Effect of Concomitant Lafutidine on Adjuvant S-1 for Head and Neck Cancer: A Comparative Study

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Abstract. Background/Aim: This study evaluated the utility of the histamine H2-receptor antagonist lafutidine in patients taking oral fluorouracil (S-1) for head and neck squamous cell carcinoma (HNSCC), by comparing patients with and without concomitant lafutidine. **Patients and Methods:** Study subjects comprised 63 patients who received adjuvant S-1 following curative resection of HNSCC at our institutions between August 1, 2013 and December 31, 2019. The primary endpoint was the completion rate of S-1 therapy. **Results:** For the lafutidine-treated group, the median completion rate was significantly greater (94.4% *vs.* 24.6%, $p = 0.01$), and progression-free and overall survival were both significantly prolonged compared to the non-lafutidine group. In terms of adverse events, the incidence of diarrhoea was significantly reduced ($p<0.00189$) in the lafutidine-treated group. **Conclusion:** Taking lafutidine during S-1 treatment appeared to reduce gastrointestinal disturbance and increased the S-1 completion rate, improving both progression-free and overall survival as a result.

Curative treatment for locally advanced head and neck cancer has conventionally involved a combination of surgery and radiotherapy (1). Because the head and neck region not only carries out functions that play crucial roles in daily life, but is also an important site cosmetically, recent years have seen attempts to use concurrent chemoradiotherapy as curative treatment, with the goal of sparing organs and their functions. In cases of advanced cancer, however, the prognosis cannot be considered satisfactory, even for patients who have undergone curative therapy, and adjuvant chemotherapy following curative treatment is reportedly useful (1, 2).

Two large-scale Japanese studies of adjuvant chemotherapy for advanced head and neck cancer have been reported. The first, a comparative trial conducted by Tsukada *et al.*, administered tegafur and uracil (UFT) to patients for 1 year following curative therapy for head and neck cancer (3). The study included patients with I-IV primary squamous cell carcinoma of the head and neck with no distant metastasis. Although both the 3-year overall survival (OS) rate (UFT group, 77.9%; untreated group, 72.9%) and 3-year relapse-free survival rate (UFT group, 73.4%; untreated group, 66.2%) tended to be better in the UFT-treated group, the difference was not significant. The distant recurrence

rate, however, was significantly lower in the UFT group (7.9% *vs.* 14.6%, respectively; $p = 0.034$), suggesting that UFT is useful as adjuvant chemotherapy.

The second large-scale study was the ACTS-HNC study by Tsukahara *et al.*, as a comparative trial of S-1 and UFT (4). Both 3-year disease-free survival and 3-year relapse-free survival tended to be better in the S-1-treated group, and OS was significantly better ($p = 0.022$). However, the incidence of mucositis/stomatitis as an adverse event was significantly higher in the S-1 group than in the UFT group. The 1-year completion rate for S-1 was low, at 43%, and control of adverse events was conjectured to have affected treatment completion. Although the value of adjuvant chemotherapy for advanced head and neck cancer has become a focus of attention, no previous studies have found that adjuvant chemotherapy significantly improves OS compared with placebo, and adjuvant chemotherapy is therefore not included in the National Comprehensive Cancer Network guidelines (5).

Gastrointestinal toxicity may contribute to reducing the completion rate of S-1 therapy. Controlling adverse events may thus lead to better outcomes. A study showed that in patients with gastric cancer, the use of lafutidine together with S-1 as postoperative adjuvant chemotherapy significantly reduced the

incidence of gastroesophageal reflux and diarrhoea as adverse events. The frequency of S-1 dose reduction or withdrawal was significantly lower in patients who also took lafutidine (30% *vs.* 83%, $p = 0.027$), and its therapeutic effect may have been enhanced (6). Lafutidine is an H2 blocker. In Japan, this pharmacotherapy is indicated for gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis; acute gastritis and acute exacerbation of chronic gastritis; and as a pre-anaesthetic medication (7). In basic experiments on mice, the use of lafutidine in combination with 5-fluorouracil reportedly suppressed 5-fluorouracil-induced gastric mucosal damage *via* capsaicin-sensitive sensory neurons (8). Administration of lafutidine in combination with S-1 for head and neck cancer may thus reduce the incidence of adverse events and increase the completion rate in the same way as for gastric cancer, potentially enhancing the therapeutic effects of S-1.

