SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 11: 3369-3376, 2016

# Clinicopathological evaluation of pre-operative chemoradiotherapy with S-1 as a treatment for locally advanced oral squamous cell carcinoma

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Received October 16, 2014; Accepted July 10, 2015

DOI: 10.3892/ol.2016.4411

**Abstract.** The administration of pre-operative chemotherapy with S-1 and concurrent radiotherapy at a total dose of 30 Gy was clinicopathologically evaluated as a treatment for locally advanced oral squamous cell carcinoma (OSCC) in the present study. The participants comprised 81 patients with OSCC, consisting of 29 patients with stage II disease, 12 patients with stage III disease and 40 patients with stage IV disease. All patients received a total radiation dose of 30 Gy in daily fractions of 2 Gy, 5 times a week, for 3 weeks, and the patients were concurrently administered S-1 at a dose of 80-120 mg, twice daily, over 4 consecutive weeks. Radical surgery was performed in all cases at 2-6 weeks subsequent to the end of pre-operative chemoradiotherapy. The most common adverse event was oropharyngeal mucositis, but this was transient in all patients. No severe hematological or non-hematological toxicities were observed. The clinical and histopathological response rates were 70.4 and 75.3%, respectively. Post-operatively, local failure developed in 6 patients (7.4%) and neck failure developed in 2 patients (2.5%). Distant metastases were found in 7 patients (8.6%). The overall survival rate, disease-specific survival rate and locoregional control rate at 5 years were 87.7, 89.9 and 90.6%, respectively. Locoregional recurrence occurred more frequently in patients that demonstrated a poor histopathological response compared with patients that demonstrated a good response (P<0.01). These results indicate that pre-operative S-1 chemotherapy with radiotherapy at a total dose of 30 Gy is feasible and effective for patients with locally advanced OSCC, and that little or no histopathological response may be a risk factor for locoregional recurrence in this treatment.

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*Abbreviations:* OSCC, oral squamous cell carcinoma; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; OS, overall survival rate; DSS, disease-specific survival rate; LRC, locoregional control rate

*Key words:* oral squamous cell carcinoma, preoperative treatment, chemoradiotherapy, S-1, survival rate

## Introduction

Oral squamous cell carcinoma (OSCC) accounts for ~3% of all malignancies worldwide (1). Despite this low frequency of occurrence, the 5-year overall survival rate of patients with OSCC has not exceeded 55% over the previous decade, due to the local aggressiveness and high recurrence rate of the disease (2). Advanced OSCC remains refractory and results in mortality in >50% of cases (1).

Complete locoregional control is crucial in the treatment of OSCC, as distant metastases are rarely identified at the initial presentation (3). Therefore, multimodal treatment has typically been implemented for advanced OSCC in order to control locoregional disease, generally consisting of radical surgery followed by radiotherapy (4). The issue with this combined therapeutic approach is the high recurrence rate at primary or regional sites within the first 2 years subsequent to treatment (5). As a result, 5-year survival rates have been low in patients treated with this therapy (5).

Pre-operative chemoradiotherapy has become an established component of the clinical management of locoregionally advanced operable OSCC (6-10). Kirita *et al* has previously reported that pre-operative cisplatin (CDDP)-based intravenous chemotherapy and concurrent radiotherapy (total dose, 40 Gy) resulted in a clinical tumor response of 92.8% and a good prognosis, with a 79.3% 5-year overall survival rate, in

patients with resectable advanced OSCC (10). Several studies have also demonstrated an improved 5-year survival rate subsequent to using this treatment in patients with advanced OSCC (7-9). Although the platinum-based chemotherapeutic regimens used in these protocols significantly improve local tumor control, adverse events, including nausea, vomiting, renal damage, anorexia and hematological toxicity, are severe issues (10).

S-1 is an oral fluoropyrimidine preparation that consists of tegafur, the dihydropyrimidine dehydrogenase inhibitor 5-chloro-2,4-dihydroxypyridine and potassium oxonate, which inhibits orotate phosphoribosyl transferase in the gastrointestinal tract, thereby reducing the gastrointestinal toxicity of 5-fluorouracil (11). A pre-clinical study using human oral cancer xenograft models has demonstrated improved responses from the combination of S-1 and fractionated radiotherapy compared with either treatment alone (12). Furthermore, Harada *et al* reported the feasibility and efficacy of S-1 chemotherapy, performed concomitantly with radiotherapy at a dose of 40 Gy, as a pre-operative treatment protocol for advanced OSCC in a phase I trial (13). However, no consensus has been reached concerning the optimal treatment combination, dose or timing. In the present study, retrospective clinicopathological evaluation of pre-operative chemotherapy with S-1 and concurrent radiotherapy at a total dose of 30 Gy was performed in locoregionally advanced operable OSCC.

