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ORIGINAL ARTICLE

Frequency and predictors of detecting early locoregional recurrence/disease progression of oral squamous cell carcinoma with high-risk factors on imaging tests before postoperative adjuvant radiotherapy

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Abstract

Background To clarify the frequency and predictors of detecting early locoregional recurrence/disease progression (LR/DP) during the interval between surgery and postoperative adjuvant radiotherapy with/without chemotherapy in patients with oral squamous cell carcinoma.

Methods Data on 65 patients who had undergone the initial radical surgery for previously untreated oral squamous cell carcinoma which were scheduled to receive adjuvant radiotherapy with/without chemotherapy were reviewed.

Results Of the 65 patients, 63 (97%) were margin-positive/close and/or extracapsular extension-positive (hereinafter, high-risk factors). Eighteen (28%) patients had abnormal findings suggestive of LR/DP on postoperative imaging. Fifteen (23%) patients were diagnosed with LR/DP and treatment policy was changed. Univariate and multivariate analyses revealed higher frequencies of abnormal findings suggestive of LR/DP (univariate/multivariate analysis, $p=0.020/0.036$), diagnosing of LR/DP, and changing the treatment policy (univariate/multivariate analysis, $p=0.042/0.046$), among the patients who underwent postoperative diagnostic imaging tests or radiotherapy-planning contrast-enhanced (CE) CT without diagnostic imaging tests as compared with those who underwent radiotherapy-planning non-CECT without such tests.

Conclusion The frequency of detecting of early LR/DP before postoperative adjuvant treatment in oral squamous cell carcinoma patients with high-risk factors was high. Furthermore, postoperative diagnostic imaging tests and radiotherapy-planning CECT may be useful to detect early LR/DP in oral squamous cell carcinoma patients before postoperative adjuvant therapy.

Keywords Oral · Squamous cell carcinoma · Adjuvant radiotherapy · Postoperative · Surgery · Recurrence

Introduction

The standard therapy for oral squamous cell carcinoma patients is surgery, and adjuvant therapy is considered based on the results of pathological examination after surgery [1]. As the basic treatment policy at our institution, based on the results of pivotal randomized-controlled trials, we recommend postoperative chemoradiotherapy for oral squamous cell carcinoma patients when pathological examination shows positive margin and/or extracapsular node extension (hereinafter, high-risk factors) [2–4].

Because of aggressive feature of oral squamous cell carcinoma, abnormal findings suggestive of locoregional recurrence/disease progression (LR/DP) are sometimes detected on postoperative diagnostic imaging tests and adjuvant-radiotherapy-planning CT.

If abnormal findings suggestive of LR/DP fail to be detected on postoperative imaging tests, the opportunity to select optimal treatment interventions, including salvage surgery, salvage definitive radiotherapy with/without chemotherapy, or palliative therapy, to improve the clinical outcomes, is missed. In addition, it may also be difficult to set an appropriate radiation field. However, few studies

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have evaluated the frequency of detecting abnormal findings suggestive of LR/DP or the frequency of treatment policy change before adjuvant therapy in patients with oral squamous cell carcinoma [5–7].

The purpose of this study was to clarify the frequency and predictors of detecting abnormal findings suggestive of LR/DP on imaging tests performed before postoperative adjuvant therapy and the frequency treatment policy change based on the findings, in patients with oral squamous cell carcinoma.

Materials and methods

The medical records of 861 consecutive previously untreated oral squamous cell carcinoma patients without previous history of head-and-neck cancer who had undergone initial radical surgery between December 2008 and February 2018 were identified. Six hundred and seventy patients were diagnosed margin negative and ECE negative and were followed. Thirty patients who are diagnosed margin positive in carcinoma in situ component, 31 patients who were diagnosed close to margin, and 2 patients who were diagnosed horizontal margin positive were followed without additional treatment. Among the patients who were diagnosed margin positive or ECE positive, 10 patients received additional resection, 7 patients were decided to be followed strictly, 27 patients were judged not to have tolerability for additional treatment and because of their general condition, complication, age, poor compliance for treatment and were followed, 11 patients refused additional treatment and were followed, 4 patients had another primary cancer other than head-and-neck and were decided not to receive additional treatment and were followed, and 4 patients were diagnosed LR/DP before postoperative multidisciplinary tumor board (Fig. 1).

In this study, we reviewed data on the remaining 65 patients who were scheduled to receive adjuvant radiotherapy with/without chemotherapy based on the decisions of a multidisciplinary tumor board.

