**Table 1** Patient characteristics

| Characteristics | Number of subjects (%) | | |
|---|---|---|---|
| | Total, $n = 72$ | Early phase II study, $n = 36$ | Late phase II study, $n = 36$ |
| Sex | | | |
| Male | 56 (77.8) | 30 (83.3) | 26 (72.2) |
| Female | 16 (22.2) | 6 (16.7) | 10 (27.8) |
| Age | | | |
| Median age (range) | 61 (41–74) | 60.5 (44–74) | 62.5 (41–74) |
| P.S. (ECOG) | | | |
| 0 | 48 (66.7) | 22 (61.1) | 26 (72.2) |
| 1 | 22 (30.6) | 13 (36.1) | 9 (25.0) |
| 2 | 2 (2.8) | 1 (2.8) | 1 (2.8) |
| Disease status | | | |
| Advanced | 25 (34.7) | 10 (27.8) | 15 (41.7) |
| Recurrent | 47 (65.3) | 26 (72.2) | 21 (58.3) |
| Histopathological diagnosis | | | |
| Squamous cell carcinoma | 61 (84.7) | 32 (88.9) | 29 (80.6) |
| Adenoid cystic carcinoma | 4 (5.6) | 1 (2.8) | 3 (8.3) |
| Others | 7 (9.7) | 3 (8.3) | 4 (11.1) |
| Primary lesion | | | |
| Oral cavity | 8 (11.1) | 8 (22.2) | 0 |
| Paranasal cavity | 8 (11.1) | 3 (8.3) | 5 (13.9) |
| Nasopharynx | 8 (11.1) | 4 (11.1) | 4 (11.1) |
| Oropharynx | 12 (16.7) | 6 (16.7) | 6 (16.7) |
| Hypopharynx | 18 (25.0) | 7 (19.4) | 11 (30.6) |
| Larynx | 6 (8.3) | 3 (8.3) | 3 (8.3) |
| Salivary gland | 7 (9.7) | 1 (2.8) | 6 (16.7) |
| Others | 5 (6.9) | 4 (11.1) | 1 (2.8) |
| Prior treatment | | | |
| Chemotherapy* | 62 (86.1) | 32 (88.9) | 30 (83.3) |
| Cisplatin-based chemotherapy | 55 (76.4) | 29 (80.6) | 26 (72.2) |
| Others | 7 (9.7) | 3 (8.3) | 4 (11.1) |
| Surgery | 36 (50.0) | 20 (55.6) | 16 (44.4) |
| Radiotherapy | 60 (83.3) | 30 (83.3) | 30 (83.3) |

*PS* performance status, *ECOG* Eastern Cooperative Oncology Group

* Including adjuvant chemotherapy, neoadjuvant chemotherapy, and chemoradiotherapy

## Efficacy

Thirty-six patients in each study were assessed for efficacy (Table 3). Overall response rates (RRs) in the early and late trial were 33.3% (95% CI: 18.6, 51.0%) and 36.1% (95% CI: 20.8, 53.8%), respectively. In combined analysis of two trials, RR according to WHO and RECIST criteria were 34.7% (95% CI: 23.9, 46.9%) and 29.0% (95% CI: 18.7, 41.2%), respectively. RR according to the WHO criteria in the 55 patients who received prior platinum-based chemotherapy was 32.7% and 30.4% in the 23 patients who received prior platinum-based chemotherapy for recurrent/metastatic disease (Table 4). RR in the 60 patients who received prior radiotherapy, including adjuvant therapy, neoadjuvant therapy, and chemoradiotherapy, was 30.0 and 58.3% in the 12 patients who did not receive prior radiotherapy.

The median duration of response was 8.5 months (95% CI: 5.4, 11.5 months) in the early trial, 6.9 months (95% CI: 3.2, 7.9 months) in the late trial, and 7.4 months (95% CI: 5.4, 9.4 months) in total.

The median follow-up period in all patients was 13.8 months (range: 1.6-33.8 months). Median TTP and MST were 3.4 months (95% CI: 3.0, 4.6 months; Fig. 1) and 14.3 months (95% CI: 11.0, 19.4 months; Fig. 2), respectively. In the 64 patients excluding those with nasopharyngeal cancer, median TTP and MST were 3.2 months (95% CI: 2.9, 4.3 months) and 13.0 months