## Materials and methods

*Patients and staging*. In total, 81 patients with advanced resectable primary OSCC that were treated at the Department of Oral and Maxillofacial Surgery at Kyushu University Hospital (Fukuoka, Japan) between January 2004 and December 2010 were evaluated in the present study. All patients with advanced OSCC in this period underwent pre-operative chemoradiotherapy, with the exception of patients that could not undergo S-1 as a chemotherapy regimen due to serious systemic disease or extreme old age, who were excluded from the present study. The average patient age was 60.7±12.9 years (range, 22-81). In total, 65 patients were male and 16 were female. Informed consent was obtained from all patients for all aspects of the pre-operative chemoradiotherapy and radical surgery prior to the initiation of any procedure or treatment and the study was approved by the ethics committee of Kyushu University Hospital. All patients demonstrated a performance status of <2, according to the National Cancer Institute common toxicity criteria, version 4.0. (14), and possessed adequate hematological, renal and hepatic function for receiving the treatment regimen with S-1.

Patients were tattooed in at least 4 regions around the tumor at the time of incisional biopsy, and they underwent examination by computed tomography (CT), magnetic resonance imaging, ultrasonography, gastroscopy and thoracic X-ray. Tumor scintigraphy or F-18 fluorodeoxyglucose positron emission tomography was performed for the detection of distant metastasis. Tumor stage was classified according to the tumor-node-metastasis classification of the International Union Against Cancer (15). In the present study, endophytic tumors with a maximum size of >30 mm were classified as advanced OSCC, even if cervical lymph node metastasis was not clinically identified. Lymph nodes with rim enhancement or heterogeneous enhancement on CT examination were considered to demonstrate metastasis, regardless of the length of the short axis diameter. Lymph nodes measuring ≥10 mm in the short axis diameter were also considered to demonstrate metastasis, as reported in previous studies (16,17). Additionally, lymph nodes with peripheral vascularity, aberrant multi-focal vascularity or non-vascularity on power Doppler ultrasonography were considered to demonstrate metastasis (16,17). Tumor histological grades were defined according to the WHO classification (18). The mode of tumor invasion was determined by hematoxylin-eosin staining of the specimens according to the criteria reported by Yamamoto *et al* (19), as follows: Grade 1, well-defined borderline; grade 2, cords, less-marked borderline; grade 3, groups of cells, no distinct borderline; grade 4, diffuse invasion; grade 4C, cord-like type; and grade 4D, widespread type. The patient and tumor characteristics are reported in Table I.

Table I. Characteristics of 81 patients with locally advanced oral squamous cell carcinoma.

| Characteristics | Total, n (%) |
|---|---|
| Gender | |
| Male | 65 (80.2) |
| Female | 16 (19.8) |
| Age | |
| ≥65 years | 33 (40.7) |
| <65 years | 48 (59.3) |
| Primary site | |
| Tongue | 41 (50.6) |
| Gingiva | 29 (35.8) |
| Oral floor | 9 (11.1) |
| Buccal mucosa | 2 (2.5) |
| Clinical stage | |
| II | 29 (35.8) |
| III | 12 (14.8) |
| IV | 40 (49.4) |
| Histological grade | |
| Grade 1 | 45 (54.2) |
| Grade 2 | 36 (45.8) |
| Mode of invasion | |
| 1/2/3 | 65 (80.2) |
| 4C/4D | 16 (19.8) |
| Pre-operative treatment | |
| Completion | 69 (85.2) |
| Cessation | 12 (14.8) |
| Local recurrence | |
| Yes | 6 (7.4) |
| No | 75 (92.6) |
| Neck recurrence | |
| Yes | 2 (2.5) |
| No | 79 (97.5) |

Table II. Incidence of adverse events in 81 patients with locally advanced oral squamous cell carcinoma.