At our institutions, some patients with a history of conditions such as gastritis and reflux esophagitis are treated with lafutidine irrespective of whether they are receiving S-1. However, as far as we are aware, no previous studies have investigated the effects of additional lafutidine on the completion rate of S-1 therapy for head and neck cancer.

Our objective in this study was therefore to categorize patients undergoing adjuvant chemotherapy with S-1 for head and neck cancer into two groups according to whether lafutidine was administered, and to retrospectively investigate the effects of lafutidine on completion of S-1 treatment.

Patients and Methods

Patients. We conducted a retrospective study of patients who received adjuvant chemotherapy with S-1 after curative treatment for head and neck squamous cell carcinoma in Tokyo Medical University Hospital or Tokyo Medical University Hachioji Medical Center between August 1, 2013 and December 31, 2019.

Patients. Inclusion criteria were: i) treatment with S-1 as adjuvant chemotherapy within 3 months of completing initial curative treatment; ii) histological confirmation of squamous cell carcinoma; and iii) identification of the primary site as the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, nasal cavity, or maxillary sinus. Patients who did not meet these criteria or who declined to participate in the study were excluded.

Administration of S-1 and lafutidine. The initial (first) dose of S-1 was designated as the reference dose (first dose) relative to body surface area. S-1 was administered orally twice daily, with each dose consisting of 40 mg for patients with body surface area <1.25 m^2, 50 mg for those with body surface area of 1.25 m^2 to <1.5 m^2, and 60 mg for those with body surface area ≥1.5 m^2. Following the methods of Tsukahara *et al.* (4), S-1 was administered in a 21-day cycle consisting of 14 consecutive days of administration followed by a 7-day drug holiday, with cycles continued for 1 year. Computed tomography was performed every 3-4 months after starting S-1 therapy, and the response to treatment was evaluated by a specialist radiologist. The response evaluation was determined according to the New Response Evaluation Criteria in Solid Tumours (RECIST) guidelines version 1.1 (9). Treatment was continued until either clear appearance of progressive disease, appearance of intolerable toxicity, or the attending physician determined that the patient should be withdrawn for some other reason. The criteria for dose determination, reduction, withdrawal, and resumption were based on the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 (10), with the dose reduced or the medication withdrawn in

the event of the appearance of grade 3 or worse toxicity (Table I). Lafutidine was administered orally at a dose of 10 mg twice daily.

Staging method. TNM classification was determined according to the Union for International Cancer Control version 7 criteria(11).

Study endpoints. The primary endpoint was the 1-year completion rate of S-1, and the secondary endpoints were progression-free survival (PFS), OS, and incidences of adverse events. The completion rate was evaluated in terms of the relative dose intensity, calculated as the ratio of the actual dose administered compared with the planned dose during the administration period. A non-parametric Mann–Whitney *U*-test was used for statistical analyses of the lafutidine and non-lafutidine groups. The values of 2- and 3-year OS and PFS were calculated by Kaplan–Meier method and log-rank testing was used for statistical analysis, with values of $p<0.05$ regarded as significant.

Adverse events were evaluated in accordance with the CTCAE, and the two groups were compared using Fisher's exact test. PFS was defined as the time from the first dose of S-1 to tumour progression, and OS as the time from

the first dose of S-1 to death.

Statistical analysis and ethics. All statistical analyses were conducted using the EZR graphical user interface (Saitama Medical Center, Jichi Medical University, Saitama, Japan) in the R software environment for statistical calculation and graphics (R Foundation for Statistics Computing, Vienna, Austria) (12). This study was approved by the Ethics Committee of Tokyo Medical University (approval number T2020-0257) and was conducted in compliance with the Declaration of Helsinki. Written informed consent obtained from all patients prior to enrolment.

Results

Background characteristics of patients. A total of 108 patients were treated with S-1 during the study period. No patients declined to participate in the study. Eleven patients were excluded because the cancer was a histological type other than squamous cell carcinoma, five because the primary site was unclear 13 because they were treated with S-1 for a purpose other than adjuvant chemotherapy, and in 15 cases because the patient was taking a gastric

mucosal-protective medication other than lafutidine. One patient was also excluded after being referred to another hospital immediately after having started treatment and was followed-up for less than 1 week. The final study cohort comprised 63 patients. Of these 63 patients treated with S-1, 41 were also taking lafutidine, and 22 were not taking any form of gastrointestinal-protective medication (proton pump inhibitor, H2 blocker, anti-gastrin medication, or similar medication).