**Table 2** Adverse events

| | Total ($n = 72$) | | | | Early phase II study ($n = 36$) | | | | Late phase II study ($n = 36$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≥Grade 1 | | ≥Grade 3 | | ≥Grade 1 | | ≥Grade 3 | | ≥Grade 1 | | ≥Grade 3 | |
| | No. of patients | % | No. of patients | % | No. of patients | % | No. of patients | % | No. of patients | % | No. of patients | % |
| Nausea | 22 | 30.6 | 2 | 2.8 | 9 | 25.0 | 1 | 2.8 | 13 | 36.1 | 1 | 2.8 |
| Anorexia | 19 | 26.4 | 4 | 5.6 | 10 | 27.8 | 1 | 2.8 | 9 | 25 | 3 | 8.3 |
| Constipation | 22 | 30.6 | 6 | 8.3 | 10 | 27.8 | 5 | 13.9 | 12 | 33.3 | 1 | 2.8 |
| Fatigue | 47 | 65.3 | 2 | 2.8 | 25 | 69.4 | 1 | 2.8 | 22 | 61.1 | 1 | 2.8 |
| Peripheral neuropathy | 55 | 76.4 | 4 | 5.6 | 27 | 75.0 | 1 | 2.8 | 28 | 77.8 | 3 | 8.3 |
| Pneumonitis | 8 | 11.1 | 4 | 5.6 | 5 | 13.9 | 3 | 8.3 | 3 | 8.3 | 1 | 2.8 |
| Alopecia | 68 | 94.4 | | | 34 | 94.4 | | | 34 | 94.4 | | |
| Rash | 28 | 38.9 | | | 15 | 41.7 | | | 13 | 36.1 | | |
| ALT | 25 | 34.7 | | | 17 | 47.2 | | | 8 | 22.2 | | |
| Leukopenia | 65 | 90.3 | 27 | 37.5 | 32 | 88.9 | 13 | 36.1 | 33 | 91.7 | 14 | 38.9 |
| Neutropenia | 60 | 83.3 | 22 | 30.6 | 29 | 80.6 | 13 | 36.1 | 31 | 86.1 | 9 | 25.0 |
| Anemia | 59 | 81.9 | 9 | 12.5 | 29 | 80.6 | 3 | 8.3 | 30 | 83.3 | 6 | 16.7 |
| Thrombocytopenia | 7 | 9.7 | | | 6 | 16.7 | | | 1 | 2.8 | | |

*ALT* alanine aminotransferase

**Table 3** Response according to WHO and RECIST criteria

| Criteria | Study | Number of patients | | | | | | RR (%) | 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| | | Assessable patients | CR | PR | NC/SD | PD | NE | | |
| WHO | Total | 72 | 5 | 20 | 23 | 18 | 6 | 34.7 | 23.9, 46.9 |
| | Early | 36 | 2 | 10 | 9 | 11 | 4 | 33.3 | 18.6, 51.0 |
| | Late | 36 | 3 | 10 | 14 | 7 | 2 | 36.1 | 20.8, 53.8 |
| RECIST | Total | 69 | 4 | 16 | 33 | 9 | 7 | 29.0 | 18.7, 41.2 |
| | Early | 35 | 2 | 7 | 15 | 7 | 4 | 25.7 | 12.5, 43.3 |
| | Late | 34 | 2 | 9 | 18 | 2 | 3 | 32.4 | 17.4, 50.5 |

*CR* complete response, *PR* partial response, *NC* no change, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *RR* response rate, *CI* confidence interval, *WHO* World Health Organization, *RECIST* response evaluation criteria in solid tumors

(95% CI: 9.9, 16.9 months), respectively. As 11 patients (15.3%) had non-squamous cell carcinomas histology, which included 4 with adenoid cystic carcinoma and 7 with either mucoepidermoid tumor, adenocarcinoma, poorly differentiated carcinoma, acinar cell carcinoma, carcinoma, large cell carcinoma, or undifferentiated carcinoma, MST was also determined excluding these patients. MST was 13.4 months in the 61 patients with squamous cell carcinomas and 11.7 months in the 45 patients with squamous cell carcinomas of the oral cavity, paranasal cavity, oropharynx, hypopharynx, and larynx cancer. In the 23 patients who had received prior platinum-based chemotherapy for recurrent/metastatic disease, median TTP and MST were 3.2 months (95% CI: 2.5, 6.7 months) and 11.4 months (95% CI: 7.4, 19.4 months), respectively.

## Discussion

Here, we conducted early and late phase II trials of weekly paclitaxel in patients with recurrent or metastatic HNC. Results demonstrated comparable safety and efficacy between the two trials. Further, the combined RR of the two trials was comparable to those previously reported in studies of tri-weekly paclitaxel in patients with advanced or recurrent HNC [6, 27]. All adverse events that occurred in the two trials were manageable, and no treatment-related deaths were observed. Although most patients had received prior chemotherapy, MST was 14.3 months, which was superior to that of previous studies in first-line patients with recurrent or metastatic HNC.

Of interest, MST in the 64 patients excluding those with nasopharyngeal cancer and in the 23 who had received

**Table 4** Response rates according to patient characteristics (WHO)

| Characteristic | Number of patients | | | | | RR (%) |
|---|---|---|---|---|---|---|
| | CR | PR | NC | PD | NE | |
| Sex | | | | | | |
| Male | 3 | 16 | 19 | 14 | 4 | 33.9 |
| Female | 2 | 4 | 4 | 4 | 2 | 37.5 |
| Age (Years) | | | | | | |
| <65 | 4 | 12 | 12 | 16 | 6 | 32.0 |
| ≥65 | 1 | 8 | 11 | 2 | | 40.9 |
| Histopathological diagnosis | | | | | | |
| Squamous cell carcinoma | 3 | 16 | 21 | 16 | 5 | 31.1 |
| Adenoid cystic carcinoma | | 1 | 1 | 2 | | 25.0 |
| Others | 2 | 3 | 1 | | 1 | 71.4 |
| Primary lesion | | | | | | |
| Oral cavity | | 4 | 1 | 2 | 1 | 50.0 |
| Nasal cavity | | | | 1 | | 0 |
| Paranasal cavity | 1 | 2 | 4 | 1 | | 37.5 |
| Maxillary sinus | | | | 1 | | 0 |
| Nasopharynx | 1 | 3 | 3 | | 1 | 50.0 |
| Oropharynx | 1 | 4 | 3 | 4 | | 41.7 |
| Hypopharynx | 1 | 4 | 8 | 3 | 2 | 27.8 |
| Larynx | | 1 | 2 | 2 | 1 | 16.7 |
| Salivary gland | 1 | 2 | 1 | 2 | 1 | 42.9 |
| Tympanum | | | 1 | | | 0 |
| External auditory canal | | | | 2 | | 0 |
| Prior radiotherapy | | | | | | |
| None | | 7 | 1 | 3 | 1 | 58.3 |
| Radiotherapy* | 5 | 13 | 22 | 15 | 5 | 30.0 |
| Prior chemotherapy | | | | | | |
| None | 1 | 3 | 3 | 2 | 1 | 40.0 |
| Cisplatin-based chemotherapy | 4 | 14 | 17 | 16 | 4 | 32.7 |
| Others | | 3 | 3 | | 1 | 42.9 |

