# Preoperative S-1 Therapy for Squamous Cell Carcinoma of The Head and Neck During the Waiting Period Before Surgery

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**Research Article**

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# Abstract

***Background***: In patients with squamous cell carcinoma of head and neck (SCCHN), delayed surgery can result in poorer postoperative function and prognosis due to the growth of the tumor and the extended surgery. Further, delay may even make the tumor unresectable. To prevent tumor growth during the waiting period before surgery, S-1 has been administrated preoperatively at several facilities in Japan. To date, however, the safety and efficacy of preoperative S-1 remains unclear.

***Methods***: We conducted a retrospective cohort study of 118 patients with SCCHN treated with S-1 before radical surgery at 2 institutions in Japan. We evaluated the safety of S-1 therapy, which was evaluated by the incidence of grade 3 or greater adverse events (AEs). The rate of achievement of the non-growth of tumors was also calculated.

***Results***: Regarding safety, 125 AEs of all grades were recorded in 71 patients (60%). Of these, grade 3 AEs were detected in 3 patients (3%), and no grade 4 or 5 AEs occurred. The non-growth rate of primary lesions and lymph node metastases was 89% and 85%, respectively.

***Conclusion***: Our data showed that preoperative S-1 therapy might be useful with acceptable toxicity on an outpatient basis in patients with SCCHN.


# Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is an aggressive malignancy with a mortality rate of 40–50% [1–4] which accounts for the majority of the deaths from head and neck cancers. Many SCCHN patients present with locoregionally advanced disease with lymph node metastasis. [5] Delay of the initiation of treatment in SCCHN is associated with tumor progression which can cause poorer postoperative function such as masticatory, swallowing disorder, dysarthria and cosmetic problems. [6–9] In addition, tumor growth also result in tracheostomy, inability to perform minimally invasive surgery such as transoral surgery, inability to preserve the larynx, or unresectability by invasion into critical organs such as the common and internal carotid artery. However, it tends to take long to time to prepare surgery for patients with advanced diseases due to the requirement of operation duration and medical staff.

S-1, a fluoropyrimidine preparation that combines tegafur with gimeracil and oteracil potassium, is an oral antitumor agent suitable for administration against SCCHN on an outpatient basis. Two phase II studies of S-1 therapy, one each in patients with advanced or recurrent head and neck cancer, reported effectiveness with acceptable toxicity. [10,11] Additionally, the beneficial effect of S-1 as adjuvant therapy was shown in a phase III study, [12] while other studies showed its effectiveness in combination with radiation therapy for SCCHN. [13,14]

Of note, several facilities in Japan have adopted S-1 therapy during the waiting period before surgery with an aim to suppress tumor growth and achieve individual specific goals, such as the prevention of carotid artery invasion and airway obstruction. However, since few cases of preoperative therapeutic evaluation

have been reported, no detailed data on S-1 therapy during the waiting period before surgery in SCCHN have been reported and the efficacy and safety of this therapy remains unclear.

Here, we conducted a multicenter retrospective cohort study to investigate the efficacy and safety of S-1 therapy during the waiting period before surgery in SCCHN.

## Results

# Patient characteristics and treatment

Characteristics of the 118 patients are summarized in Table 1. Median age was 65 years (range, 26-85 years) and males were predominant (78%). Nearly all patients were at PS 0 or 1. Most patients were in the normal range for BMI (64%). Primary tumor site was the oral cavity in 57 cases (48%), hypopharynx in 31 (26%), oropharynx in 11 (9%), larynx in 9 (8%), and other in 10 (8%). Further, 71% had a history of smoking and 75% had a history of drinking. As for tumor stage, both patients with early and advanced diseases were included, although no patients had distant metastases. Patients who underwent salvage surgery after definitive treatment accounted for 23%, including postoperative recurrence in 14% and post-irradiation recurrence in 16%. Ten percent had a history of chemotherapy.

