Efficacy of adjuvant chemotherapy with S-1 in stage II oral squamous cell carcinoma patients: A comparative study using the propensity score matching method

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Abstract

It has been reported that 20% of early-stage oral squamous cell carcinoma (OSCC) patients treated with surgery alone (SA) may exhibit postoperative relapse within 2–3 years and have poor prognoses. We aimed to determine the safety of S-1 adjuvant chemotherapy and the potential differences in the disease-free survival (DFS) between patients with T2N0 (stage II) OSCC treated with S-1 adjuvant therapy (S-1) and those treated with SA. This single-center retrospective cohort study was conducted at Kumamoto University, between April 2004 and March 2012, and included 95 patients with stage II OSCC. The overall cohort (OC), and propensity score-matched cohort (PSMC) were analyzed. In the OC, 71 and 24 patients received SA and S-1, respectively. The time to relapse (TTR), DFS, and overall survival were better in the S-1 group, but the difference was not significant. In the PSMC, 20 patients each received SA and S-1. The TTR was significantly lower in the S-1 group than in the SA group, while the DFS was significantly improved in the former. S-1 adjuvant chemotherapy may be more effective than SA in early-stage OSCC.

Introduction

Oral cancer, and predominantly oral squamous cell carcinoma (OSCC), is a major cause of morbidity and mortality worldwide. The survival rate of these patients has not improved, despite advances and innovations in the diagnostic techniques and treatments used [1]. Locally advanced OSCC is generally associated with particularly poor prognoses owing to the difficulty in controlling it with surgery and adjuvant radiotherapy or concurrent chemoradiotherapy [2, 3]. However, even in case of early-stages disease (T1-2N0), which can be cured by therapy, more than 80% of the cases being subjected to curative surgery may exhibit postoperative...
relapse within the first 2 to 3 years [4, 5]. Therefore, it is essential to control local recurrence and/or regional lymph node metastasis to improve the patients’ prognoses.

S-1, a novel oral fluoropyrimidine preparation (Taiho Pharmaceutical, Tokyo, Japan), is designed to improve the antitumor activity of 5-FU, while also reducing gastrointestinal toxicity. S-1 contains tegafur (a prodrug of 5-FU), gimeracil (inhibits the 5-FU degeneration enzyme, dihydropyrimidine dehydrogenase), and oteracil (reduces the gastrointestinal toxicity of 5-FU) [6–8]. In patients with various cancers, including those of the head and neck, S-1 administered alone or in combination with other chemotherapeutic agents has been shown to improve the outcomes [9–12].

Recently, the Adjuvant Chemotherapy with S-1 after Curative Treatment in Patients with Head and Neck Cancer (ACTS-HNC) study, which enrolled patients with advanced head and neck squamous cell carcinoma (HNSCC), reported significantly better overall survival (OS) in the S-1 group than in the control group [13]. Furthermore, reports have confirmed the efficacy of S-1 after curative surgery in gastric and pancreatic cancer [10, 14, 15]. These results encouraged us to investigate whether S-1 could be considered as a treatment option after curative surgery in patients with OSCC, even in early-stage disease. The primary aim of this study was to evaluate the efficacy and safety of S-1 compared with surgery alone (SA) in patients with stage II OSCC.

### Material and methods

#### Study population

The study population comprised patients with cT2N0 (stage II) OSCC. They were diagnosed based on the histological and radiological findings, including computed tomography (CT), magnetic resonance imaging, ultrasonography, and positron emission tomography-computed tomography (PET-CT) findings. All tumors were staged according to the TNM classification of the American Joint Committee on Cancer, 7th edition [16], and the degree of differentiation was determined according to the classification of the World Health Organization [17]. Histopathological tumor invasion phenotypes were categorized with respect to the mode of invasion [18]. In our department, elective neck dissection is only performed for cases of N0 oral cancer for the purpose of reconstruction, and a “wait-and-see policy” has been adopted. Therefore, all patients enrolled in the present study only underwent resection of the primary tumor. After completion of curative surgery, we confirmed whether the patients met the eligibility criteria. Those treated with SA and S-1 at the Department of Oral and Maxillofacial Surgery, Kumamoto University Hospital were enrolled from April 2004, with observation continuing until March 2012. This study was conducted with the approval of the Ethics Committee of Kumamoto University (approval number, 747), in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent before enrollment in the study.