*CR* complete response, *PR* partial response, *NC* no change, *PD* progressive disease, *NE* not evaluable, *RR* response rate, *WHO* World Health Organization

* Including adjuvant therapy, neoadjuvant therapy, and chemoradiotherapy

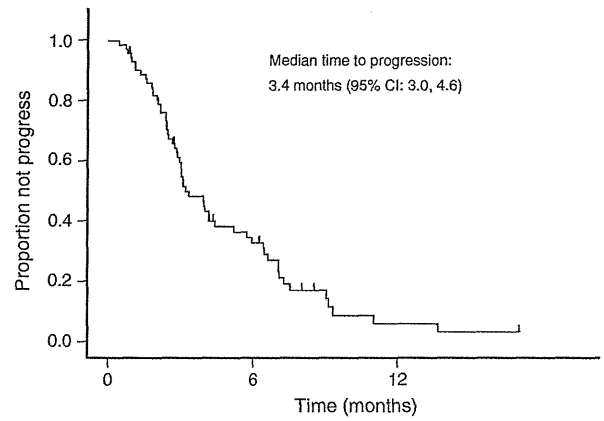


**Fig. 1** Combined time to progression from the early and late phase II studies. The median time to progression was 3.4 months (95% CI: 3.0, 4.6 months)

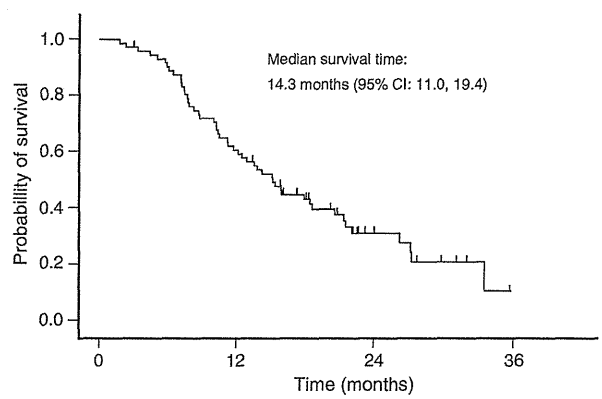


**Fig. 2** Combined overall survival from the early and late phase II studies. The median follow-up time of patients for overall survival was 13.8 months, with a median overall survival time of 14.3 months (95% CI: 11.0, 19.4 months)

prior platinum-based chemotherapy for recurrent/metastatic disease was 13.0 and 11.4 months, respectively. Allowing for the fact that this was a nonrandomized trial with a relatively small number of patients, these results are nevertheless better than those in the previous studies, particularly in showing that weekly paclitaxel was active in the treatment of HNC whether patients had received prior platinum-based chemotherapy or not.

Recently, the addition of cetuximab to platinum-based chemotherapy was shown to significantly prolong overall survival without exacerbating chemotherapy-associated toxicity or quality of life in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) [10]. Furthermore, the addition of cetuximab to paclitaxel was also shown to exert promising activity in a first-line setting of a phase II trial, which had an RR of 71% and a complete response rate of 20%. Weekly paclitaxel might therefore be a good alternative to platinum-based chemotherapy for first-line patients with recurrent or metastatic SCCHN.

Treatment options for patients with recurrent or metastatic HNC who are refractory to platinum-based chemotherapy are limited. Several second-line chemotherapy regimens with cytotoxic agents, including methotrexate, vinorelbine, bleomycin, docetaxel, and S-1, have been investigated in the treatment of patients with recurrent or metastatic HNC after previous platinum-based chemotherapy [7, 11–14, 36]. Response rates and MST in these studies were 10–46.2% and less than 5 months, respectively, and it has accordingly not been possible to draw definitive conclusions on their clinical benefit.

Recently, a single institutional prospective study of weekly paclitaxel (80 mg/m$^2$, weekly, 6 consecutive weeks) in SCCHN patients in whom platinum-based chemotherapy failed demonstrated a response rate of 43.3% and MST of 8.5 months [9]. Although this rate is superior to that of the present study, the study was conducted at a single institution and had no independent safety and efficacy assessment committee, while our study was a multicenter trial with independent safety and efficacy assessment committees. Further, our present study demonstrated a better duration of response and survival, which might be associated with the higher dose of paclitaxel in the present study.

A combined analysis of second-line use of cetuximab with or without platinum-based chemotherapy for patients with recurrent/metastatic SCCHN in whom platinum-based chemotherapy failed concluded that cetuximab would be effective as monotherapy and could be considered a therapeutic option [29]. However, the response rate, median TTP and MST of cetuximab alone in these patients were 13%, 2.3, and 5.9 months, respectively, indicating the need for further optimization of treatment options.