Table 1
Patient characteristics at baseline.

| | N = 118 | (%) |
|---|---|---|
| Sex | | |
| Male | 92 | (78) |
| Female | 26 | (22) |
| Age [26-85 (median 65)] | | |
| < 65 years | 57 | (48) |
| ≥ 65 years | 61 | (52) |
| ECOG performance status | | |
| 0 | 86 | (73) |
| 1 | 31 | (26) |
| ≥ 2 | 1 | (1) |
| BMI [16-31.6 (median 21.2)] | | |
| < 18.5 | 20 | (17) |
| ≥ 18.5, < 25 | 75 | (64) |
| ≥ 25 | 23 | (19) |
| Primary tumor site | | |
| Oral cavity | 57 | (48) |
| Hypopharynx | 31 | (26) |
| Oropharynx | 11 | (9) |
| p16-positive | 3 | (3) |
| Larynx | 9 | (8) |
| External auditory canal | 3 | (3) |
| Paranasal sinus | 2 | (2) |
| Cervical esophagus | 2 | (2) |
| Unknown | 3 | (3) |
| Histology | | |
| Squamous cell carcinoma | 118 | (100) |

| | | N = 118 | (%) |
|---|---|---|---|
| Smoking | | | |
| | Ever | 84 | (71) |
| | Never | 34 | (29) |
| Alcohol | | | |
| | Ever | 89 | (75) |
| | Never | 29 | (25) |
| T category | | | |
| | 1 | 2 | (2) |
| | 2 | 35 | (30) |
| | 3 | 45 | (38) |
| | 4 | 3 | (3) |
| | 4a | 20 | (17) |
| | 0 [a] | 13 | (11) |
| N category | | | |
| | 0 | 45 | (38) |
| | 1 | 23 | (19) |
| | 2a | 3 | (3) |
| | 2b | 24 | (20) |
| | 2c | 5 | (4) |
| | 3b | 18 | (15) |
| M category | | | |
| | 0 | 118 | (100) |
| Salvage surgery | | | |
| | Yes | 27 | (23) |
| | No | 91 | (77) |
| Previous surgery | | | |
| | Yes | 16 | (14) |

| | N = 118 | (%) |
|---|---|---|
| No | 102 | (86) |
| Previous radiotherapy | | |
| Yes | 19 | (16) |
| No | 99 | (84) |
| Previous chemotherapy | | |
| Yes | 12 | (10) |
| Previous use of S-1 | 4 | (3) |
| No | 106 | (90) |
| Institution | | |
| IUHW | 75 | (64) |
| Kitasato University | 43 | (36) |

[a] T staging of recurrent cases with no primary lesion was defined as T0.

*ECOG* Eastern Cooperative Oncology Group, *IUWH* International University of Health and Welfare Mita Hospital, *BMI* Body mass index

Details of S-1 administration are summarized in Table 2. Median administration period was 14 days (range, 7-28 days), with 7-13 days in 26 cases (22%), 14-20 days in 81 (predominant; 69%), and 21-28 days in 11 (9%). Median period from the end of administration to surgery was 13 days (range, 5-35 days), with 5-13 days in 64 cases (predominant; 54%), 14-20 days in 33 (28%), and 21-35 days in 21 (18%). Hence, patients typically underwent surgery about one week after taking S-1 for two weeks. Administration dose was reduced by one step in 34 cases (29%), and administration was discontinued due to adverse events (AEs) in 6 cases (5%).

Table 2
Details of the administration of S-1.

| | N = 118 | (%) |
|---|---|---|
| Period of administration of S-1 [7-28 (median 14)] (days) | | |
| 7-13 | 26 | (22) |
| 14-20 | 81 | (69) |
| 21-28 | 11 | (9) |
| Period from the end of S-1 to surgery [5-35 (median 13)] (days) | | |
| 5-13 | 64 | (54) |
| 14-20 | 33 | (28) |
| 21-35 | 21 | (18) |
| Administered dose of S-1 | | |
| Standard | 84 | (71) |
| 1-step reduction | 34 | (29) |
| Discontinuation of administration | | |
| Yes | 6 | (5) |
| No | 112 | (95) |

# Characteristics of resected tumors

Resected tumors are characterized in Table 3. Maximum tumor diameter could be measured in 108 cases with a median of 27.5 mm (range, 0-90 mm) after formalin fixation. In 2 cases, the tumor had completely disappeared pathologically. Surgical margin was negative in 114 of 118 cases (97%). Differentiation was well, moderate, and poor in 37%, 52%, and 11%, respectively, in 98 cases. Positive rates of vascular invasion, lymphatic invasion, and perineural invasion were 51%, 38%, and 29%, respectively, in 101 cases.