#### Eligibility criteria

To further improve the outcomes in patients with early-stage OSCC, we began administering adjuvant chemotherapy with S-1 from 2004. The eligibility criteria for adjuvant chemotherapy with S-1 for patients with cT2N0 oral carcinoma were as follows: (1) curative surgery only for the primary tumor, (2) histologically verified SCC of the oral cavity, (3) no residual tumor (primary lesion) confirmed on diagnostic imaging or biopsy, (4) performance status of 0–1 and normal hematologic parameters (white blood cell count ≥ 3500/mm³, hemoglobin level ≥ 9.0 g/dL, and platelet count ≥ 100,000/mm³), liver function (total bilirubin level ≤ 1.5 mg/dL, and aspartate transaminase [AST] level and alanine transaminase [ALT] levels ≤ ULN×2.5), renal
function (creatinine level ≤ 1.2 mg/dL and creatinine clearance ≥ 60 mL/min), and (5) absence of severe complications. In order to focus on evaluating the treatment efficacy of S-1, patients who underwent elective neck dissection and sentinel lymph node biopsies were excluded [19]. In addition, patients who previously received systemic therapy or radiotherapy and had distant metastasis, concomitant malignancies, active inflammatory disease, active gastric/duodenal ulcers, severe heart disease, or other severe concurrent disease were excluded. Pregnant or lactating women were also excluded.

**Treatment**

After the completion of curative surgery, patients who consented to undergo S-1 adjuvant chemotherapy were assigned to the S-1 group, and those who refused S-1 adjuvant chemotherapy were assigned to the SA group. In the S-1 group, patients received 80 mg/day (body surface area [BSA] < 1.25 m²), 100 mg/day (BSA ≥ 1.25 to < 1.5 m²), or 120 mg/day (BSA ≥ 1.5 m²) of S-1, in two divided doses, daily, for 2 weeks, followed by a 1-week period of rest [11]. Administration of S-1 was started within 8 weeks after surgery, and the duration of treatment was 1 year. If adverse events meeting the criteria for temporary treatment withdrawal occurred, treatment was discontinued and was resumed when the criteria for treatment resumption were satisfied. If adverse events meeting the criteria for dose reduction developed, the dose was reduced by one level before treatment was resumed.

**Follow-up evaluations**

After being allocated to the appropriate treatment group, the patients were followed-up for the evaluation of tumor control. We recorded local recurrence of the tumor, regional lymph node metastasis, and distant metastasis as local, regional, and distant failure, respectively. In patients with failed tumor control, we considered salvage surgery, radiotherapy, and/or additional chemotherapy. The survival after treatment was measured from the date of surgery to the date of death or last follow-up. The hematologic and non-hematologic toxicities of S-1 were prospectively scored according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.

**Statistical analyses**

The characteristics of the patients in the S-1 and SA groups were compared using Mann-Whitney’s U and Fisher’s exact tests for categorical and continuous factors, respectively, for the overall cohort (OC). For the propensity score-matched cohort (PSMC), the Wilcoxon signed-rank test was used for continuous factors and the exact McNemar test or stratified conditional logistic regression analysis was used for categorical factors.

The primary endpoint was disease-free survival (DFS), defined as the time from the date of surgery to the date of confirmation of recurrence, delayed cervical lymph node metastasis, distant metastasis, or the diagnosis of secondary cancer or death from any cause, whichever occurred first. The secondary endpoints were OS and safety. OS was defined as the time from the date of surgery to the date of death from any cause. The time to relapse (TTR) was defined as the time from surgery to the diagnosis of local recurrence or cervical lymph node metastasis. The OS and DFS were calculated using the Kaplan-Meier method, and the difference between the two groups was analyzed using the log-rank test. The hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by multivariate analyses, performed using the Cox proportional hazards regression model.