Although the number of patients who had previously received platinum-based chemotherapy for recurrent/metastatic disease in the present study was small, weekly paclitaxel showed a superior response rate and survival to that of previously reported agents and may therefore also be promising in second-line treatment following cisplatin-based regimens. Recently, weekly taxane-based chemotherapy was shown to exhibit promising activity as an induction chemotherapy in the primary therapy setting [17, 25, 33], suggesting that this dose-dense strategy may be particularly applicable to sequential treatment programs for HNC.

Long-term administration of weekly paclitaxel increases the incidence and severity of peripheral neuropathy, which often reduces quality of life. In our present patients who experienced peripheral neuropathy, 14.5% recovered and 7.3% remitted, while 78.2% failed to recover by the end of the protocol. Such sustained peripheral neuropathy may be limiting for patients receiving longer-term palliative therapy. Several studies have investigated anti-neuropathy drugs, including amifostine, gabapentin, and vitamin E, but all failed to demonstrate any benefit for these patients [2, 8, 18, 19, 21, 23]. The development of effective anti-neuropathy drugs is desirable.

Several limitations of the present study warrant mention. First, subjects included eight patients with nasopharyngeal cancer, which is considered to carry a better prognosis than other HNCs. Second, subjects included chemo-naive patients and patients who had not been confirmed to be refractory to platinum-based chemotherapy. Third, the present trials were nonrandomized, and differences in patient populations due to selection bias may have influenced outcomes and toxicity rates and thereby limit comparisons between studies. Fourth, the study included a range of histological subtypes. In other words, the subjects represented a markedly heterogeneous population.

In summary, this study demonstrated that weekly paclitaxel has promising activity with acceptable toxicity in the treatment of recurrent or metastatic HNC. Paclitaxel may be a good treatment option for recurrent or metastatic HNC.

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# Phase I trial of chemoradiotherapy with the combination of S-1 plus cisplatin for patients with unresectable locally advanced squamous cell carcinoma of the head and neck

Makoto Tahara,[1,4,5] Hironobu Minami,[2,6] Mitsuhiko Kawashima,[3] Kenji Kawada,[2,7] Hirofumi Mukai,[2] Minoru Sakuraba,[4] Kazuto Matsuura,[4,8] Takashi Ogino,[3] Ryuichi Hayashi[4] and Atsushi Ohtsu[1]

[1]Departments of Gastroenterology and Gastrointestinal Oncology, [2]Hematology and Medical Oncology, [3]Radiation Oncology, and [4]Head and Neck Oncology & Plastic and Reconstructive Surgery, National Cancer Center Hospital East, Chiba, Japan

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**The aim of the present study was to determine the maximum tolerated dose (MTD) of S-1 in combination with chemoradiotherapy (CRT) in patients with unresectable locally advanced squamous cell carcinoma of the head and neck, and evaluate the difference in pharmacokinetics of S-1 when administered as a suspension via a feeding tube or orally as a capsule. Chemotherapy consisted of administration of S-1 twice daily on days 1–14 at escalating doses of 40, 60 and 80 mg/m$^2$ per day, and cisplatin at 20 mg/m$^2$ per day on days 8–11, repeated twice at a 5-week interval. Single daily radiation of 70 Gy in 35 fractions was given concurrently starting on day 1. Two additional cycles of chemotherapy were planned after the completion of CRT. Before starting CRT, each patient received S-1 via two different administration methods. Twenty-two patients were enrolled. The MTD was reached with S-1 at 80 mg/m$^2$ per day, with two of six patients experiencing febrile neutropenia lasting more than 4 days. All four patients whose creatinine clearance was decreased to <60 mL/min after the first cycle of chemotherapy developed febrile neutropenia lasting more than 4 days. Pharmacokinetic analysis revealed that the 5-fluorouracil area under the curve did not significantly differ by the administration route. S-1 at 60 mg/m$^2$ per day for 14 days was well tolerated with concurrent CRT. Administration of S-1 as a suspension or by whole capsule can be considered therapeutically interchangeable. Although these data are preliminary, activity was highly promising, and this approach warrants further investigation. (*Cancer Sci* 2011; 102: 419–424)**

Head and necks cancers are the sixth most common cancer in the world, and approximately 500 000 new cases are projected annually.(1) An estimated 60% of these patients will present with locally advanced disease (stage III/IV).

In the last 20 years, the integration of concurrent chemoradiotherapy (CRT) has advanced the treatment of locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN), improving locoregional control and overall survival (OS) compared with radiotherapy (RT) alone while allowing organ preservation. However, half of these cases will recur, indicating a clear need for further therapeutic intervention. Moreover, although ample data provide a high level of evidence for the benefit of platinum-based CRT for unresectable locally advanced SCCHN,(2) an optimal CRT regimen is yet to be defined.

S-1 is a novel oral fluoropyrimidine derivative that consists of tegafur, 5-chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) at a molar ratio of 1:0.4:1. Tegafur is a prodrug of 5-fluorouracil (5-FU).(3) CDHP augments the activity of 5-FU by inhibiting dihydropyrimidine dehydrogenase (DPD). Oxo reduces gastrointestinal (GI) toxicity by inhibiting orotate phosphoribosyl transferase and 5-FU phosphorylation in intestinal mucosa.