Table 3
Characteristics of resected tumors.

| | | N | (%) |
|---|---|---|---|
| Maximum diameter (mm) (N = 108) | 0 – 90 (median 27.5) | | |
| Surgical margin (N = 118) | | | |
| | Positive | 4 | (3) |
| | Negative | 114 | (97) |
| Differentiation (N = 98) | | | |
| | Well | 36 | (37) |
| | Moderate | 51 | (52) |
| | Poor | 11 | (11) |
| Vascular invasion (N = 101) | | | |
| | Positive | 52 | (51) |
| | Negative | 49 | (49) |
| Lymphatic invasion (N = 101) | | | |
| | Positive | 38 | (38) |
| | Negative | 63 | (62) |
| Perineural invasion (N = 101) | | | |
| | Positive | 29 | (29) |
| | Negative | 72 | (71) |

# Safety (Adverse events)

AEs of the 118 patients during the study period are summarized in Table 4. For all grades, 125 AEs were detected in 71 patients (60%). Anemia was the most common AE (31%). No grade 4 or 5 AE were reported while grade 3 AEs were detected in 3 patients (3%), comprising one each of anemia, anorexia, and hypokalemia. Among these, 2 patients who developed grade 3 anemia or hypokalemia had the same AE of grade 2 before S-1 administration, respectively. S-1 was discontinued in 3 patients due to grade 2 maculopapular rash, grade 2 diarrhea plus grade 3 anorexia, and grade 2 watering of the eyes due to dacryocystitis. The median duration of administration for these 6 discontinued cases was 10 days (range, 7-14 days). Surgery was postponed in 3 patients, including 2 patients postponed for 6 and 7 days due to grade 1 fever, and 1 patients postponed for 12 days due to influenza of the patient's family. There was no cancellation of surgery due to AEs.

Table 4
Summary of adverse events (N=118).

| Adverse events | Any grade (N) | (%) | Grade 3 (N) | (%) |
|---|---|---|---|---|
| Anemia | 37 | (31) | 1 | (1) |
| Creatinine increased | 9 | (8) | 0 | (0) |
| Hyperkalemia | 9 | (8) | 0 | (0) |
| Hypoalbuminemia | 8 | (7) | 0 | (0) |
| Platelet count decreased | 7 | (6) | 0 | (0) |
| Chronic kidney disease | 5 | (4) | 0 | (0) |
| Rash maculopapular | 5 | (4) | 0 | (0) |
| Serum amylase increased | 5 | (4) | 0 | (0) |
| Anorexia | 3 | (3) | 1 | (1) |
| ALT increased | 3 | (3) | 0 | (0) |
| AST increased | 3 | (3) | 0 | (0) |
| CPK increased | 3 | (3) | 0 | (0) |
| Diarrhea | 3 | (3) | 0 | (0) |
| Fever | 3 | (3) | 0 | (0) |
| Hyponatremia | 3 | (3) | 0 | (0) |
| Hyperglycemia | 2 | (2) | 0 | (0) |
| Hypokalemia | 2 | (2) | 1 | (1) |
| Malaise | 2 | (2) | 0 | (0) |
| Nausea | 2 | (2) | 0 | (0) |
| Watering eyes | 2 | (2) | 0 | (0) |
| ALP increased | 1 | (1) | 0 | (0) |
| Dizziness | 1 | (1) | 0 | (0) |
| Epistaxis | 1 | (1) | 0 | (0) |
| Hypercalcemia | 1 | (1) | 0 | (0) |
| Hyperuricemia | 1 | (1) | 0 | (0) |
| Neutrophil count decreased | 1 | (1) | 0 | (0) |
| Pharyngitis | 1 | (1) | 0 | (0) |

| Adverse events | Any grade (N) | (%) | Grade 3 (N) | (%) |
|---|---|---|---|---|
| Pruritus | 1 | (1) | 0 | (0) |
| WBC decreased | 1 | (1) | 0 | (0) |
| Total | 125 | | 3 | |
| | (71 patients) | (60) | (3 patients) | (3) |

*ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *CPK* Creatine phosphokinase, *ALP* Alkaline phosphatase, *WBC* White blood cell