Prognostic and disease progression factors were considered for inclusion in the final models after calculating the coefficients and examining and ensuring that the proportion of missing
data was below 25% [20]. All factors showing significance on univariate analysis were considered to fit the model. All factors with \( P < 0.2 \) were reviewed to avoid missing important factors and were then examined using multivariate analysis [21]. Two-sided probabilities were used, and \( P < 0.05 \) was considered statistically significant, unless otherwise noted. The propensity score was calculated using a binary logistic regression that included the patients’ characteristics. A propensity score, which reflected the probability of receiving S-1, was assigned to each patient. The S-1 and SA patients were randomly matched one-to-one, using greedy matching within propensity score calipers with no replacement [22]. The propensity scores were matched using a caliper width of 0.2 logits of the standard deviation to achieve a good covariate balance [22, 23]. The standardized differences were used to measure covariate balance, with an absolute standardized difference within 10% representing sufficient balance. The two matched subgroups were then analyzed for OS and DFS. Statistical analyses were performed using the Stata Statistical Software Program, Release 14.1 (StataCorp LP, College Station, TX, USA) and NCSS 10 Statistical Software Program (2015) (NCSS; LLC, Kaysville, UT, USA).

**Results**

**Patient characteristics**

From April 2004 to March 2012, a total of 95 cT2N0M0 OSCC patients were enrolled; 24 patients were assigned to the S-1 group and 71 to the SA group. The patient characteristics are summarized in Table 1. The only characteristic that significantly differed between the two groups was age (\( P < 0.001 \), Table 1).

**Study treatments**

The numbers of patients in the S-1 group who received the study treatment after 3, 6, and 12 months were 19 (79.2%), 17 (70.8%), and 14 (58.3%), respectively (Table 2). The reasons for discontinuing treatment in this group were the development of recurrence or metastasis in 2 (8.3%) patients and the physician’s judgement (mainly because of the occurrence of adverse events) in 8 (33.4%) patients.

**Adverse events**

Table 3 shows the all-grade adverse events that occurred at an incidence rate of 4.2% (1 patient) or higher. An increase in the total bilirubin level was observed in 11 (45.8%) patients, anorexia was noted in 10 (41.7%) patients, anemia in 9 (37.5%) patients, fatigue and weight loss in 8 (33.3%) patients, thrombocytopenia in 7 (29.2%) patients, leukopenia, AST level increase and hyperpigmentation in 6 (25.0%) patients, rash/desquamation in 5 (20.8%) patients, ALT level increase in 4 (16.7%) patients, nausea in 3 (12.5%) patients, and vomiting in 2 (8.3%) patients. The following adverse events occurred at a severity of grade 3: anorexia in 2 (8.3%) patients and an increase in the total bilirubin level in 1 (4.2%) patient; they were in the S-1 group (Table 3). There were no treatment-related deaths in the S-1 group.

**Survival analyses in the OC**

In the OC, 71 patients received SA and 24 received S-1. Although there were no significant differences, the S-1 group showed a better TTR, DFS, and OS than the SA group (Figs 1, 2A and 2B). In particular, the DFS was better in the S-1 group (Fig 2A).
Survival analyses in the PSMC

In the PSMC, 20 patients each from the S-1 and SA groups were subjected to analysis after one-to-one propensity score matching (Table 4). As shown in Table 4, all baseline characteristics of patients in the PSMC were well-balanced \( (P \geq 0.05) \). The TTR of the S-1 group was significantly lower than that of the SA group \( (P = 0.047) \). In the S-1 group, a significant improvement in prognoses was observed with respect to the DFS \( (P = 0.047) \), but not with
respect to the OS ($P = 0.073$; Figs 3, 4A and 4B). Although there was no statistical significance, the proportion of patients with cervical lymph node metastasis in the S-1 group tended to be smaller than that in the SA group (Table 4).

### Explanatory data analysis

In the OC, local recurrence developed in 9 patients in the SA group and 3 patients in the S-1 group. The HR was 1.249 (95% CI; 0.3377–4.616; Fig 5A). Delayed cervical lymph node metastasis developed in 14 patients in the SA group and 2 patients in the S-1 group. The HR was 2.809 (95% CI; 0.6377–12.38; Fig 5B). In the OC, comparison of the survival time from local recurrence or delayed cervical lymph node metastasis between the treatment groups revealed that the HR for death was 4.271 (95% CI; 0.5411–32.680) in the SA group compared to the S-1 group (Fig 5C). In contrast, in the PSMC, local recurrence developed in 4 patients in the SA group and 3 patients in the S-1 group. The HR was 1.869 (95% CI; 0.4157–8.404; Fig 6A). Delayed cervical lymph node metastasis developed in 5 patients in the SA group and 2 patients in the S-1 group. The HR was 3.191 (95% CI; 0.6152–16.55; Fig 6B). In the PSMC, comparison of the survival time from local recurrence or delayed cervical lymph node metastasis between