S-1 has been shown to be active against head and neck cancer, producing a response rate of 34%.(4) The combination of cisplatin (CDDP) and S-1 shows promising activity (response rate 67.6%) with acceptable toxicity for locally advanced head and neck cancer.(5) The combination of S-1 and fractionated radiotherapy is more effective against human oral cancer xenografts than either modality alone.(6)

A previous study demonstrated that the combination of S-1 and fractionated radiotherapy was more effective against human oral cancer xenografts than either treatment alone,(6) while another demonstrated that S-1 had a greater effect on radiosensitivity in human non-small-cell lung cancer xenografts in mice than uracil/tegafur (UFT), which also is an oral fluoropyrimidine derivative but does not contain CDHP.(7,8) CDHP enhanced radiosensitivity in human lung cancer cells in a dose escalation-dependent manner, suggesting that S-1 might be a more powerful enhancer of radiosensitivity in cancer than 5-FU or UFT.

Against this, however, no study has reported the feasibility and safety of S-1 in combination with CRT in patients with locally advanced SCCHN. We therefore conducted a single institutional, phase I, dose-escalation study of S-1 in combination with CRT in patients with unresectable locally advanced SCCHN.

Because CRT not only improves locoregional control but also exacerbates toxicities such as mucositis and dysphagia, patients may have difficulty in swallowing capsules. S-1 should therefore be administered as a suspension via a feeding tube. To date, however, no adequate bioavailability data for S-1 when administered as a suspension via a feeding tube has been available. For this reason, we also evaluated the difference in pharmacokinetics of S-1 when administered as a suspension via a feeding tube or orally by capsule.

## Patients and Methods

**Eligibility.** Eligibility for the present study required a histologically or cytologically confirmed diagnosis of SCCHN with unresectable locally advanced disease, including postoperative local recurrence. Careful evaluation for unresectability was required from a multidisciplinary conference, which included head and neck surgeons, radiation oncologists and medical

[5]To whom correspondence should be addressed. E-mail: matahara@east.ncc.go.jp
Present addresses:
[6]Medical Oncology, Kobe University Graduate School of Medicine, Kobe, Japan.
[7]Medical Oncology, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan.
[8]Department of Head and Neck Surgery, Miyagi Cancer Center, Natori, Japan.

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oncologists. Criteria for unresectability were carefully defined as follows: (i) technical unresectability, considered to mean tumors fixed to the carotid artery, mastoid, base of the skull or cervical spine; and (ii) physician determination of low surgical curability based on neck lymph node metastases such as N2c-3. Medical unsuitability for resection was not sufficient for patient eligibility; eligibility also required an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, age 20–75 years and adequate organ function. Written informed consent was required from all patients before the start of any therapy.

Patients were excluded if they had any of the following conditions: previous chemotherapy or radiotherapy; concurrent active malignancy except excised intramucosal gastric or esophageal cancer that could be removed by endoscopic mucosal resection; pharyngeal fistula; active bleeding from the GI tract; active infection; serious medical problem that might interfere with the achievement of study objectives; pregnancy or lactation; or expected survival <3 months.

**Treatment.** Baseline evaluation included patient history, physical examination, panendoscopy, dental evaluation, head and neck magnetic resonance imaging (MRI), computed tomography (CT) scan of the chest and abdomen, routine laboratory studies and electrocardiography (EKG). The treatment schedule is shown in Fig. 1.

Radiotherapy was done with 70 Gy/35 fractions over 7 weeks using six mega volt (MV) X-ray and 3-D radiotherapy techniques, and was started on day 1. Intensity-modulated radiotherapy was unavailable during this study. Gross tumor volume (GTV) was determined based on endoscopic or radiographic findings. Clinical target volume (CTV) was defined by adding 0.5 to 1 cm to the GTV. Planning target volume (PTV) was determined by adding appropriate margins to the CTV with consideration for physiological organ motion and daily set-up error. All patients underwent prophylactic nodal irradiations encompassing bilateral upper, middle and lower jugular, accessory and retropharyngeal lymph nodes up to 40–46 Gy. An additional 24–30 Gy was added to the PTV. Maximum dose to the spinal cord was restricted to 46 Gy, and posterior neck node was boosted using a 9–12 MeV electron beam as indicated. The radiotherapy dose was prescribed to the midplane along the beam axis, and dose deviation within the PTV was restricted to ±5% of the prescribed dose.

Chemotherapy consisted of administration of S-1 twice daily on days 1–14 at escalating doses of 40, 60 and 80 mg/m$^2$ per day, and 2-h infusion of CDDP at 20 mg/m$^2$ per day on days 8–11, repeated twice with a 5-week interval. Hydration consisted of 1 L of normal saline solution over 2 h prior to CDDP, as well as mannitol 12.5 gm by i.v. bolus infusion and 2 L of normal saline solution over 4 h following CDDP administration. Two additional cycles of S-1 and CDDP at the same dose level of CRT, repeated with a 4-week interval, were planned 4 weeks after the completion of CRT. Neutrocytes had to have recovered to at least 2000 cells/mm$^3$ and grade 1 creatinine or >50 mL/min of creatinine clearance was required by the time of the next cycle.