Table II shows the clinical characteristics of all 63 patients, comprising 49 men and 14 women (median age=62 years; range=28-82 years). The primary site was the oropharynx in 15 cases, the hypopharynx in 16, the oral cavity in 13, the larynx in 10, the nasopharynx in eight, and the nasal cavity in one. Tumour was III in 13 cases and IV in 50. No difference in the sex ratio was seen between groups (p = 0.582), but members of the lafutidine group were significantly younger (median age=65.5 *vs.* 58.0 years; p = 0.0065).

Completion rate. Figure 2 shows the median completion rate was 94.4% for the lafutidine group and 24.6% for the non-lafutidine group, showing a significant difference (p = 0.01).

PFS. Figure 3 shows the Kaplan–Meier curve for PFS. Median PFS for the lafutidine group was 103 months [95% confidence interval (CI)=72.3 months- not estimable], compared to 55 months (95% CI=14.7-84.6%) for the non-lafutidine group. The 2-year PFS rate was 90.0% (95% CI=75.6-96.1%) for the lafutidine group and 68.2% (95% CI--44.6-83.4%) for the non-lafutidine group (p = 0.00426). The 3-year PFS rate was 87.1% (95% CI=71.6-94.4%) for the lafutidine group and 58.4% (95% CI=35.2-75.8%) for the non-lafutidine group (p = 0.00426).

OS. Figure 4 shows the Kaplan–Meier curve for OS. Median OS was not achieved in either group. Two- and 3-year OS rates were identical, at 95.1% (95% CI=81.9-98.8%) for the lafutidine group and 68.2% (95% CI=44.6-83.4%) for the non-lafutidine group (p = 0.0142).

Adverse events. Table III shows the incidences of adverse events in decreasing order of frequency. Adverse events of CTCAE grade 1 or above were evaluated. An adverse event was counted if it appeared after starting S-1 administration or in the event of a dose reduction or withdrawal of S-1. Multiple adverse events

were common, while 33 out of the 63 patients did not experience any adverse events. A significant difference was seen in the incidence of diarrhea (p<0.00189), but no other significant differences were observed for any other adverse events.

Discussion

One study of lafutidine use in patients receiving S-1 as adjuvant therapy after gastric cancer surgery reported a significant reduction in the incidence of adverse events such as gastroesophageal reflux and diarrhoea, and potentially enhancing the usefulness of S-1 (6). In light of that report, we considered that lafutidine might also reduce adverse events of S-1 in patients with head and neck cancer, and therefore conducted the present study to investigate this hypothesis.

The median S-1 completion rate was 93.7% in the lafutidine group but only 23.8% in the non-lafutidine group, representing a significant difference. Both PFS and OS were also significantly prolonged in the lafutidine group. In terms of adverse events, the incidence of diarrhoea was significantly reduced. Using the gastrointestinal-protective agent lafutidine might therefore alleviate gastrointestinal toxicity, significantly reducing adverse events and improving the completion rate, potentially extending PFS and OS as a result of the longer

duration of anti-tumour pharmacotherapies. However, the present results must be interpreted with caution, as the greater age of patients in the non-lafutidine group might also have been important.

Previous studies have demonstrated the value of S-1 for a variety of cancer types, including gastrointestinal and head and neck cancer (12-14). However, numerous reports have also described treatment-limiting adverse events, and adverse event control is therefore important (16, 17).

We conducted a comparative investigation of previous studies of S-1-induced gastrointestinal damage and the gastrointestinal-protective effect of lafutidine. Oral fluorouracil, an anticancer agent, is used to treat not only gastric cancer, but also a wide range of other cancers, including head and neck cancer. For gastric cancer, the combined use of S-1 with surgery improves OS compared with surgery alone, and accumulating evidence supports the use of S-1 as adjuvant chemotherapy (13). S-1 has also been shown to be effective for head and neck cancer in various studies (16, 17). This agent has been shown to prolong OS compared with UFT as adjuvant chemotherapy but the incidence of adverse events was also high, and measures to reduce adverse events in future were considered necessary (4, 14). S-1 consists of tegafur, a prodrug converted to