### Table 2. Treatment completion rates with S-1 adjuvant chemotherapy.

| Duration   | N   | (%)  |
|------------|-----|------|
| 3 months   | 19  | (79.2)|
| 6 months   | 17  | (70.8)|
| 12 months  | 14  | (58.3)|

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### Table 3. Adverse events with S-1 adjuvant chemotherapy.

| Adverse events          | S-1 (n = 24) | All grade (%) | Grade 3+4 (%) |
|-------------------------|--------------|---------------|---------------|
|                         | n            | (%)           | n             | (%)           |
| Leukopenia              | 6            | (25.0)        | 0             | (0.0)         |
| Neutropenia             | 1            | (4.2)         | 0             | (0.0)         |
| Thrombocytopenia        | 7            | (29.2)        | 0             | (0.0)         |
| Anemia                  | 9            | (37.5)        | 0             | (0.0)         |
| Total bilirubin increase| 11           | (45.8)        | 1             | (4.2)         |
| AST increase            | 6            | (25.0)        | 0             | (0.0)         |
| ALT increase            | 4            | (16.7)        | 0             | (0.0)         |
| Fatigue                 | 8            | (33.3)        | 0             | (0.0)         |
| Anorexia                | 10           | (41.7)        | 2             | (8.3)         |
| Weight loss             | 8            | (33.3)        | 0             | (0.0)         |
| Rash/desquamation       | 5            | (20.8)        | 0             | (0.0)         |
| Hyperpigmentation       | 6            | (25.0)        | 0             | (0.0)         |
| Diarrhea                | 1            | (4.2)         | 0             | (0.0)         |
| Mucositis/Stomatitis    | 0            | (0.0)         | 0             | (0.0)         |
| Nausea                  | 3            | (12.5)        | 0             | (0.0)         |
| Vomiting                | 2            | (8.3)         | 0             | (0.0)         |

Abbreviations: AST, aspartate transaminase and ALT, alanine transaminase

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the treatment groups indicated that the HR for death was 5.691 (95% CI; 0.6637–48.80) in the SA group compared to the S-1 group (Fig 6C).

**Discussion**

This study was designed to evaluate the efficacy of adjuvant chemotherapy after curative surgery in patients with stage II OSCC. Tsukahara et al. recently reported convincing evidence for the benefits of adjuvant chemotherapy in patients with advanced head and neck cancer, who underwent curative therapy including surgery, radiotherapy, and chemoradiotherapy [13]. Therefore, we believe that investigating the effects of S-1 adjuvant chemotherapy in patients with early-stage OSCC may be valuable for establishing new treatment strategies. To the best of our knowledge, the present study is the first to indicate that adjuvant chemotherapy with S-1 improved the DFS in patients with stage II OSCC who received curative surgery for only the primary tumor compared to the DFS in a control group. Recently, Luryi et al. reported that in population-level data analyses, adjuvant chemotherapy is associated with compromised survival in patients with early-stage OSCC [24]. The study did not provide a detailed description of the chemotherapy regimens and included patients who underwent elective neck dissection; therefore, a detailed analysis of the differences in the results between this study and our study was not possible. However, it is necessary to understand the results of these studies and to interpret them carefully. The differences in the results may be related to the characteristic pharmacological action of S-1, as described below.

The treatment completion rate in the S-1 group was 58.3%. This rate was higher than the rate of 43.4% observed in a phase III study (ACTS-HNC) among patients with advanced...
Fig 2. Cumulative survival curves of the S-1 adjuvant therapy (S-1 adjuvant) and surgery alone (surgery alone) groups in the overall cohort. (A) Disease-free survival. (B) Overall survival. DFS, Disease-free survival; OS, overall survival; OC, overall cohort.

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In view of these findings, clinicians should carefully consider both hematologic and non-hematological toxicities, and provide supportive therapy to prevent the discontinuation of S-1. However, the low incidence rates of grade 3 or higher grade adverse events in our study support the notion that S-1 administration may be an acceptable treatment option to further improve the prognoses of patients with stage II OSCC.