| | Grade, n | | |
|---|---|---|---|
| Adverse event | 1 | 2 | 3 |
| Hematological toxicity | | | |
| Leukocytopenia | 12 | 14 | 3 |
| Neutropenia | 8 | 15 | 3 |
| Anemia | 38 | 4 | 0 |
| Thronbocytopenia | 16 | 2 | 0 |
| Non-hematological toxicity | | | |
| Dermatitis | 9 | 0 | 0 |
| Oropharyngeal mucositis | 8 | 58 | 15 |
| Nausea | 9 | 0 | 0 |
| Diarrhea | 4 | 0 | 0 |
| Dry mouth | 48 | 0 | 0 |

*Pre-operative chemoradiotherapy regimen*. The patients were prepared for radiotherapy by undergoing planning CT. The patients received external beam irradiation to the primary tumor and metastatic lymph nodes in daily fractions of 2 Gy, 5 times weekly, for 3 weeks. Oral administration of S-1 (TS-1; Taiho Pharmaceutical Co., Ltd., Tokyo, Japan), twice daily, was commenced 1 week prior to radiotherapy and was continued throughout the radiotherapy period. Standard individual doses of S-1 were calculated according to the body surface area (BSA), as follows: BSA <1.25 $m^2$, 80 mg; BSA ≥1.25 and <1.5 $m^2$, 100 mg; BSA ≥1.5 $m^2$, 120 mg. However, in patients with reduced renal function, demonstrated by decreased creatinine clearance values (normal range, ≥80 ml/min), S-1 was administered at a lower dose, generally one step lower than the standard dose. Adverse events were evaluated according to the National Cancer Institute common toxicity criteria, version 4.0 (14). The pre-operative chemoradiotherapy regimen is summarized in Fig. 1.

*Surgery*. Radical surgery was performed 2-6 weeks (mean, 26.4±5.82 days) subsequent to the end of the pre-operative chemoradiotherapy. The primary tumors were resected with safety margins of ≥10 mm from the tattoos around the tumor, regardless of the clinical response. Neck dissection was required for the treatment of patients with clinically involved lymph nodes and for patients that required an extraoral approach or the transfer of vascularized flaps. Immediate surgical reconstruction was undertaken using local flaps or vascularized free flaps.

*Clinicopathological evaluation of treatment*. The clinical response to pre-operative chemoradiotherapy was determined at 2-3 weeks subsequent to the end of chemotherapy administration, according to the response evaluation criteria in solid tumors guidelines, version 1.1 (20). Complete response (CR) was defined as the disappearance of all target lesions, with reduction in the short axis of any pathological lymph nodes to <10 mm. Partial response (PR) was defined as a minimum decrease of 30% in the sum of the diameters of the target lesions, using the baseline sum of the diameters as a reference. Progressive disease (PD) was defined as a minimum increase of 20% in the sum of the diameters of the target lesions, using the smallest sum recorded during the study as a reference, and with an absolute increase of ≥5 mm in the sum of the diameters. Stable disease (SD) was indicated by insufficient shrinkage to qualify for PR and insufficient increase to qualify for PD, using the smallest sum diameter recorded during the study as a reference. The same diagnostic modalities as those initially applied were used to evaluate the clinical response.

The classification of therapeutic efficacy established by Shimosato *et al* (21) was used to evaluate the histopathological response of primary site tumors, as follows: Grade 0, no noticeable change; grade I, minimal cellular changes, but the majority of tumor cells appear viable; grade IIa, despite the presence of cellular changes and partial destruction of the tumors, the tumor remains readily recognizable and numerous tumor cells appear viable; grade IIb, tumor destruction is extensive, but viable cell nests are present in small regions of the tumor (up to one-quarter of the tumor mass, excluding areas of coagulative necrosis); grade III, only a small number of scattered, markedly altered, and presumably non-viable tumor cells are present, singly or in small clusters, and a small number or no viable cells are observed; and grade IV, no tumor cells remaining in any section. The slicing of the resected specimens was performed using a step-section method at intervals of 5 mm.

*Statistical analysis*. All statistical analyses in the present study were performed using JMP software version 8 (SAS Institute Japan, Ltd., Tokyo, Japan). Associations between the incidence of locoregional recurrence and clinical or histopathological response were assessed using Fisher's exact test. The survival time was measured from the first day of treatment until mortality or the last patient contact. Survival rates were calculated using the Kaplan-Meier method, and the P-value was calculated using the log-rank test. $P<0.05$ was considered to indicate a statistically significant difference.