fluorouracil, together with gimeracil, which inhibits dihydropyrimidine dehydrogenase, and oteracil, which inhibits the phosphorylation of fluorouracil in the digestive tract. When administered orally, oteracil reduces the gastrointestinal damage caused by fluorouracil. The gastrointestinal-protective action of lafutidine has been widely reported. Lafutidine has a powerful effect in suppressing the secretion of gastric acid *via* its H2-receptor antagonistic action (18), and acts to increase gastric mucus via capsaicin-sensitive sensory nerves (19). In basic experiments using rats with sodium dextran sulphate-induced ulcerative colitis, a comparison of lafutidine and famotidine to treat 5-fluorouracil-induced intestinal mucositis showed that rates of diarrhoea and weight loss were significantly lower in the lafutidine group (8). The present study of patients with head and neck cancer also found that taking lafutidine during S-1 treatment alleviated gastrointestinal toxicity. Namikawa *et al.* also reported that the use of lafutidine together with S-1 reduced the incidence of diarrhoea, and the incidence of diarrhoea was similarly significantly reduced in the present study (6). The gastrointestinal mucosal-protective action is likely mediated by the capsaicin-sensitive sensory neurons identified in the basic experiments on rats described above (8). Lafutidine was also reportedly effective in preventing the recurrence

of stomatitis during chemotherapy (20), but the present study did not identify any significant difference.

The limitations of this study include its nature as a retrospective study at a single institution with limited sample size, and the possibility of variation in patient attributes. At our hospitals, we also follow the approach of Namikawa *et al.* (6) in using mainly lafutidine as prophylaxis for S1-induced gastrointestinal toxicity. We therefore excluded patients taking other types of gastrointestinal mucosal-protective medication because of their small numbers, and were unable to compare these medications with lafutidine.

Our findings suggest that supportive therapy with lafutidine may be effective for improving the completion rate of oral S-1 therapy but the fact that patients in the non-lafutidine group were older may also have affected the results. We were unable to conduct age-stratified analyses of S-1 because of the small number of study patients. Increasing the completion rate of S-1 therapy will be an important issue in the future. Our results suggested that concomitant use of lafutidine may improve the completion rate. Further large-scale randomized controlled trials will be required to demonstrate the efficacy of this addition.

Conflicts of Interest

The Authors report no conflict of interest.

Authors' Contributions

Isaku Okamoto, Koichiro Yoshino, and Kiyoaki Tsukahara designed the study. Koichiro Yoshino wrote the main article text and prepared the Figure. Koichiro Yoshino, Isaku Okamoto, Hiroki Sato, Takuro Okada, Kunihiko Tokashiki, Takahito Kondo, Kiyoaki Tsukahara were involved with data collection. Isaku Okamoto and Koichiro Yoshino performed the analysis. All Authors discussed the results of the study, made comments on the article, and gave final approval of the version to be published.

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Table I. Criteria for dose reduction and resumption.

Parameter	**Dose reduction**	**Treatment resumption**
Leukocytes	<2,000 mm^{-3} (grade ≥3)	≥3,000 mm^{-3}
Neutrophils	<1,000 mm^{-3} (grade ≥3)	≥1,500 mm^{-3}
Platelets	<50,000 mm^{-3} (grade ≥3)	≥100,000 mm^{-3}
Haemoglobin	<8.0 g dl^{-1} (grade ≥3)	≥9.0 g dl^{-1}
Total bilirubin	≥3 mg dl^{-1}	<1.5 mg dl^{-1}
AST, ALT	≥150 IU l^{-1}	<100 IU l^{-1}
Creatinine	≥1.2 mg dl^{-1}	<1.2 mg dl^{-1}
Other adverse events	Grade ≥3	Grade ≤1

ALT: Alanine aminotransferase ; AST: aspartate aminotransferase.

Table II. Background characteristics of patients.