Table 4. Patient characteristics in the propensity score-matched cohort.

| Characteristics | Surgery alone n (%) | S-1 adjuvant n (%) | P-value |
|-----------------|---------------------|--------------------|---------|
| Age (years)     |                     |                    |         |
| Median          | 64.0                | 64.0               | 0.674   |
| < 65            | 22                  | 11 (50.0)          | > 0.999 |
| > 65            | 18                  | 9 (50.0)           |         |
| Sex             |                     |                    |         |
| Male            | 25                  | 13 (52.0)          | > 0.999 |
| Female          | 15                  | 7 (46.7)           |         |
| Oral subsite    |                     |                    |         |
| Tongue          | 23                  | 10 (43.5)          | 0.573   |
| Maxilla         | 3                   | 2 (66.7)           |         |
| Mandible        | 10                  | 6 (60.0)           |         |
| Oral floor      | 1                   | 1 (100.0)          |         |
| Buccal mucosa   | 3                   | 1 (33.3)           |         |
| Clinical phenotype |                 |                    |         |
| Superficial     | 16                  | 8 (50.0)           | 0.698   |
| Exophytic       | 10                  | 4 (40.0)           |         |
| Endophytic      | 14                  | 8 (57.1)           |         |
| Differentiation |                     |                    |         |
| Grade I         | 30                  | 16 (53.3)          | 0.754   |
| Grade II        | 10                  | 4 (40.0)           |         |
| Mode of invasion|                     |                    |         |
| I, II           | 13                  | 6 (46.2)           | 0.517   |
| III             | 19                  | 12 (63.2)          |         |
| IVc, IVd        | 8                   | 2 (25.0)           |         |
| Local recurrence|                     |                    |         |
| No              | 33                  | 16 (48.5)          | > 0.999 |
| Yes             | 7                   | 4 (57.1)           |         |
| Delayed cervical lymph node metastasis | | | |
| No              | 33                  | 15 (45.5)          | 0.453   |
| Yes             | 7                   | 5 (71.4)           |         |
| Distant metastasis |                 |                    |         |
| No              | 38                  | 19 (50.0)          | 1.000   |
| Yes             | 2                   | 1 (50.0)           |         |

(a) Wilcoxon signed-rank test for continuous factors,
(b) Exact McNemar test for 2 x 2 categorical factors and
(c) Stratified conditional logistic regression for 2 x m categorical factors were used to calculate P-values between treatment options and clinicopathologic factors in 40 OSCC patients.

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HNSCC [13]. This difference may be attributed to the decrease in residual function in patients with advanced HNSCC, who underwent definitive therapy. In view of these findings, clinicians should carefully consider both hematologic and non-hematological toxicities, and provide supportive therapy to prevent the discontinuation of S-1. However, the low incidence rates of grade 3 or higher grade adverse events in our study support the notion that S-1 administration may be an acceptable treatment option to further improve the prognoses of patients with stage II OSCC.
It is not clear why patient survival in the S-1 group was better than that in the SA group. Although there was no statistically significant difference between the groups, the present data, including the results of explanatory data analyses, showed that the cumulative rates of local recurrence and delayed cervical lymph node metastasis in the S-1 group tended to be smaller than those in the SA group in both the OC and PSMC. In addition, the time from recurrence or delayed cervical lymph node metastasis to death tended to be longer in the S-1 group. As observed in a previous study (ACTS-HNC) [13], these results possibly indicate that S-1 contributes to disease control after loco-regional failure in patients with OSCC. Among the various clinicopathological characteristics, local recurrence and/or regional lymph node metastasis have been proposed to be the prognostic indicators following surgery in patients with OSCC [25, 26]. Tumor angiogenesis is a hallmark of cancer; it is the essential process underlying tumor growth and progression, and, thereby, contributes to recurrence or metastasis. However, S-1 and its metabolites have been shown to suppress angiogenesis [27–29]. The anti-angiogenic effect of chemotherapy is known to be optimized through the metronomic administration of such drugs for prolonged periods [30]. Collectively, the survival benefit of S-1 administration in this study was probably attributable to both, the cytotoxic and anti-angiogenic activities.

