes	0 (0-5)	2 (1-4)	<0.001 ^a

^aP<0.05. p, pathological; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

associated with poorer survival outcomes. These findings suggest that adverse pathologic features should not be considered a homogeneous group, as their prognostic significance may differ. Therefore, further analyses were performed of the patients with other risk (+) features who did not receive postoperative adjuvant therapy to identify the prognostic factors.

One of the main findings of the present study was that multivariate analysis identified pT3 or pT4 primary tumors and LI as independent prognostic factors for poorer DSS and OS among patients with other risk (+) features who did not receive postoperative adjuvant therapy. Although postoperative adjuvant therapy was not associated with improved DSS in patients with pT3 or pT4 primary tumors and LI, only a small number of patients received postoperative adjuvant therapy.

Therefore, these results should be interpreted with caution and cannot be generalized. Nevertheless, our results suggest that pT3 or pT4 primary tumors and LI may represent important adverse pathologic features to be considered when selecting patients for postoperative adjuvant therapy.

Another important finding was that multivariate analysis identified pN2 or pN3 nodal disease and VI as independent prognostic factors for worse RFS, but not DSS or OS. These findings suggest that recurrence did not necessarily lead to poorer DSS or OS, possibly because a proportion of recurrent tumors could be successfully salvaged. Although pN2 or pN3 nodal disease has traditionally been considered an indication for postoperative adjuvant therapy (5,6), our findings suggest that the indication for postoperative adjuvant therapy in patients

Table IV. Relationship between postoperative adjuvant therapy and recurrence.

Variable	Other risk (+) (n=112)		P-value
	Surgery-only (n=104)	Surgery + adjuvant (n=8)	
Local recurrence, n (%)			1
(-)	81 (77.9)	7 (87.5)	
(+)	23 (22.1)	1 (12.5)	
Regional recurrence, n (%)			0.2
(-)	86 (82.7)	5 (62.5)	
(+)	18 (17.3)	3 (37.5)	
Distant metastasis, n (%)			0.5
(-)	96 (92.3)	7 (87.5)	
(+)	8 (7.7)	1 (12.5)	
Salvage surgery, n (%)			0.6
(-)	13 (36.1)	2 (50)	
(+)	23 (63.9)	2 (50)	
Salvage rate (%)	15/36 (41.7)	1/4 (25)	1

Table V. Multivariate Cox regression analysis of factors associated with OS, DSS, and RFS in 104 other risk (+) patients without adjuvant therapy.

Variable	OS			DSS			RFS		
	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI
Sex									
Female vs. male	0.3	1.5	0.7-3.2	0.75	1.2	0.44-3.42	0.8	1.1	0.6-2.1
Age, years									
<70 vs. ≥70	0.14	2.2	0.8-6.0	0.7	0.8	0.28-4.45	0.5	1.3	0.6-2.9
ECOG PS									
0 and 1 vs. 2 and 3	0.036	3.2	1.08-9.5	0.1	3.3	0.7-13.23	0.38	1.6	0.58-4.36
Primary site									
Others vs. tongue	0.38	0.58	0.2-2.0	0.1	0.3	0.06-1.74	0.5	0.7	0.3-1.9
Surgical margin									
Clear vs. close	0.96	1.03	0.3-3.4	0.3	2.1	0.48-7.92	0.9	0.93	0.3-2.6
pT stage									
1-2 vs. 3-4	0.007	4.45	1.5-13.3	0.03	9.5	1.19-71.44	0.4	1.38	0.66-2.88
pN stage									
0 and 1 vs. ≥2	0.86	0.9	0.3-2.8	0.4	1.7	0.46-6.14	0.003	3.2	1.5-6.9
Perineural invasion									
(-) vs. (+)	0.15	2	0.8-4.9	0.3	2	0.52-6.41	0.13	1.89	0.8-4.3
Vascular invasion									
(-) vs. (+)	0.08	2.2	0.9-5.5	0.15	2.5	0.79-9.52	0.03	2.45	1.1-5.56
Lymphatic invasion									
(-) vs. (+)	<0.001	5.82	2.5-13.3	<0.001	8.8	3.01-23.25	<0.001	6.0	2.9-12.5

DSS, disease-specific survival; OS, overall survival; RFS, recurrence-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

with pN2 or pN3 nodal disease should be carefully considered, taking into account the potential for successful salvage treatment, as well as treatment-related adverse events and QOL.

To the best of our knowledge, several studies have reported an association between other risk features (minor or intermediate) and survival outcomes (OS, DSS, or RFS), although

the risk features evaluated differed among studies (5,6,14–16). Collectively, these reports suggest that close margins, invasion pattern, pT3 or pT4 primary tumors, pN2 or pN3 nodal disease, and PNI or LI are associated with poor prognosis, although the prognostic significance of individual risk features has varied across studies. Our findings regarding pT3 or pT4 primary tumors and LI are consistent with previous reports. However, our findings regarding pN2 or pN3 nodal disease are not consistent with previous studies. Several previous studies have suggested that pN2 or pN3 nodal disease is a significant prognostic factor for poor prognosis, but other reports suggest that the presence of four or more lymph node metastases is associated with significantly worse survival (17). Because of the limited number of cases in our study, we were unable to stratify patients according to the number of metastatic lymph nodes. Regarding salvage rates, Brown *et al* (7) reported a significantly decreased salvage rate of 11% for surgery followed by postoperative adjuvant therapy compared with 47% for surgery alone, suggesting that salvage treatment may be less successful after postoperative RT. Conversely, Liu *et al* (5) reported no difference in the salvage rate between these two groups at the time of recurrence. ORN is a well-recognized late adverse event arising from RT in patients with OSCC, and it can critically affect QOL (4,18). From this perspective, patients with other risk features that were not identified as independent prognostic factors may not require consideration for postoperative adjuvant therapy. Instead, treatment decisions should be made based on tumor aggressiveness, the likelihood of successful salvage treatment, treatment-related late adverse events, and QOL.

This study has limitations, including its single-center, retrospective design, small sample size, and the fact that eligibility for postoperative adjuvant therapy was determined by physician discretion, general condition, and/or disease status. In addition, only eight patients with other risk features received postoperative adjuvant therapy, which limited the ability to evaluate its therapeutic impact. These factors may have introduced significant selection bias into the analysis of treatment outcomes and limited the generalizability of our findings. Therefore, further large-scale multicenter studies are needed to enhance the generalizability of the results and establish a more comprehensive understanding of other risk features.

In conclusion, among patients with other risk (+) features, pT3 or pT4 primary tumors and LI were identified as independent prognostic factors for DSS and OS. These findings may help refine patient selection for postoperative adjuvant therapy among patients with other risk (+) features.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested by the corresponding author.

Authors' contributions

TN, HF and TY contributed to study conception and design. Data were collected by HF, TN, KO, KM and TM, and analyzed by TN and HF. The draft of the manuscript was written by TM, and all authors commented on previous versions of the manuscript. TN, HF and KO confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol conformed to the ethical principles of The Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labor, and Welfare, Japan. Approval was obtained from the Institutional Review Board of Nagasaki University Hospital (approval no. 25080704). As this was a retrospective study, the research plan was published on the homepages of the participating hospitals' websites using an opt-out approach for consent in accordance with the ethics committee's requirements.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools (ChatGPT; OpenAI) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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