Characteristic		S-1 alone (n=22)	S-1 + lafutidine (n=41)	Whole cohort
Age, years	Mean	64	58	60
	Median (range)	65.5 (28-78)	58 (28-72)	62 (28-78)
Sex, n (%)	Male	18 (81.8)	31 (75.6)	49 (78)
	Female	4 (18.1)	10 (24.4)	14 (22)
History of smoking, n (%)	Non-smoker	2 (9.0)	9 (22.0)	11 (17)
	Smoker	13 (59.0)	29 (70.7)	42 (67)
	Unknown	7 (31.8)	3 (7.3)	10 (16)
History of alcohol use, n (%)	Non-drinker	3 (13.6)	7 (17.0)	10 (16)
	Drinker	14 (63.6)	27 (65.9)	41 (65)
	Unknown	5 (22.7)	7 (17.0)	12 (19)
ECOG PS, n (%)	0	21 (95.5)	41 (100.0)	62 (98)
	1	0	0	0 (0)
	2	1 (4.5)	0	1 (2)
	3	0	0	0 (0)
Primary tumour site, n (%)	Nasal cavity	0	1 (2.4)	1 (2)
	Nasopharynx	3 (13.6)	5 (12.2)	8 (13)
	Oropharynx	6 (27.3)	9 (22.0)	15 (24)
	Hypopharynx	4 (18.2)	12 (29.3)	16 (25)
	Larynx	5 (22.7)	5 (12.2)	10 (16)
	Oral cavity	3 (13.6)	10 (24.4)	13 (21)
T Category, n (%)	T1	3 (13.6)	6 (14.6)	9 (14)
	T2	5 (22.7)	11 (26.8)	16 (25)
	T3	5 (22.7)	10 (24.4)	15 (24)
	T4	9 (40.9)	14 (34.1)	23 (37)
N Category, n (%)	N0	4 (18.2)	4 (9.8)	8 (13)
	N1	4 (18.2)	5 (12.2)	9 (14)
	N2	10 (45.5)	28 (68.3)	38 (60)
	N3	4 (18.2)	4 (9.8)	8 (13)
M Category, n (%)	M0	19 (86.4)	39 (95.1)	58 (92)
	M1	3 (13.6)	2 (4.9)	5 (8)
UICC, n (%)	1	0	0	0 (0)
	2	0	0	0 (0)

	3	5 (22.7)	8 (19.5)	13 (21)
	4	17 (77.3)	33 (80.5)	50 (79)
Definitive treatment, n (%)	Surgery	13 (59.1)	29 (70.7)	42 (67)
	Radiation	14 (63.6)	26 (63.4)	40 (63)
	Surgery + radiation	7 (31.8)	13 (31.7)	20 (32)

ECOG PS: Eastern Cooperative Oncology Group performance status; UICC:

Union for International Cancer Control.

Table III. Grade 1 or above adverse events according to Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 (10).

Adverse event	N (Total)	S-1 alone (N=22), n (%)	S-1 + lafutidine (N=41), n (%)	*p*-Value*
Diarrhoea	8	7 (31.8)	1 (2.4)	0.00189
Vomiting	7	4 (18.2)	3 (7.3)	0.226
Oral mucositis	6	4 (18.2)	2 (4.9)	0.171
Fatigue	6	2 (9.1)	4 (9.8)	>0.99
Nausea	6	4 (18.2)	2 (4.9)	0.171
Loss of appetite	5	2 (9.1)	3 (7.3)	>0.99
Neutropenia	1	1 (4.5)	0 (0.0)	0.349
Anaemia	4	3 (13.6)	1 (2.4)	0.118
White blood cell count decreased	3	2 (2.0)	1 (1.0)	0.277
Dermatitis	2	0 (0.0)	2 (4.9)	0.538
Increased creatinine	2	1 (4.5)	1 (2.4)	>0.99