Among early-stage OSCC patients, END has been shown to result in higher survival rates than therapeutic neck dissection [31]. However, END results in overtreatment in more than 70% of early OSCC patients and a high rate of complications [32]. In order to resolve these problems, sentinel lymph node biopsy (SLNB), which is less invasive and improves patients’ quality of life, has gained popularity in the treatment of patients with early-stage OSCC [33–
Fig 4. Cumulative survival curves of the S-1 adjuvant therapy (S-1 adjuvant) and surgery alone (surgery alone) groups in the propensity score-matched cohort. (A) Disease-free survival. (B) Overall survival. DFS, Disease-free survival; OS, overall survival.

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Fig 5. Explanatory data analysis in overall cohort. (A) Cumulative local recurrence rate of the S-1 adjuvant therapy (S-1 adjuvant) and surgery alone (surgery alone) groups. (B) Cumulative delayed cervical lymph node metastasis rate of the S-1 adjuvant therapy (S-1 adjuvant) and surgery alone (Surgery alone) groups. (C) Survival from loco-regional failures to death in patients with local recurrence/ delayed cervical lymph node metastasis.

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Fig 6. Explanatory data analysis in the propensity score-matched cohort. (A) Cumulative local recurrence rate of the S-1 adjuvant therapy (S-1 adjuvant) and surgery alone (surgery alone) groups. (B) Cumulative delayed cervical lymph node metastasis rate of the S-1 adjuvant therapy (S-1 adjuvant) and surgery alone (surgery alone) groups. (C) Survival from loco-regional failures to death in patients with local recurrence/delayed cervical lymph node metastasis.

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36]. However, SLNB may not be universally applicable in routine medical practice. Therefore, in addition to SLNB, S-1 may warrant consideration as a therapeutic option in the cervical management of patients with early OSCC who undergo curative resection only for the primary tumor.

A limitation associated with our study is the small sample size; further studies with larger sample sizes are required to confirm the superiority of S-1 adjuvant chemotherapy over SA. In addition, comparative studies with other treatment options should be considered to confirm the superiority of S-1.

In conclusion, this retrospective study suggests that S-1 therapy was more effective than SA in the PSMC. We believe that S-1 adjuvant chemotherapy followed by curative surgery should be considered the standard of care in future phase III trials including patients with stage II (T2N0) OSCC.

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References

1. Shah JP, Gil Z. Current concepts in management of oral cancer surgery. Oral Oncol. 2009; 45: 394–401. https://doi.org/10.1016/j.oraloncology.2008.05.017 PMID: 18674952

2. Kao J, Laval A, Teng MS, Huang D, Genden EM. Adjuvant radiotherapy and survival for patients with node-positive head and neck cancer: an analysis by primary site and nodal stage. Int J Radiat. 2008; 71: 362–370. https://doi.org/10.1016/j.ijrobp.2007.09.058 PMID: 18164833

3. Kiyota N, Tahara M, Okano S, Kawashima M, Matsuura K, Onozawa Y, et al. Phase II feasibility trial of adjuvant chemoradiotherapy with 3-weekly cisplatin for Japanese patients with post-operative high-risk squamous cell carcinoma of the head and neck. Jpn J Clin Oncol. 2012; 42: 927–933. https://doi.org/10.1093/jjco/hys128 PMID: 22923484

4. Capote A, Escorial V, Munoz-Guerra MF, Rodríguez-Campo FJ, Gamallo C, Nava L. Elective neck dissection in early-stage oral squamous cell carcinoma—does it influence recurrence and survival? Head Neck. 2007; 29: 3–11. https://doi.org/10.1002/hed.20482 PMID: 17103411

5. Huang TY, Hsu LP, Wen YH, Huang TT, Chou YF, Lee CF, et al. Predictors of locoregional recurrence in early stage oral cavity cancer with free surgical margins. Oral Oncol. 2010; 46: 49–55. https://doi.org/10.1016/j.oraloncology.2009.10.011 PMID: 20005769

6. Inoue S, Ohtani H, Tsujimoto M, Hori S, Sawada Y. Development of a pharmacokinetic model to optimize the dosage regimen of TS-1, a combination preparation of tegafur, gimeracil and oteracil potassium. Drug Metab Pharmacokinet. 2007; 22: 162–168. https://doi.org/10.2133/dmpk.22.162 PMID: 17603216
Efficacy of adjuvant chemotherapy with S-1 for stage II oral squamous cell carcinoma