# Efficacy (Tumor response)

Tumor response to preoperative S-1 therapy is summarized in Table 5. In the 35 cases that could be image-evaluated, median diameter of the primary site was 32 mm (range, 10-72 mm) and median rate of change in diameter after administration of S-1 was -10% (range, -70-+50%). Thirty-one cases (89%) were evaluated as effective (≥ 0% decrease) and 4 (11%) as non-effective (> 0% increase). Further, in the 27 cases that could be image-evaluated, median diameter of the metastatic lymph node was 21 mm (range, 11-73 mm) and median rate of change in diameter was ±0% (range, -42-+38%). Twenty-three cases (85%) were evaluated as effective and 4 (15%) as non-effective.

Table 5
Tumor response to preoperative S-1 therapy.

| | Primary site | | Metastatic lymph node | |
|---|---|---|---|---|
| | N=35 | | N=27 | |
| Maximum diameter (mm) | 10 - 72 | (median 32) | 11 - 73 | (median 21) |
| Rate of change after S-1 therapy (%) | -70 - +50 | (median -10) | -42 - +38 | (median ±0) |
| Tumor response | N | (%) | N | (%) |
| Effective (≥ 0% decrease) | 31 | (89) | 23 | (85) |
| Non-effective (> 0% increase) | 4 | (11) | 4 | (15) |

Figure 1 shows a representative case with S-1 therapy before surgery.

# Factors affecting the efficacy and the safety of S-1 therapy

Background factors and details of S-1 administration were not significantly associated with tumor non-growth or the occurrence of grade 3 AEs with S-1 therapy (Supplemental table 1, 2). Regarding pathological features, although no association was seen with the degree of differentiation, efficacy rate was higher in cases without vascular (100% vs 76%), lymphatic (92% vs 75%) or perineural invasion (92% vs 78%) than in cases with these invasions (Table 6).

Table 6
Analysis of the characteristics of resected tumors on efficacy.

| | | Effective [a] | Non-effective [a] | p-value |
|---|---|---|---|---|
| Differentiation | Well (N= 13) | 11 (85) | 2 (15) | 1 |
| | Moderate (N= 17) | 15 (88) | 2 (12) | |
| | Poor (N= 2) | 2 (100) | 0 (0) | |
| Vascular invasion | Positive (N= 17) | 13 (76) | 4 (24) | 0.103 |
| | Negative (N= 17) | 17 (100) | 0 (0) | |
| Lymphatic invasion | Positive (N= 8) | 6 (75) | 2 (25) | 0.229 |
| | Negative (N= 26) | 24 (92) | 2 (8) | |
| Perineural invasion | Positive (N= 9) | 7 (78) | 2 (22) | 0.281 |
| | Negative (N= 25) | 23 (92) | 2 (8) | |

[a] Evaluation of the primary lesion.

# Discussion

To our knowledge, our cohort has the largest number of the patients with SCCHN who was treated with S-1 preoperatively. In Japan, many patients have been treated with S-1 before surgery in purpose of preventing tumor growth when surgery could not be carried out promptly, without detailed data on the safety and efficacy of preoperative S-1 administration.

With regard to safety, no grade 4 or 5 AEs were reported, and grade 3 AEs occurred in only 3% in our cohort. Only 5% of patients discontinued treatment due to AEs. Although surgery was postponed for 6 to 12 days in 3 of 118 patients, the surgical margins were free in these patients. There was no patient whose surgery was canceled due to AEs of S-1. AEs of S-1 in this study were less frequent and milder than those in previous clinical trials, which might be influenced by the shorter administration period and higher frequency of dose reduction. Also, mild AEs might be underestimated due to the retrospective nature of the study, although severe AEs were less likely to be oversight.

Even though the main purpose of S-1 therapy in our cohort was to prevent the various problems associated with potential tumor growth during the waiting period before surgery, the efficacy of postoperative S-1 was unclear due to the retrospective, uncontrolled design of this study. There is also no evidence that preoperative chemotherapy improves survival in patients with SCCHN. [15–17] The therapeutic effect of the primary site and metastatic lymph node could be evaluated by imaging in only 35 and 27 out of 118 patients enrolled in this study, however, the non-growth rate was as high as 89% and 85%, respectively. It seemed that pathological features such as vascular invasion, lymphatic invasion and

perineural invasion might be associated with the tumor growth under preoperative S-1 administration. Since there is no consensus to reduce the extent of the resection area after the tumor shrinkage with preoperative chemotherapy in SCCHN, the surgical margins were set based on the maximum tumor range.