As the basic policy of surgery, the resection margin was defined by the anatomical location and the diagnosis of the primary tumor based on the preoperative CT/MR imaging with a predefined safety zone at least 10 mm. In some cases that the tumor was approaching critically important anatomical features such as major blood vessels or nerves, marginal safety zones were used.

As the basic treatment policy at our institution, oral squamous cell carcinoma patients who are 75 years old or younger with high-risk factors are recommended to receive adjuvant concurrent chemoradiotherapy (66 Gy/33 fr) with tri-weekly/weekly cisplatin. On the other hand, patients with high-risk factors who are older than 75 years old, and who are not considered to be able to tolerate adjuvant concurrent chemoradiotherapy, are recommended to receive adjuvant radiotherapy alone (66 Gy/33 fr).

In daily practice at our institution, postoperative diagnostic imaging tests are often performed before scheduled adjuvant therapy and contrast medium on radiotherapy-planning CT is often used, based on the attending doctors' decisions. All CT studies (both diagnostic tests and radiotherapy planning) were performed using a 320-detector-row CT system (Aquilion ONE Vision; Canon Medical Systems, Otawara, Japan) with a dedicated head-and-neck protocol

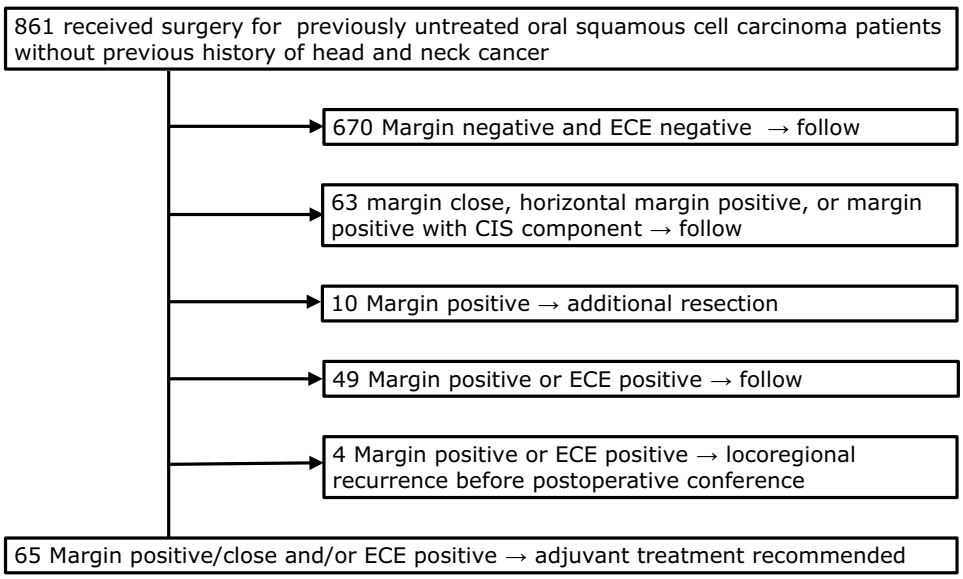

Fig. 1 Flowchart of the patients

and reconstruction. MRI and FDG-PET were also performed to yield additional quantitative information in some subjects.

The charts and diagnostic reports of the patients with oral squamous cell carcinoma were reviewed to evaluate the frequency of detecting abnormal findings suggestive of LR/DP on imaging tests performed before postoperative adjuvant therapy, and also to determine the frequency of changing the treatment policy.

All diagnostic imaging tests [contrast-enhanced (CE) CT, CEMRI, and FDG-PET/CT] were reviewed by radiologists. Although radiotherapy-planning CT images are not routinely reviewed by experienced head-and-neck radiologists, the attending radiation oncologists consulted radiologists to review the radiotherapy-planning CT images when they noted any abnormalities on radiotherapy-planning CT.

Patients were retrospectively re-staged based on the UICC 7th TNM system. The primary subsite, results of histopathological examination, and types of postoperative imaging tests were reviewed. In the histopathological examination, the patients were classified according to the margin status as margin-negative, close (< 5 mm), or margin-positive.

Statistical analysis was performed with SPSS, Ver. 22. We conducted univariate analysis using the Chi-square test for categorical variables and *t* test for continuous variables, to identify predictors of detecting abnormal findings suggestive of recurrence/disease progression on imaging tests, and also to identify predictors of changing the treatment policy. We also used multivariate logistic regression analyses. Differences were deemed significant when the two-tailed *p* value was less than 0.05.