7. Malet-Martino M, Martino R. Clinical studies of three oral produgs of 5-fluorouracil (capcitabine, UFT, S-1): a review. Oncologist. 2002; 7: 288–323. https://doi.org/10.1038/oncologist.7-4-288 PMID: 12185293

8. Shirasaka T, Shimamoto Y, Ohshima H, Yamaguchi M, Kato T, Yonekura K, et al. Development of a novel form of a oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anti-cancer Drugs. 1996; 7: 548–557. https://doi.org/10.1097/00001813-199607000-00010 PMID: 8862723

9. Kawahara M, Furuse K, Segaya Y, Yoshimori K, Matsu K, Kudoh S, et al. Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. Br J Cancer. 2001; 85: 939–943. https://doi.org/10.1054/bjoc.2001.2031 PMID: 11592762

10. Sakuramoto S, Sasako M, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007; 357: 1810–1820. https://doi.org/10.1056/NEJMoa072252 PMID: 17978289

11. Tsukuda M, Kida A, Fuji M, Kono N, Yoshihara T, Hasegawa Y, et al. Randomized scheduling feasibility study of S-1 for adjuvant chemotherapy in advanced head and neck cancer. Br J Cancer. 2005; 93: 884–849. https://doi.org/10.1038/sj.bjc.6602804 PMID: 16189518

12. Van den Brande J, Schoffski P, Schellens JH, Roth AD, Duffaud F, Weigang-Kohler K., et al. EORTC Early Clinical Studies Group early phase II trial of S-1 in patients with advanced or metastatic colorectal cancer. Br J Cancer. 2003; 88: 648–653. https://doi.org/10.1038/sj.bjc.6600781 PMID: 12659110

13. Tsukahara K, Kubota A, Hasegawa Y, Takemura H, Taguchi T, et al. Randomized phase III trial of adjuvant chemotherapy with S-1 after curative treatment in patients with squamous-cell carcinoma of the head and neck (ACTS-HNC). PLoS One. 2015; 10: e0116965, https://doi.org/10.1371/journal.pone.0116965 PMID: 25671770

14. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol. 2011; 29: 4387–4393. https://doi.org/10.1200/JCO.2011.36.5908 PMID: 22010012

15. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet. 2016; 388: 248–257. https://doi.org/10.1016/S0140-6736(16)30589-9 PMID: 27265347

16. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual. 7th ed. New York; Springer; 2010

17. Barnes L, Eveson JW, Reichart P, Sidransky D. Pathology and genetics of head and neck tumours. Lyon: IARC; 2005.

18. Yamamoto E, Kohama G, Sunakawa H, Iwai M, Hiratsuka H. Mode of invasion, bleomycin sensitivity, and clinical course in squamous cell carcinoma of the oral cavity. Cancer. 1983; 51: 2175–2180. https://doi.org/10.1002/1097-0142(19830615 )51:12<2175::aid-cncr2820511205 >2.0.co;2-m PMID: 6189571

19. Hiraki A, Fukuda D, Nagata M, Shiraiishi S, Kawahara K, Matsuya Y, et al. Sentinel lymph node biopsy reduces the incidence of secondary neck metastasis in patients with oral squamous cell carcinoma. Mol Clin Oncol. 2016; 5: 57–60. https://doi.org/10.3892/mco.2016.882 PMID: 27330766

20. Burton A, Altman DG. Missing covariate data within cancer prognostic studies: a review of current reporting and proposed guidelines. Br J Cancer. 2004; 91: 4–8. https://doi.org/10.1038/sj.bjc.6601907 PMID: 15189094

21. Newgard CD, Hedges JR, Arthur M, Mullins RJ. Advanced statistics: the propensity score—a method for estimating treatment effect in observational research. Acad Emerg Med. 2004; 11: 953–961. https://doi.org/10.1197/j.aem.2004.02.530 PMID: 15347546

22. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Stat. 1985; 39: 33–38. https://doi.org/10.1080/00031305.1985.10479383

23. Rosenbaum PR. Design of observational studies. Springer Series in Statistics. 1st ed. New York: Springer-Verlag; 2010 https://doi.org/10.1007/978-1-4419-1213-8