## Results

*Patient characteristics*. The primary site was the tongue in 41 patients (50.6%), the gingiva in 29 patients (35.4%) and the oral floor in 9 patients (11.1%). Of the OSCC patients, 29 patients demonstrated stage II disease (35.8%), 12 demonstrated stage III disease (14.8%), and 40 demonstrated stage IV disease (49.4%). Out of the 81 patients that received pre-operative chemoradiotherapy, 69 patients (85.2%) completed treatment according to the planned schedule. In the remaining 12 patients (14.8%), treatment was stopped to prevent the side-effects from becoming severe, as the satisfactory response of the primary tumor was obtained. The local and neck recurrence rates were 7.4 and 2.5%, respectively. Reconstruction was performed using a microvascular flap in 73 patients, a cervical island flap in 4 patients, a split-thickness skin graft in 3 patients and primary closure in 1 patient (data not shown).

*Toxicity*. Patients that experienced toxicities during treatment or within 2 weeks subsequent to chemoradiotherapy are reported in Table II. With regard to hematological

Table III. Clinical response of primary tumors subsequent to pre-operative chemoradiotherapy in 81 patients with locally advanced oral squamous cell carcinoma.

| | Clinical response, n | | | | |
|---|---|---|---|---|---|
| T classification | CR | PR | SD | PD | Response rate, % |
| T2 | 5 | 28 | 6 | 0 | 84.6 |
| T3 | 0 | 4 | 2 | 0 | 66.7 |
| T4 | 1 | 19 | 12 | 4 | 55.6 |
| Total | 6 | 51 | 20 | 4 | 70.4 |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table IV. Histopathological evaluation of the response rate of primary tumors in 81 patients with locally advanced oral squamous cell carcinoma subsequent to pre-operative chemoradiotherapy.

| | Histopathological response, n | | | | | |
|---|---|---|---|---|---|---|
| T classification | I | IIa | IIb | III | IV | Response rate, % |
| T2 | 1 | 3 | 21 | 2 | 12 | 89.7 |
| T3 | 0 | 3 | 2 | 0 | 1 | 50.0 |
| T4 | 5 | 8 | 16 | 1 | 6 | 63.9 |
| Total | 6 | 14 | 39 | 3 | 19 | 75.3 |

T classification, tumor stage classification.

toxicity, leukocytopenia of grades 1 and 2 developed in 28 patients (34.6%), and 3 patients experienced grade 3 toxicity. Neutropenia of grades 1 and 2 was observed in 23 patients (28.4%) and grade 3 was observed in 3 patients. Anemia or thrombocytopenia of grades 1 and 2 occurred in 42 patients (51.9%) and 18 patients (22.2%), respectively. No patients in the present study experienced grade 4 hematological toxicities. With regard to non-hematological toxicities, grade 1-3 oropharyngeal mucositis was observed in all patients, of which 15 patients (18.5%) experienced grade 3 mucositis. Dry mouth was the second most common adverse event and occurred in 48 patients (59.3%). Dermatitis developed in 9 patients (11.1%), nausea in 9 patients (11.1%) and diarrhea in 4 patients (4.9%). The complications or late adverse events, including radiation osteomyelitis, that are associated with pre-operative chemoradiotherapy were not identified during radical surgery or post-operatively.

*Efficacy*. The clinical responses of the primary tumors are reported in Table III. CR was achieved by 6 patients (7.4%), and partial response was observed in 51 patients (63.0%). The clinical response rate, calculated as the sum of the patients that achieved complete and partial response, was 84.6% for T2 tumors, 66.7% for T3 tumors and 55.6% for T4 tumors. The histopathological effect achieved following pre-operative chemoradiotherapy was grade IV in 19 patients, grade III in 3 patients, grade IIb in 39 patients, grade IIa in 14 patients and grade I in 6 patients. The histopathological response rate, defined as grades IIb-IV, was 75.3% (Table IV). The association between the clinical and histopathological responses was further examined. The results revealed that the patients with good clinical response demonstrated good histopathological response, indicating that the clinical response correlated positively with histopathological response (Table V).