*Fisher’s exact test

Figure 1

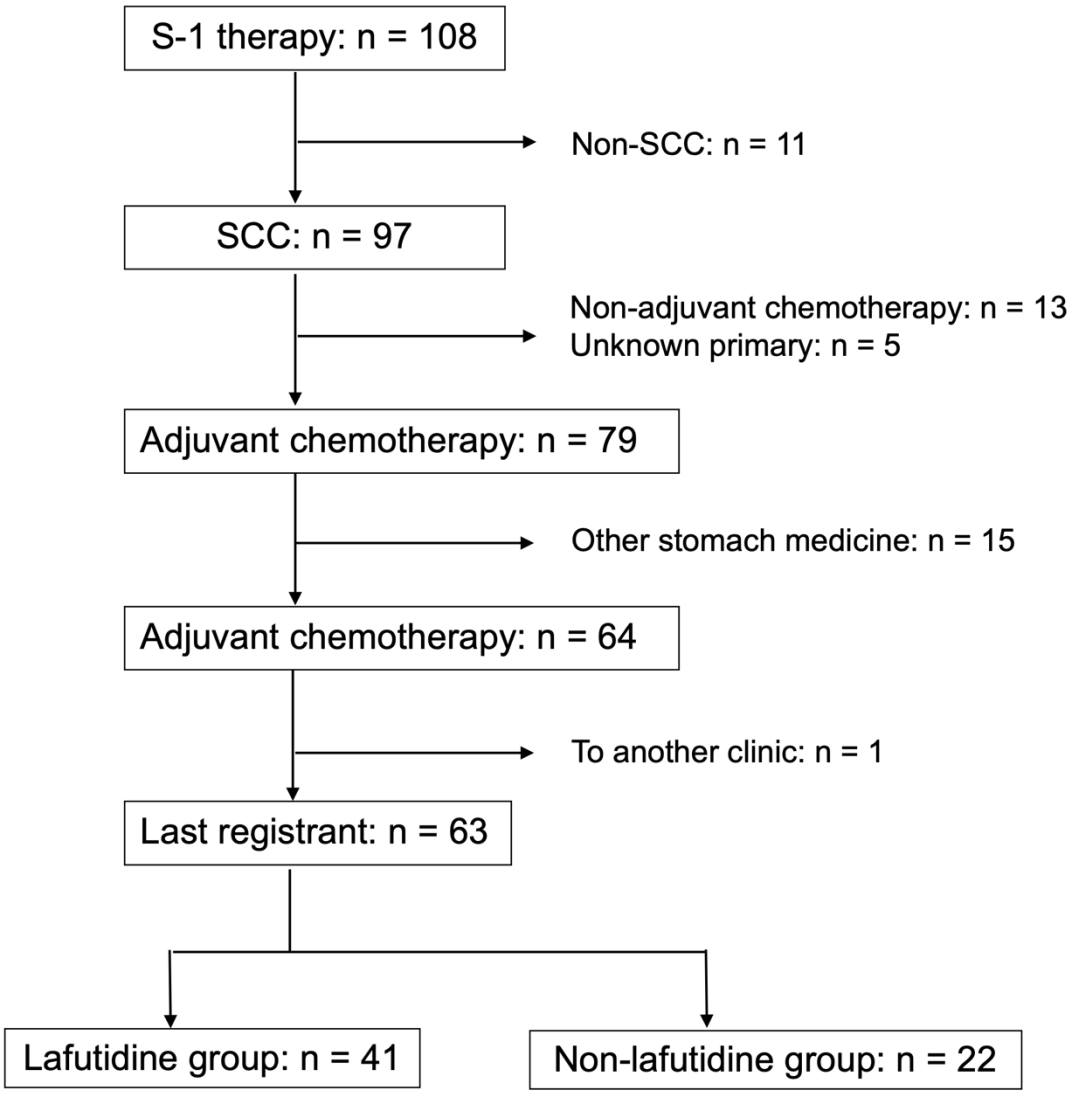
S-1 therapy: n = 108
Non-SCC: n = 11
SCC: n = 97
Non-adjuvant chemotherapy: n = 13
Unknown primary: n = 5
Adjuvant chemotherapy: n = 79
Other stomach medicine: n = 15
Adjuvant chemotherapy: n = 64
To another clinic: n = 1
Last registrant: n = 63
Lafutidine group: n = 41
Non-lafutidine group: n = 22