24. Yonekura K, Basaki Y, Chikahisa L, Okabe S, Hashimoto A, Miyamoto K, et al. Treatment factors associated with survival in early-stage oral cavity cancer: analysis of 6830 cases from the National Cancer Data Base. JAMA Otolaryngol Head Neck Surg 2015; 141: 593–598. https://doi.org/10.1001/jamaoto.2015.0719 PMID: 25974757

25. Gonzalez-Garcia R, Naval-Gias L, Roman-Romero L, Sastre-Perez J, Rodriguez-Campo FJ. Local recurrences and second primary tumors from squamous cell carcinoma of the oral cavity: a retrospective analytic study of 500 patients. Head Neck. 2008; 31: 1168–1180. https://doi.org/10.1002/hed.21088 PMID: 19408289
26. Scully C, and Bagan J. Oral squamous cell carcinoma overview. Oral Oncol. 2009; 45: 301–308. doi.org/10.1016/j.oraloncology.2009.01.004 PMID: 19249237

27. Yonekura K, Basaki Y, Chikahisa L, Okabe S, Hashimoto A, Miyamoto K, et al. UFT and its metabolites inhibit the angiogenesis induced by murine renal cell carcinoma, as determined by a dorsal air sac assay in mice. Clin Can Res 1999; 5: 2185–2191.

28. Harada K, Supriatno, Kawashima Y, Yoshida H, Sato M. S-1 inhibits tumorigenicity and angiogenesis of human oral squamous cell carcinoma cells by suppressing expression of phosphorylated Akt, vascular endothelial growth factor and fibroblast growth factor-2. Int J Oncol. 2007; 30: 365–374. PMID: 17203218

29. Ooyama A, Oka T, Zhao HY, Yamamoto M, Akiyama S, Fukushima M. Anti-angiogenic effect of 5-Fluorouracil-based drugs against human colon cancer xenografts. Cancer Lett. 2008; 267: 26–36. doi.org/10.1016/j.canlet.2008.03.008 PMID: 18420342

30. Kerbel RS, Kamen BA. The anti-angiogenic basis of metronomic chemotherapy. Nat Rev. Cancer. 2004; 4: 423–436. doi.org/10.1038/nrc1369 PMID: 15170445

31. D’Cruz AK, Vaish R, Kapre N, Dandekar M, Gupta S, Hawaldar R, et al. Elective versus therapeutic neck dissection in node-negative oral cancer. N Engl J Med 2015; 373: 521–529. doi.org/10.1056/NEJMoa1506007 PMID: 26027881

32. Acevedo JR, Fero KE, Wilson B, Sacco AG, Mell LK, Coffey CS, et al. Cost-effectiveness analysis of elective neck dissection in patients with clinically node-negative oral cavity cancer. J Clin Oncol. 2016; 34: 3886–3891. doi.org/10.1200/JCO.2016.68.4563 PMID: 27551113

33. Agrawal A, Civantos FJ, Brumund KT, Chepeha DB, Hall NC, Carroll WR, et al. [(99m)Tc] Tilmanocept accurately detects sentinel lymph nodes and predicts node pathology status in patients with oral squamous cell carcinoma of the head and neck: Results of a phase III multi-institutional trial. Ann Surg Oncol. 2015; 22: 3708–3715. doi.org/10.1245/s10434-015-4382-x PMID: 25670018

34. Govers TM, Takes RP, Baris Karakullukcu M, Hanning G, Merkx MA, Grutters JP, et al. Management of the N0 neck in early stage oral squamous cell cancer: a modeling study of the cost-effectiveness. Oral Oncol. 2013; 49: 771–777. doi.org/10.1016/j.oraloncology.2013.05.001 PMID: 23735238

35. Hernando J, Villarreal P, Alvarez-Marcos F, Gallego L, Garcia-Consuegra L, Junquera L. Comparison of related complications: sentinel node biopsy versus elective neck dissection. Int J Oral Max Surg, 2014; 43: 1307–1312. doi.org/10.1016/j.ijom.2014.07.012 PMID: 25128262

36. Schilling C, Stockl SJ, Haerle SK, Broglie MA, Huber GF, Sorensen JA, et al. Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer. Eur J Cancer. 2015; 51:2777–84. doi.org/10.1016/j.ejca.2015.08.023 PMID: 26597442