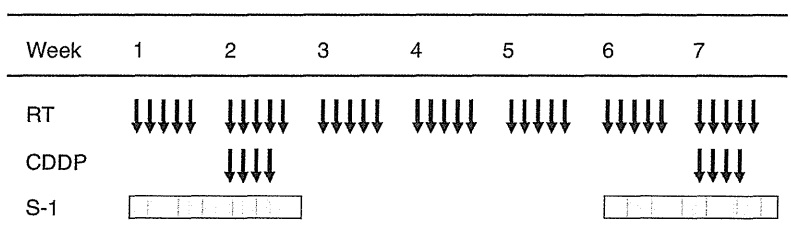
All patients underwent emplacement of a percutaneous endoscopic gastrostomy (PEG) feeding tube prior to the initiation of treatment. Prophylactic use of granulocyte-colony stimulating factor was not permitted. Additional treatment was not permitted unless persistent disease or disease progression was observed. When a patient had persistent or recurrent disease at the completion of CRT, surgical salvage was considered.

**Toxicity.** Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 2.0. Any of the following adverse events observed within 30 days after the completion of CRT was deemed a dose-limiting toxicity (DLT): (i) febrile neutropenia lasting more than 4 days; (ii) grade 4 thrombocytopenia; (iii) grade 3 or 4 non-hematological toxicities except grade 3 anorexia, nausea, vomiting, stomatitis, esophagitis, infection due to stomatitis, dysphagia and skin toxicity; (iv) cessation of treatment due to an adverse event; or (v) treatment-related death. The maximum-tolerated dose (MTD) was defined as the dose at which more than two of six patients experienced a DLT. The recommended safe dose for further study was assessed at the dose level immediately below the MTD.

A minimum of three assessable patients was treated at each dose level. If one of the three patients at a given dose experienced a DLT, three more patients were accrued at the same dose level. If more than two of six patients at a given dose experienced a DLT, three more patients were treated at the next lower dose level. If less than one of six patients experienced a DLT, an additional six patients were accrued at the same dose level to determine the recommended dose.

**Sample collection.** Before the initiation of CRT, patients who gave consent underwent pharmacokinetic investigation. A single dose of S-1 as a capsule formulation was administrated orally 4 days before the start of CRT (day -4), while the same dose was given through a feeding tube as a suspension 2 days before the start of CRT (day -2). Suspensions were prepared by simple dissolution of a S-1 capsule in hot water. Peripheral blood samples were drawn before and at 0.5, 1, 2, 4, 6, 8, 10 and 24 h after each administration. Heparinized blood was centrifuged at 3000 rpm for 15 min at 4°C, and plasma was stored at −80°C.

**Pharmacokinetic analysis.** Tegafur, 5-FU, CDHP and Oxo were analyzed according to the method of Matsushima *et al.*[9] Pharmacokinetic parameters of Tegafur, 5-FU, CDHP and Oxo were estimated according to a standard noncompartmental method. Maximum plasma concentration ($C_{max}$) and time to $C_{max}$ ($T_{max}$) were taken from the observed data. The area under the plasma-concentration time curve (AUC) for time 0 to infinity was estimated by summing AUC from 0 to time t ($AUC_{0-t}$) and $C_{tlast}/k$, where $C_{tlast}$ was the concentration at the last measured point. The apparent rate constant of elimination ($k$) was estimated by linear regression on the logarithm of the plasma




RT: 2 Gy/Fr x 33 or 35 Fr (total 70 Gy)
CDDP: 20 mg/m$^2$/day, iv, days 8–11, days 43–46
S-1: 40, 60, 80 mg/m$^2$/day, twice daily po, days 1–14, days 36–49

**Fig. 1.** Treatment schedule. Two additional cycles of S-1 and cisplatin (CDDP) at the same dose level of the chemoradiotherapy (CRT), repeated at a 4-week interval, were planned 4 weeks after the completion of the CRT. RT, radiotherapy.



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concentrations versus time, and $AUC_{0-t}$ was estimated using the log trapezoidal method.

**Criteria for response.** Tumor responses were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) by panendoscopy, MRI of the head and neck and CT scan of the chest and abdomen.

**End-points and statistical methods.** The primary end-point in the present study was the MTD and DLT of S-1 in combination with a fixed dose of CDDP and RT. Safety and feasibility of this treatment were evaluated in patients with unresectable locally advanced SCCHN. Secondary end-points included complete response rate, progression-free survival (PFS), locoregional PFS, overall survival (OS) and pharmacokinetics of S-1 when administered as a suspension via the feeding tube.

The survival curve was estimated using the Kaplan–Meier method. Safety and efficacy analyses were both conducted on an intention-to-treat (ITT) population, defined as all patients enrolled in the study who received at least one dose of RT. A subject's PFS was defined as the time from the date of the first administration of CRT to the first documentation of disease progression, subsequent therapy or death. The OS was determined from the date of the first administration of CRT to the date of death or the last confirmed date of survival. Locoregional PFS was defined as the time from the date of the first administration of CRT to the first documentation of locoregional disease progression. Statistical data were obtained using the SPSS software package (SPSS 11.0 Inc., Chicago, IL, USA).

This study was conducted at the National Cancer Center Hospital East. The protocol was approved by the Institutional Review Board at the National Cancer Center.

## Results

**Patient and disease characteristics.** Twenty-two patients were enrolled between February 2003 and January 2005. One patient did not receive CRT because it made the performance status worse due to disease progression, leaving 21 patients in the ITT population. Patient characteristics in the ITT population are listed in Table 1. The most common site of the primary lesion was the hypopharynx (59%). One patient had unresectable local recurrence after total larnyngectomy for hypopharyngeal cancer and the other 20 had never received any prior treatment for head and neck cancer.