Taken together, our data showed that S-1 therapy had acceptable safety profile when administrated during the preoperative waiting period in patients with SCCHN. Prospective, randomized controlled trial of preoperative S-1 therapy in patients with SCCHN is warranted to elucidate the efficacy of this regimen.

## Patients And Methods

# Patients and tumors

The study was conducted under a retrospective cohort design that enrolled patients with SCCHN treated with S-1 before radical surgery from January 2012 to November 2020 at two facilities in Japan: Kitasato University Hospital and International University of Health and Welfare Mita Hospital. The charts of 133 consecutive patients who required more than 1 month before surgery and treated with S-1 were reviewed. All cases were histologically diagnosed as SCCHN in the treating facility. We excluded patients with administration of 2 or more courses of S-1, with a dose reduction of 2 steps or more, and with treatment for less than 7 days or every other day. We also excluded cases in which the patient cancelled surgery regardless of S-1 administration. Finally, 118 patients were eligible for analysis. Collected information included patient and tumor characteristics, imaging examinations, treatment modality, histological findings including surgical margin and AEs. Clinical stage was classified using the 8th edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM staging system and Eastern Cooperative Oncology Group performance status (ECOG PS) was evaluated just prior to administration of S-1. T category of recurrent cases without a primary lesion was defined as T0. AEs were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Review Boards (IRBs) of the two facilities. With regard to consent, informed consent was waived by the IRBs. Patients could reject participation by opting-out in response to an announcement on the institutions' web sites.

# Treatment and follow-up

Patients received the standard dose of S-1 of 80 mg/day (body surface area [BSA] <1.25 $m^2$), 100 mg/day (BSA ≥1.25 to <1.5 m2), or 120 mg/day (BSA ≥1.5 m2) in two divided doses [11,12,18] for 1-4 weeks as 1 course, followed by a rest of at least one week until operation as a basic policy. Administration period and dose reduction were determined by the attending physician in consideration of the patient's general condition and period until surgery. The extent of resection was determined based solely on the maximum size of the tumor, independent of tumor reduction. Medical examination and blood tests were performed several times during the period from the start of administration to surgery to

evaluate AEs. Imaging examination by MRI, CT or both was performed in almost all cases just before or immediately after the start of S-1 administration. Imaging immediately before surgery was mainly limited to cases requiring finalization of treatment strategy. Imaging evaluation was performed by radiologists specializing in the head and neck area or head and neck cancer specialists.

# Outcomes

The endpoint of this study was safety of S-1 therapy, which was evaluated by the incidence of grade 3 or higher AEs. Effectiveness was defined by the non-growth of tumors. The rate of non-growth in image-evaluable cases was also calculated in patients whose imaging data before and after S-1 administration were available.

# Statistical analysis

We used Fisher's exact test to compare categorical variables between groups. P-values for comparison among multiple groups were corrected using the Bonferroni method. All statistical analyses were performed using EZR [19] version 1.51 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface, together with the R software environment for statistical computing and graphics (The R Foundation for Statistical Computing, Vienna, Austria). P-values of $< 0.05$ were considered statistically significant.

## Declarations

# Competing interests

The authors declare no competing interests.

# Author contributions

Conceptualization: T.M.; Methodology: T.M., C.F., and H.T.; Formal analysis and investigation: T.M., C.F., and H.T.; Acquisition of data: S.M., T.M., Y.T., K.M., K.K., S.T., and K.M.; Writing - original draft preparation: T.M.; Writing - review and editing: All authors; Supervision: K.M., S.K., and T.Y.

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# Data Availability

The datasets generated in the current study are available from the corresponding author on request.