This study was conducted with the approval of the review board of our institution.

Results

The patient characteristics are shown in Table 1. Sixty-three patients (97%) were classified as margin-positive/close and/or extracapsular extension-positive, based on the results of histopathological examination. The remaining two patients were classified by histopathology as margin-negative and extracapsular extension-negative, but margin-positive had been suspected by the head-and-neck surgeon clinically.

The types and results of the postoperative imaging tests, and the number of patients with confirmed LR/DP on biopsy are shown in Table 2. Fifty-four of the 65 patients received contrast medium for diagnostic CT, radiotherapy-planning CT, and MRI, or received FDG-PET/CT. The remaining 11 patients underwent only non-contrast-enhanced radiotherapy-planning CT without postoperative diagnostic imaging tests. Of all the patients, 18 (28%) were found to have abnormal findings suggestive of LR/DP detected in the locoregional area on diagnostic imaging tests or

Table 1 Patient characteristics

Characteristics	Number of patients
Total	65
Number of females	17
Median age (range)	65 (22–81)
Primary subsite	
Tongue	25
Floor of the mouth	10
Upper alveolus and gingiva	9
Lower alveolus and gingiva	15
Buccal mucosa	6
Pathological T classification	
T1	1
T2	2
T3	2
T4a	56
T4b	4
Pathological N classification	
x	2
0	6
1	13
2a	0
2b	31
2c	13
3	0
Stage (UICC 7th)	
III	2
IVA	60
IVB	3
Neck dissection	
None	2
Ipsilateral	29
Bilateral	34
Margin	
Negative	39
Close (< 5 mm)	6
Positive	20
Extracapsular extension	
Negative	23
Positive	40
Not available	2
Margin positive/close and/or ECE positive	63
Perineural invasion	
0	44
1	12
2	4
3	5
Vascular invasion	
0	19
1	27
2	17
3	1

Table 1 (continued)

Characteristics	Number of patients
Not available	1
Lymph invasion	
0	49
1	13
2	2
3	1
Under ongoing clinical trial	9

radiotherapy-planning CT, and 15 (23%) of all the patients were diagnosed with LR/DP, and the treatment policy was changed. Three patients had abnormal findings suggestive of LR/DP on diagnostic imaging tests, which were, however, finally diagnosed as inflammatory changes after surgery based on the decisions of a multidisciplinary tumor board; therefore, these patients received adjuvant chemoradiotherapy. None of the patients who underwent radiotherapy-planning non-CECT without diagnostic imaging tests had abnormal findings suggestive of LR/DP (0/11).

Three patients were confirmed to have LR/DP on biopsy. None of the patients had abnormal findings suggestive of distant metastasis or were diagnosed with distant metastasis.

Among the 15 patients who were diagnosed with LR/DP, 9 received salvage definitive chemoradiotherapy with a slightly higher dose of radiation (70 Gy/33 fr) than in adjuvant chemoradiotherapy, 4 patients received neoadjuvant chemotherapy (carboplatin + paclitaxel + cetuximab) followed by salvage definitive chemoradiotherapy (70 Gy/33 fr), and 1 patient received induction chemotherapy followed by palliative radiotherapy (30 Gy/10fr) because of disease progression after chemotherapy, and 1 patient was diagnosed with no indication for definitive therapy because of disease extension and received palliative radiotherapy (30 Gy/10 fr).

On univariate and multivariate analyses, patients who underwent postoperative diagnostic imaging tests or radiotherapy-planning CECT without such imaging tests showed abnormal findings suggestive of LR/DP at a significantly higher frequency (univariate/multivariate analyses, $p = 0.02/0.036$) and were also diagnosed with LR/DP and had their treatment policy changed significantly more frequently (univariate/multivariate analyses, $p = 0.042/0.046$) than patients who underwent non-CE radiotherapy-planning CT without postoperative diagnostic imaging tests. We did not identify any predictors of detecting abnormal findings suggestive of LR/DP or changing the treatment policy among the factors of age, primary subsite, days from surgery to the first postoperative imaging, or histopathological status (Tables 3, 4).

Discussion

This study suggests that postoperative diagnostic imaging tests or radiotherapy-planning CECT may be useful to detect early LR/DP in oral squamous cell carcinoma patients.