Post-operative chemoradiotherapy was performed in 10 patients that possessed >3 involved lymph nodes, extracapsular spread or nodal metastases over multiple neck levels. These patients received external beam irradiation to the cervical region in daily fractions of 2 Gy, 5 times a week, for 4 weeks (total dose, 60-70 Gy) in conjunction with the oral administration of S-1. Post-operatively, local failure developed in 6 patients (7.4%) and neck failure developed in 2 patients (2.5%). Distant metastases were observed in 7 patients (8.6%). The median duration of follow-up was 59.0 months (range, 24-108 months). The overall survival (OS), disease-specific survival (DSS) and locoregional control (LRC) rates at 5 years were 87.7, 89.9%, and 90.6, respectively (Fig. 2).

*Risk factors for locoregional recurrence*. In order to further improve the outcome of treatment for patients with advanced OSCC, the risk factors for locoregional recurrence were examined in the present study (Table VI). The incidence of locoregional recurrence was positively associated with the progression of the clinical stage ($P<0.05$). Furthermore, locoregional recurrence occurred more frequently in patients that demonstrated a poor histopathological response

Table V. Association between the clinical response and histopathological response of primary tumors in 81 patients with locally advanced oral squamous cell carcinoma.

| | Histopathological response, n | | | | | |
|---|---|---|---|---|---|---|
| Clinical response | I | IIa | IIb | III | IV | Total |
| PD | 2 | 1 | 1 | 0 | 0 | 4 |
| SD | 4 | 9 | 7 | 0 | 0 | 20 |
| PR | 0 | 4 | 31 | 2 | 14 | 51 |
| CR | 0 | 0 | 0 | 1 | 5 | 6 |
| Total | 6 | 14 | 39 | 3 | 19 | 81 |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table VI. Association between locoregional recurrence and the clinicopathological features of 81 patients with locally advanced oral squamous cell carcinoma.

| | Locoregional recurrence | | |
|---|---|---|---|
| Clinicopathological features | Yes | No | P-value |
| Age | | | 1.000 |
| ≥65 years | 4 | 44 | |
| <65 years | 4 | 29 | |
| Clinical stage | | | 0.046 |
| II | 0 | 29 | |
| III/IV | 8 | 44 | |
| Histological grade | | | 0.456 |
| 1 | 3 | 42 | |
| 2 | 5 | 31 | |
| Mode of invasion | | | 0.189 |
| 1-3 | 5 | 60 | |
| 4C or D | 3 | 13 | |
| Wait prior to procedure | | | 0.456 |
| ≥28 days | 5 | 31 | |
| <28 days | 3 | 42 | |
| Histopathological tumor response | | | <0.001 |
| I or IIa | 8 | 12 | |
| IIb-IV | 0 | 61 | |
| Depth of residual tumor | | | 0.336 |
| Superficial | 1 | 14 | |
| Deep | 7 | 37 | |

(grades I and IIa) compared with patients that demonstrated a good response (grades IIb-IV) (P<0.01). No locoregional recurrence was observed in patients with grade IIb-IV histopathological responses. The residual tumor in the patients with locoregional recurrence was more frequently identified in the muscular layers, though no significant difference was found. However, no significant associations were identified between the locoregional incidence and age, histological grade, mode of invasion, waiting period prior to surgery or depth of the residual tumor.

## Discussion

Neoadjuvant induction chemoradiotherapy followed by radical surgery has become an established treatment for the clinical management of locally advanced OSCC over the previous 20 years. Several studies have demonstrated that this treatment results in a higher overall survival rate in patients with OSCC (6-10,22-24). The inclusion of pre-operative chemoradiotherapy is credited with this improvement in the overall survival rate. The beneficial effects of neoadjuvant

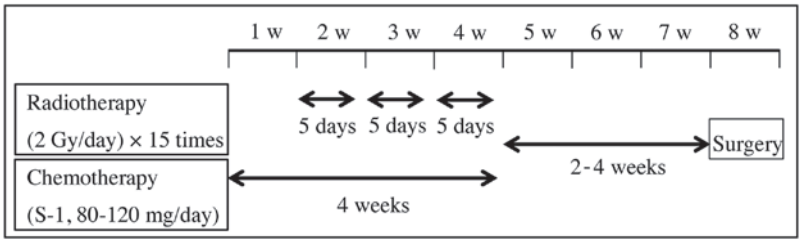


Figure 1. Summary of the pre-operative chemoradiotherapy regimen with S-1 administered for the treatment of patients with locally advanced oral squamous cell carcinoma.