**Treatment administration.** A total of 69 cycles of chemotherapy was administered. The number of cycles was two in seven patients, three in three patients, four in 10 patients and six in one patient. The reasons for the administration of less than four cycles were toxicities ($n = 2$), physician decision due to concern about tolerance ($n = 2$) and patient refusal due to achievement of complete remission ($n = 6$). One patient received six cycles due to persistent disease that could not be removed by salvage surgery.

Three patients were treated at the dose level of S-1 40 mg/m$^2$ without DLT. Of the first three patients who received S-1 at the 60 mg/m$^2$ dose level, one patient blacked out after straining at stool due to constipation on day 16 and developed grade 3 ischemic colitis, but reported recovery within 1 week under conservative treatment including hydration. Because he finished taking S-1 on day 14 and did not develop any GI toxicity including mucositis or diarrhea before suffering from this colitis, the safety committee decided that this colitis was not likely related to the study treatment. Two other patients had no DLT and dose escalation subsequently proceeded. Of the first three patients treated at a dose level of S-1 80 mg/m$^2$, one developed febrile neutropenia lasting more than 4 days, leading to the accrual of an additional three patients at this level. Thus, six patients were treated at the dose level of S-1 80 mg/m$^2$, of whom two developed febrile neutropenia lasting more than 4 days. The MTD was therefore set at 80 mg/m$^2$ per day of S-1.

**Table 1. Patients' characteristics**

| Characteristic | No. patients ($n = 21$) |
|---|---|
| *Age (years)* | |
| Median | 62 |
| Range | 45–73 |
| *Sex* | |
| Male | 19 |
| Female | 2 |
| *ECOG performance score* | |
| 0 | 15 |
| 1 | 6 |
| *Site of primary tumor* | |
| Hypopharynx | 13 |
| Pharynx | 1 |
| Oropharynx | 5 |
| Nasopharynx | 2 |
| *AJCC stage* | |
| IV | 20 |
| Local relapse | 1 |
| *T stage* | |
| T1 | 4 |
| T2 | 5 |
| T3 | 3 |
| T4 | 8 |
| Local relapse | 1 |
| *N stage* | |
| N0 | 3 |
| N2a | 1 |
| N2b | 2 |
| N2c | 6 |
| N3 | 8 |

AJCC, American Joint Committee on Cancer.

Three additional patients were treated at the dose level of S-1 60 mg/m$^2$, one of whom experienced grade 3 diarrhea with grade 3 infection. To determine the recommended dose of S-1, six additional patients (total of 12 patients) were treated at the dose level of S-1 60 mg/m$^2$, three of whom developed febrile neutropenia lasting for more than 4 days. One of them experienced febrile neutropenia lasting for 2 weeks despite using granulocyte colony-stimulating factor supports and the diagnosis of myelodysplastic syndrome was made by bone marrow study. One week after the completion of CRT, another of these three patients who experienced febrile neutropenia developed grade 3 diarrhea, which occurred 1 day after the development of febrile neutropenia. Because the administration of S-1 had finished 1 week previously, this diarrhea was not related to S-1 but to the neutropenia or antibiotic drugs, and was not regarded as a DLT.

During CRT, eight patients (38%) received administration of S-1 via a feeding tube, and a total of 14% of the planned doses of S-1 were administered via a feeding tube during CRT. The number of patients who received S-1 via a feeding tube at each dose level was one of three at 40 mg/m$^2$, four of 12 at 60 mg/m$^2$ and three of six at 80 mg/m$^2$.

All patients were treated with conventional 3-D RT and received planned doses of CDDP. One patient received a total of 68 Gy while the other 20 received 70 Gy. Four patients required the splitting of RT due to adverse events, including colitis in one patient, grade 3 dermatitis and infection in one patient and neutropenia in two patients. Of the two patients who developed neutropenia, one was treated at the dose level of S-1 80 mg/m$^2$, while the second was treated at 60 mg/m$^2$.

**Toxicity.** Overall toxicities during treatment are listed in Table 2. Grade 3 or 4 toxicities by the S-1 dose level are listed in Table 3. The incidence of grade 3 or 4 neutropenia and febrile neutropenia increased with increasing dose, with half of those

treated at 80 mg/m$^2$ experiencing febrile neutropenia. All four patients whose creatinine clearance was decreased to <60 mL/min after the first cycle of chemotherapy developed febrile neutropenia lasting more than 4 days. Of these, two each were treated at S-1 dose levels of 60 and 80 mg/m$^2$.

The incidence of grade 3 or 4 mucositis and dysphagia increased with increasing dose and occurred in all patients treated at 80 mg/m$^2$, indicating that S-1 at 80 mg/m$^2$ was intolerable in this treatment. One patient who achieved a complete response after completion of CRT experienced pharyngeal stricture as an adverse event, declined surgical treatment and is still alive without any evidence of recurrence. Fifteen patients (71%) received nutritional support via a feeding tube, with a median feeding tube duration of 199 days and 1-year feeding tube dependence of 14%.