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# Figures

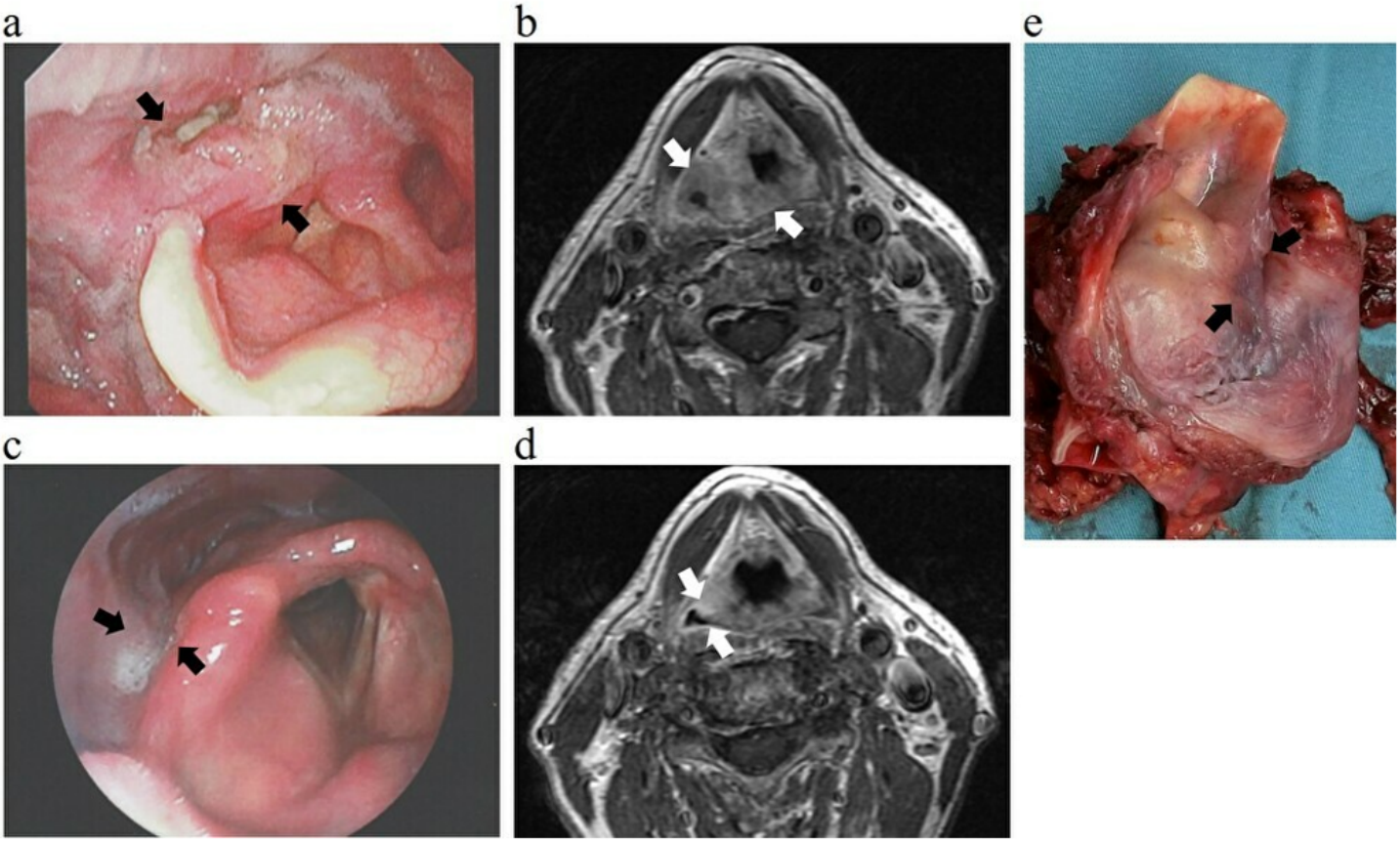


**Figure 1**

Hypopharyngeal carcinoma (cT3N0M0) was treated with S-1 during the waiting period before surgery at the standard dose for 14 days. **a, b:** Endoscopic findings and cervical MRI (axial contrast-enhanced T1WI) revealed a tumor (arrows) with a diameter of 30 mm before S-1 therapy. **c, d:** The tumor (arrows) decreased to diameter of 11 mm after S-1 therapy just before surgery. **e:** Total pharyngolaryngectomy was performed as scheduled; maximum tumor diameter of the resected specimen was 11 mm and surgical margin was negative.

## Supplementary Files

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