The previous studies that evaluated the efficacy of postoperative imaging tests before adjuvant therapy for oral cancer are summarized in Table 5 [5–7]. Our results of the current study with respect to the frequencies of detecting abnormal findings suggestive of, and eventually diagnosed as LR/

Table 2 Types of imaging

	Number of patients	Days from surgery to postoperative imaging tests median (range)	Number of patients detected abnormal findings suggestive of LR/DP	Number of patients diagnosed LR/DP and changed treatment policy	Number of patients LR/DP pathologically confirmed
With diagnostic imaging tests	27	41 (11–60)	12 (44%)	9 (33%)	0 (0%)
CECT	18		8	6	0
CEMRI	4		3	2	0
CECT and CEMRI	3		0	0	0
FDG-PET/CT	1		0	0	0
FDG-PET/CT and CEMRI	1		1	1	0
Without diagnostic imaging test	38	36 (19–65)	6 (16%)	6 (16%)	3 (8%)
Planning non-CECT	11	36 (19–65)	0 (0%)	0 (0%)	0 (0%)
Planning CECT	27	37 (24–61)	6 (22%)	6 (22%)	3 (11%)
Total	65		18 (28%)	15 (23%)	3 (5%)

CE contrast enhanced, *LR/DP* locoregional recurrence/disease progression

Table 3 Univariate and multivariate analyses for detection of abnormal findings that suggest LR/DP

Variable	Number of patients	Number of patients with abnormal findings suggesting LR/DP detected on imaging tests	Univariate analysis *p*	Multivariate analysis *p*
Age			0.36	–
Days from surgery to the first postoperative imaging			0.9	–
Primary subsite			0.92	–
pT stage				
pT1–3	4	1		
pT4a–4b	61	17	0.7	–
pN stage				
pN0–1	19	3		
pN2b–2c	44	14	0.19	0.19
Neck dissection				
None/unilateral	32	9		
Bilateral	33	9	0.94	–
Margin				
Negative	39	11		
Positive/close	26	7	0.91	–
ECE				
Negative	23	6		
Positive	40	12	0.9	–
Perineural invasion				
Negative	44	10		
Positive	21	8	0.2	0.16
Vascular invasion				
Negative	19	5		
Positive	45	13	0.83	–
Lymph invasion				
Negative	49	12		
Positive	16	6	0.24	0.27
Types of imaging tests				
Without diagnostic imaging tests with planning non-CECT	11	0		
With diagnostic imaging tests or without diagnostic imaging tests with planning CECT	54	18	0.019	0.036

CE contrast-enhanced, *LR/DP* locoregional recurrence/disease progression

DP, were consistent with these previous reports. Attention should be paid to early LR/DP between surgery and adjuvant therapy in oral squamous cell carcinoma patients with high-risk factors.

Although there is no recommended treatment policy for head-and-neck squamous cell carcinoma patients who are diagnosed with LR/DP before adjuvant treatment in the current guidelines [8–10], in the previous studies, the treatment policy was changed from adjuvant radiotherapy with/without chemotherapy to definitive radiotherapy with/without chemotherapy using a higher radiation dose than in the adjuvant setting or definitive salvage surgery when definitive treatment was feasible in oral squamous cell carcinoma patients showing abnormal findings suggestive of LR/DP on postoperative imaging tests performed before adjuvant treatment [5–7], because adjuvant radiotherapy with/without chemotherapy may not be sufficiently effective to treat LR/DP. Failure to detect abnormal findings suggestive of LR/DP on postoperative imaging may lead to loss of an opportunity to select optimal treatment interventions for LR/DP, including salvage surgery or salvage definitive radiotherapy with/without chemotherapy. In addition, the chances to confirm the absence of indications for definitive salvage therapy and to apply radiotherapy with an appropriate radiation field are also lost.

The univariate and multivariate analyses in our study revealed that, among oral squamous cell carcinoma patients, those who underwent postoperative diagnostic imaging tests and/or radiotherapy-planning CECT showed abnormal findings suggestive of LR/DP and also underwent a change in

Table 4 Univariate and multivariate analyses of treatment policy change

Variable	Number of patients	Number of patients changing treatment policy	Univariate analysis *p*	Multivariate analysis *p*
Age			0.77	0.075
Days from surgery to the first postoperative imaging			0.69	–
Primary subsite			0.93	–
pT stage				
pT1–3	4	1		
pT4a–4b	61	14	0.33	–
pN stage				
pN0–1	19	3		
pN2b–2c	44	11	0.33	–
Neck dissection				
None/unilateral	32	8		
Bilateral	33	7	0.78	–
Margin				
Negative	39	8		
Positive/close	26	7	0.55	–
ECE				
Negative	23	5		
Positive	40	10	0.58	–
Perineural invasion				
Negative	44	8		
Positive	21	7	0.15	0.18
Vascular invasion				
Negative	19	3		
Positive	45	12	0.28	–
Lymph invasion				
Negative	49	10		
Positive	16	5	0.28	–
Types of imaging tests				
Without diagnostic imaging tests with planning non-CECT	11	0		
With diagnostic imaging tests or without diagnostic imaging tests with planning CECT	54	15	0.042	0.046