Figure 2

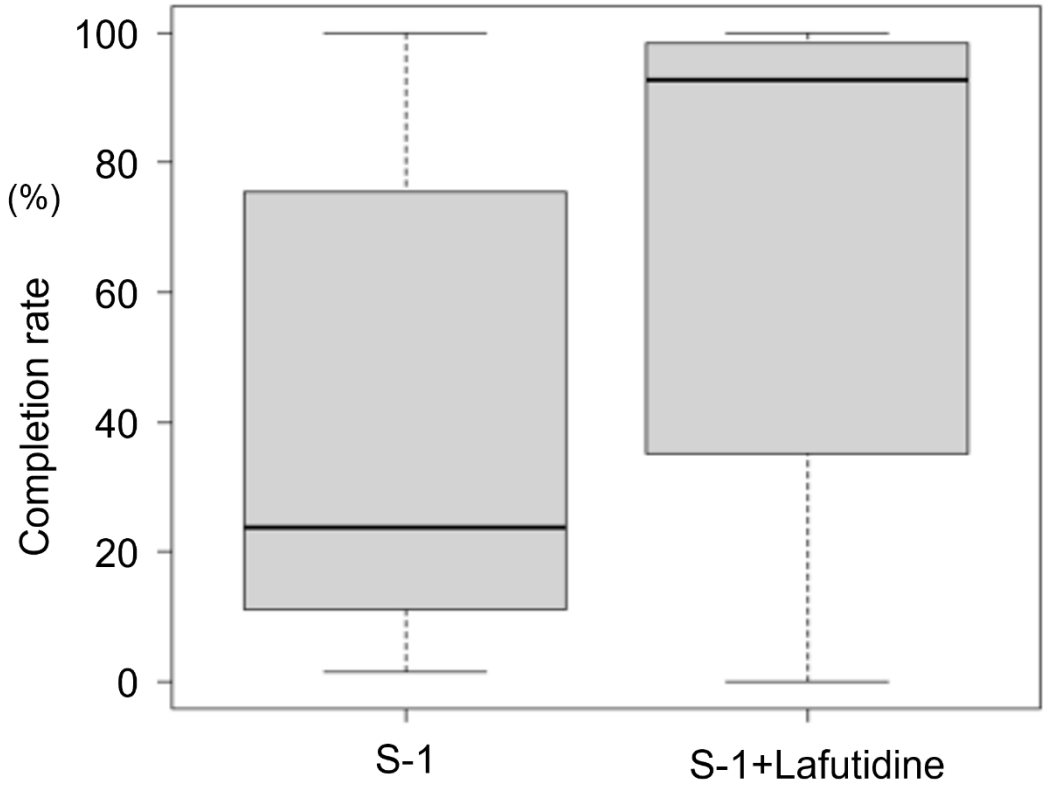

Figure 3

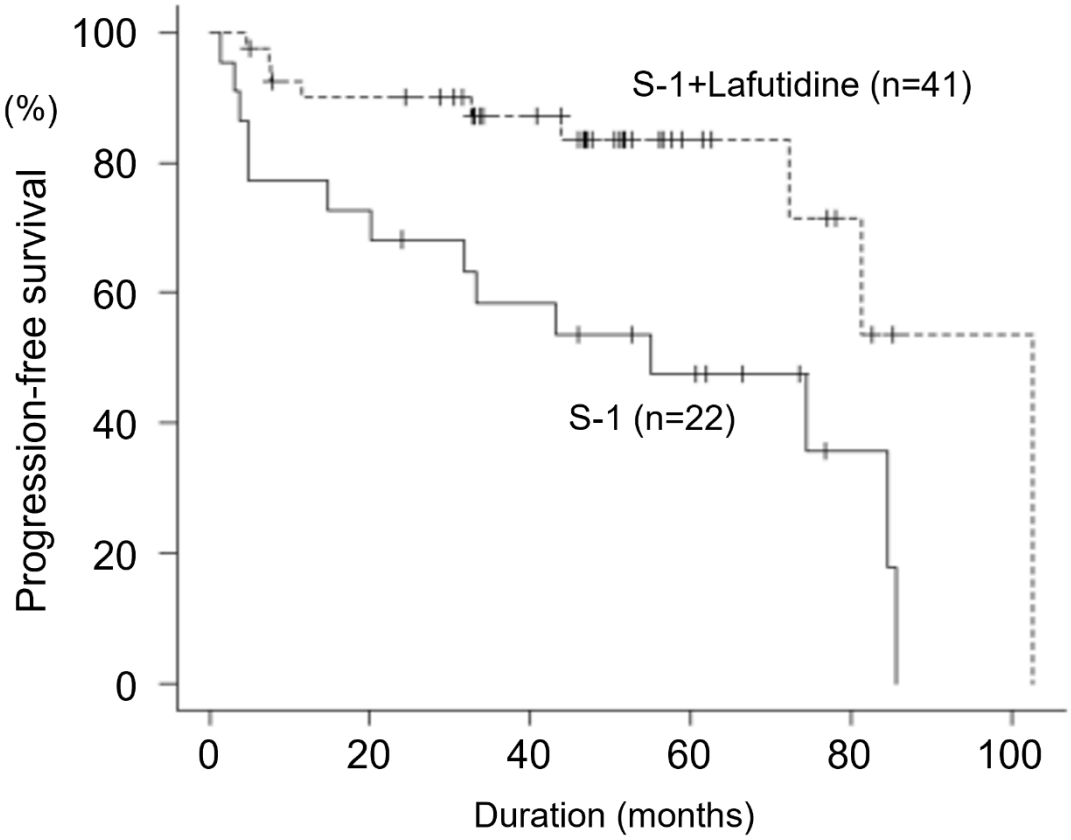
100
80
60
40
20
0
(%)
Progression-free survival
S-1+Lafutidine (n=41)
S-1 (n=22)
0
20
40
60
80
100
Duration (months)