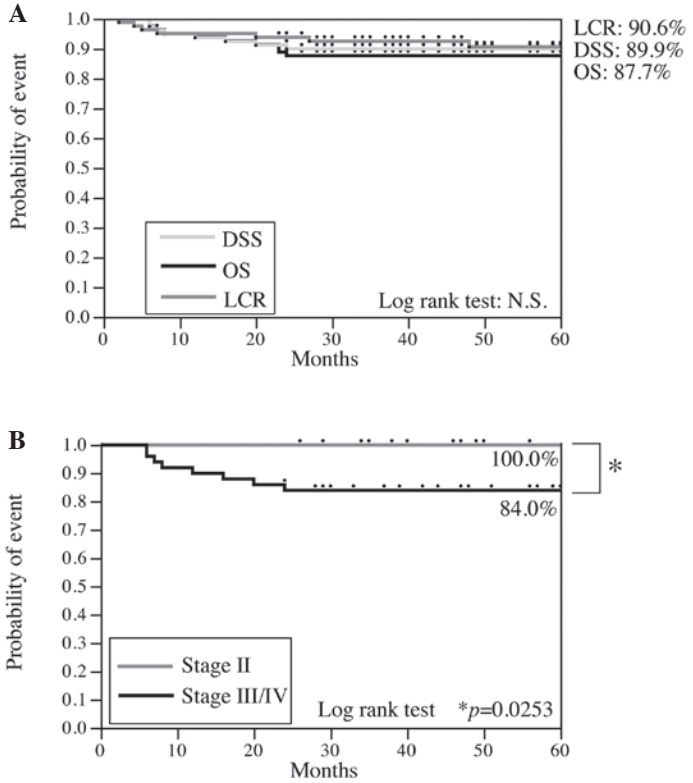


Figure 2. Survival and locoregional control rates of patients with locally advanced oral squamous cell carcinoma. (A) The LRC, DSS and OS rates at 5 years were 87.7, 89.9 and 90.6%, respectively. (B) A significant difference was identified between the 5-year DSS rates in stages II and III/IV of disease (100.0 vs. 84.0%; P<0.05). Statistical analysis was performed using the log-rank test. NS, not significant; LRC, locoregional control; DSS, disease-specific survival; OS, overall survival.

induction chemoradiotherapy followed by radical surgery include downstaging of the primary tumor, an increased resectability rate and the elimination of micrometastases. However, protocols have varied widely between institutions. Kirita *et al* treated advanced oral cancer with pre-operative cisplatin- (15 mg/m$^2$, days 1-3) or carboplatin-based intravenous chemotherapy (70-100 mg/m$^2$ carboplatin, days 1-3; 5 mg/m$^2$ peplomycin or 500 mg, 5-FU, days 4-7) administered concurrently with radiotherapy at a total dose of 40 Gy (6). Mücke *et al* also demonstrated the efficacy of low-dose radiotherapy (total dose, 20 Gy) combined with concurrent low-dose cisplatin (12.5 mg/m$^2$) for 5 days, as pre-operative therapy (24). However, Iguchi *et al* reported the use of combined intra-arterial pirarubicin and continuous intravenous 5-fluorouracil (5-FU) with a radiation dose of 40 Gy (25). This study concluded that these regimens were effective as a pre-operative treatment, with a notably high response rate and an acceptable incidence of adverse events. However, it is widely known that CDDP, a radiosensitizing agent, requires excess hydration and antidotes due to the tendency of this agent to cause renal dysfunction (26). Furthermore, the intra-arterial infusion of anticancer drugs is associated with technical difficulty and is occasionally accompanied by serious complications, such as permanent neurological deficits. Therefore, these treatments are feasible only in a limited number of patients and institutions.

Previous studies have demonstrated that the oral administration of S-1 with concurrent radiotherapy is a feasible and effective treatment for patients with advanced OSCC (13,27-29). However, only a small number of studies have assessed the use of S-1 with pre-operative chemoradiotherapy. In the present study, the feasibility and efficacy of pre-operative S-1 chemotherapy administered concurrently with radiotherapy at a total of 30 Gy was retrospectively evaluated.