CE contrast-enhanced

the treatment policy at a significantly higher frequency than patients who underwent radiotherapy-planning non-CECT without diagnostic imaging tests. It is possible that findings suggestive of LR/DP were missed in patients who underwent only planning non-CECT without diagnostic imaging tests as postoperative imaging tests. There are several guidelines which refer to the method of follow-up after surgery in patients with head-and-neck cancer [1, 9, 10]. However, these guidelines do not refer to diagnostic imaging tests that need to be performed between surgery and adjuvant radiotherapy. From the results of this study, we suggest that oral head-and-neck cancer patients with high-risk factors should undergo postoperative diagnostic imaging tests and/or radiotherapy-planning CECT prior to adjuvant therapy.

There is still debate about the most effective imaging modality to detect LR/DP and/or metastasis between surgery and postoperative radiotherapy. In all the referenced previous studies that evaluated the efficacy of diagnostic imaging tests between surgery and adjuvant treatment in patients with oral squamous cell carcinoma, the imaging modality used was FDG-PET/CT (Table 5). However, in the current study and previous reports, few oral squamous cell carcinoma patients showed any findings suggestive of distant metastasis between surgery and adjuvant radiotherapy (0–2%); furthermore, the evaluation performed using PET less than 10–12 weeks after radical surgery leads to a high false-positive rate because of the presence of postoperative inflammation, edema, or distortion [8–10], and many hospitals do not have the facilities or resources to

Table 5 Previous studies of postoperative imaging tests before adjuvant treatment for oral cancer patients

Author	Year	Number of patients	Histopathological type	Types of postoperative imaging tests	Number of patients with findings suggestive LR/DP detected on imaging tests and changed treatment policy	Number of patients with findings suggestive metastasis detected on imaging tests and changed treatment policy
Shintani	2008	14	SCC/non-SCC	FDG-PET/CT 14	2 (14%)	0 (0%)
Liao	2012	183	SCC	With FDG-PET/CT 29 Without FDG-PET/CT 154	5 (3%)	4 (2%)
Dutta	2016	44	SCC	FDG-PET/CT 44	11 (25%)	2 (2%)
Current study	2018	65	SCC	With postoperative diagnostic imaging test 27 Without postoperative diagnostic imaging test 38 with radiotherapy-planning non-CECT 11 with radiotherapy-planning CECT 27	15 (23%)	0 (0%)

CE contrast enhanced, *SCC* squamous cell carcinoma, *LR/DP* locoregional recurrence/disease progression

perform FDG-PET/CT for all oral cancer patients between surgery and adjuvant radiotherapy. In this study, 15 patients were diagnosed with LR/DP, and in most of these patients (12/15), the diagnosis was based on the findings of diagnostic CECT or radiotherapy-planning CECT alone. CT imaging is widely available, and may be helpful in an acute setting for acute clinical diagnosis. Therefore, we suggest that oral squamous cell carcinoma patients should at least undergo CECT prior to any adjuvant therapy.

We did not identify any significant predictors other than the types of imaging studies, which may have been attributed to the small number of patients.

This study had several limitations. Only 3 of the patients were confirmed to have LR/DP on histopathological examination. There were several patients who joined the ongoing clinical trial, we could not show the treatment outcomes, and we could not evaluate whether changes in the treatment policy after detecting abnormal findings suggestive of LR/DP improved the clinical outcome. Neither this study nor any previous study [5–7] showed that salvage surgery and salvage definitive radiotherapy with/without chemotherapy for early LR/DP detected before postoperative adjuvant treatment improved the clinical outcomes compared with adjuvant radiotherapy with/without chemotherapy in oral squamous cell carcinoma patients.

Conclusion

Attention should be paid to early LR/DP between surgery and adjuvant radiotherapy in oral squamous cell carcinoma patients with high-risk factors. Postoperative diagnostic imaging tests or radiotherapy-planning CECT may be useful to detect early LR/DP in oral squamous cell carcinoma patients.

Compliance with ethical standards

Conflict of interest All authors have nothing to declare.

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