Figure 4

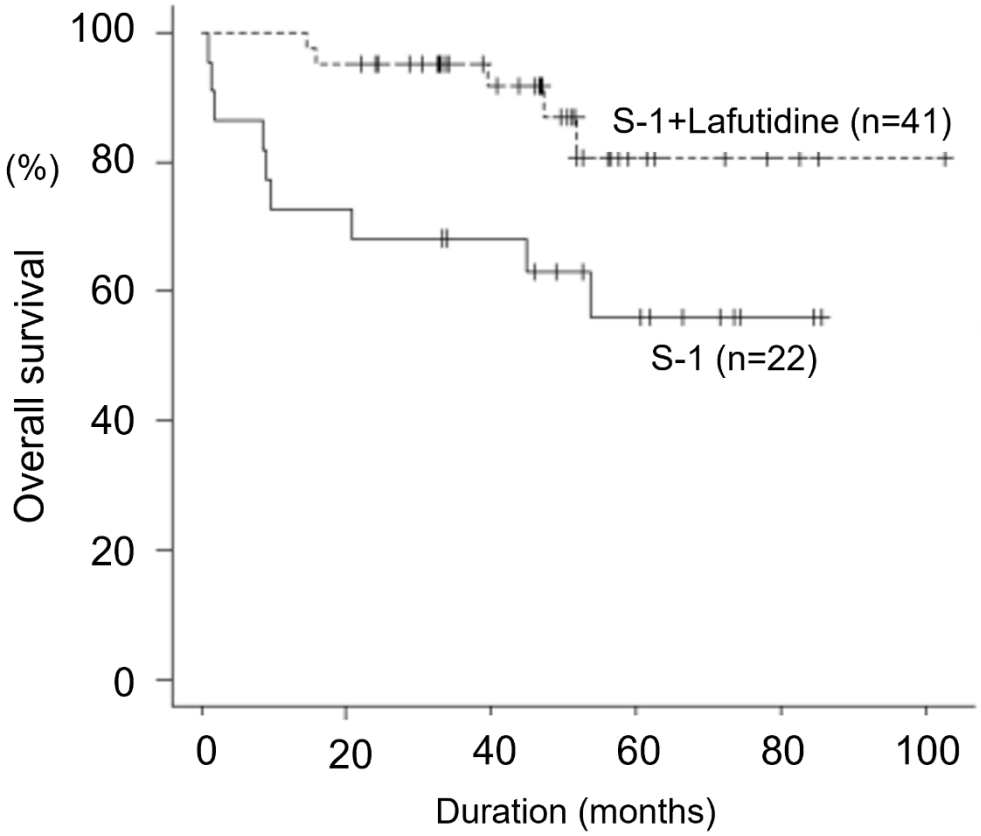
100
80
60
40
20
0
(%)
Overall survival
S-1+Lafutidine (n=41)
S-1 (n=22)
0
20
40
60
80
100
Duration (months)

Figure Legends

Figure 1. Study schema. Of the 103 patients who received S-1 therapy, a total of 63 were included in the analysis population, comprising 41 in the lafutidine group and 22 in the non-lafutidine group. SCC: Squamous cell carcinoma.

Figure 2. Completion rates. The S-1 completion rate was significantly higher in the lafutidine group than in the non-lafutidine group.

Figure 3. Progression-free survival. Progression-free survival was significantly prolonged in the lafutidine group compared to the non-lafutidine group.

Figure 4. Overall survival. Overall survival was significantly prolonged in the lafutidine group compared to the non-lafutidine group.