Harada *et al* previously demonstrated that all adverse events associated with pre-operative S-1 chemotherapy and concurrent radiotherapy were tolerable and controllable (27). In the present study, no severe grade 4 hematological, gastrointestinal or skin toxicities were encountered. Oropharyngeal mucositis was the most common adverse event, with grades 2 and 3 mucositis occurring in 71.6 and 18.5% of patients, respectively. The mucositis was transient and tolerable in all cases. In the study by Harada *et al* (27), grade 3 mucositis was observed in 84.6% of the patients that received pre-operative S-1 chemotherapy with concurrent radiotherapy at a total dose of 40 Gy. This difference in the incidence of grade 3 mucositis may be due to the difference in the total radiation dose. In addition, using a lower total radiation dose in the pre-operative treatment enables the use of a higher dose of chemoradiotherapy post-operatively, prevents osteoradionecrosis of the jaw, prevents severe late toxicity and shortens the tumor-bearing period. It is therefore suggested that this regimen has more advantages than those observed at a total dose of >40 Gy.

In the present study, the overall histological response rate (grades IIb-IV) was 75.3%. Notably, pathological CR (grade IV) was obtained in 23.5% of the patients. The outcome of this regimen was an LRC rate of 90.6%, DSS rate of 89.9% and OS rate of 87.7%. In phase II trials of pre-operative S-1 chemotherapy combined with radiotherapy at a total dose of 40 Gy for stage III/IV OSCC, the histopathological response rate of the primary tumor was 78.4% and the LRC, DSS and OS rates in this study were 91.5, 83.8 and 83.8%, respectively (27). However, a direct comparison between these previous results and the present data cannot be made due to including stage II OSCC in the present study. In the patients with stage III/IV OSCC in the present study, the histopathological response rate was 63.5% (data not shown), which was decreased compared with the response rate of previous studies. However, the OS rate of the patients with stage III/IV OSCC in the present study was 84.0%, which yielded a similar survival curve to those obtained in previous studies (6-9,23,24). Miyawaki *et al* demonstrated that the administration of S-1 chemoradiotherapy at 30 Gy to treat OSCC at stages II-IV, which was similar to the present regimen, was histopathologically effective in 73.7% of patients (30). The DSS rate of the previous study was 88.8%, which is similar to the present results (30). These results indicate that increasing the total radiation dose may not affect the patient outcome, but it yields an effective primary tumor response. The consistent patient outcome may be due to the difference in surgical margins in the resection between the present and previous studies. In the present patients, the primary tumors were resected with safety margins ≥10 mm from the tattoos around the tumor, regardless of the clinical response. Although not stated, in previous studies, the tumors may be resected at a narrower safety margin in the case of a good clinical response, which would result in a higher risk of recurrence.

In order to maximize outcomes, the risk factors for locoregional recurrence in patients receiving S-1 chemotherapy with concurrent radiotherapy were also examined. It is notable that all patients with locoregional recurrence demonstrated a poor histological tumor response of grade I or IIa. Out of the patients with stage T4 OSCC, Nomura *et al* found that the 3-year LRC rate for grade 0-III responses was 73%, which was decreased compared with the rate for grade IV pathological responses (93%), although this difference was not statistically significant (31). Furthermore, the residual cancer cells in the patients with locoregional recurrence were more frequently identified in the muscular layers, but not submucosal layer. These results indicate that an increase in the surgical margins at the bottom of the tumor in the patients with little or no histopathological response is required.

At present, the standard treatment for oral cancer remains surgery alone, with radiotherapy or concomitant chemoradiotherapy subsequent to surgery recommended for high-risk cases (32), as pre-operative chemotherapy has failed to significantly improve the OS rate in certain previous randomized controlled trials (33,34). In addition, Yanamoto *et al* hypothesized that neoadjuvant chemotherapy may increase the risk of local recurrence and lead to poor outcomes in OSCC patients (35). Overall, promising results were obtained in the present study, although limited by its retrospective nature, and in other similar studies (6-9,23,24,27). However, the efficacy of pre-operative chemoradiotherapy remains controversial, and a definitive conclusion cannot yet be reached. Additional controlled studies with a large sample size and randomized prospective design are required to resolve this clinical question.

## Acknowledgements

This study was supported by a Grant-in-Aid (grant no. 26463014) from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

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