**Table 2. Overall toxicity ($n$ = 21)**

| Toxicity | No. patients (Grade) | | | | % of patients | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | Grade 1–2 | Grade 3–4 |
| *Hematological toxicity* | | | | | | |
| Leucopenia | 8 | 4 | 3 | 5 | 57 | 38 |
| Neutropenia | 5 | 2 | 3 | 5 | 33 | 38 |
| Febrile neutropenia | – | – | 6 | 0 | – | 29 |
| Anemia | 10 | 6 | 3 | 2 | 76 | 24 |
| Thrombocytopenia | 10 | 2 | 2 | 1 | 57 | 14 |
| *Non-hematological toxicity* | | | | | | |
| Nausea | 4 | 4 | 5 | 0 | 38 | 24 |
| Vomiting | 8 | 2 | 0 | 0 | 48 | 0 |
| Anorexia | 4 | 3 | 1 | 0 | 33 | 5 |
| Fatigue | 5 | 6 | 1 | 0 | 52 | 5 |
| Mucositis | 4 | 1 | 14 | 1 | 24 | 71 |
| Dysphagia | 3 | 1 | 15 | 0 | 19 | 71 |
| Dermatitis | 3 | 12 | 3 | 0 | 71 | 14 |
| Diarrhea | 1 | 2 | 2 | 0 | 14 | 10 |
| Elevated bilirubin | 2 | 1 | 0 | 0 | 14 | 0 |
| Elevated AST | 2 | 4 | 0 | 0 | 29 | 0 |
| Elevated ALT | 3 | 4 | 0 | 0 | 33 | 0 |
| Elevated creatinine | 2 | 1 | 0 | 0 | 14 | 0 |
| Xerostomia | 7 | 12 | 0 | 0 | 90 | 0 |
| Salivary change | 3 | 9 | 0 | 0 | 57 | 0 |

ALT, alanine transaminase; AST, aspartate transaminase.

**Table 3. Grade 3 or 4 toxicity by S-1 dose level**

| | Grade 3 or 4 toxicity | | | | | |
|---|---|---|---|---|---|---|
| | S-1 dose level: 40 mg/m$^2$ per day ($n$ = 3) | | S-1 dose level: 60 mg/m$^2$ per day ($n$ = 12) | | S-1 dose level: 80 mg/m$^2$ per day ($n$ = 6) | |
| | No. patients | % | No. patients | % | No. patients | % |
| *Hematological toxicity* | | | | | | |
| Leucopenia | 1 | 33 | 5 | 42 | 2 | 33 |
| Neutropenia | 1 | 33 | 4 | 33 | 3 | 50 |
| Febrile neutropenia | 0 | 0 | 3 | 25 | 3 | 50 |
| Anemia | 0 | 0 | 4 | 33 | 1 | 17 |
| Thrombocytopenia | 0 | 0 | 2 | 17 | 1 | 17 |
| *Non-hematological toxicity* | | | | | | |
| Anorexia | 0 | 0 | 3 | 25 | 2 | 33 |
| Mucositis | 1 | 33 | 7 | 58 | 6 | 100 |
| Dysphagia | 1 | 33 | 8 | 67 | 6 | 100 |
| Dermatitis | 0 | 17 | 2 | 17 | 1 | 17 |
| Diarrhea | 0 | 1 | 2 | 17 | 0 | 0 |

**Pharmacokinetic analysis of S-1.** Pharmacokinetic data on administration of S-1 as oral capsules (day -4) and suspensions via a feeding tube (day -2) were available for 16 patients (Table 4). Tmax values for tegafur, 5-FU, CDHP and Oxo were significantly lower with the suspension than oral capsules, while Cmax values for tegafur, CDHP and Oxo were significantly higher. However, the Cmax for 5-FU and AUC of all parameters did not significantly differ by administration route. Moreover, although no clear relationship was seen between any parameter and adverse events, a weak correlation was seen between the AUC of tegafur and the rate of neutropenia ($P$ = 0.106).

**Treatment outcomes.** Of the 21 patients treated with CRT, 18 experienced a complete response. Two additional patients who had been diagnosed with residual neck lymph node metastasis underwent salvage neck dissection, and pathology revealed no residual tumor. With a median follow up of 49 months (range,

**Table 4. Phamacokinetics of S-1 by the administration route ($n$ = 15)**

| | Administration route | | | |
|---|---|---|---|---|
| | Oral ($n$ = 15) | Feeding tube ($n$ = 15) | Ratio | $P$-value |
| *Tegafur* | | | | |
| $T_{max}$ (min) | | | | |
| Median | 126.0 | 65.0 | 0.50 | 0.0012 |
| Range | 30–483 | 28–246 | 0.13–1.03 | |
| $C_{max}$ (ng/mL) | | | | |
| Median | 1571.0 | 1841.1 | 1.11 | 0.0009 |
| Range | 729–2373 | 804–2658 | 0.95–1.49 | |
| AUC (μg × min/mL) | | | | |
| Median | 1416.6 | 1421.8 | 0.99 | 0.64 |
| Range | 573.2–3888.1 | 408.1–4306.5 | 0.71–1.16 | |
| *5-FU* | | | | |
| $T_{max}$ (min) | | | | |
| Median | 239.0 | 121 | 0.78 | 0.013 |
| Range | 60–483 | 59–246 | 0.26–2.00 | |
| $C_{max}$ (ng/mL) | | | | |
| Median | 120.1 | 107.4 | 1.00 | 0.56 |
| Range | 26.5–188.6 | 29.4–176.5 | 0.73–1.47 | |
| AUC (μg × min/mL) | | | | |
| Median | 33.6 | 29.4 | 0.94 | 0.63 |
| Range | 12.5–54.2 | 16.8–48.7 | 0.64–1.34 | |
| *CDHP* | | | | |
| $T_{max}$ (min) | | | | |
| Median | 120.0 | 62 | 0.50 | 0.0009 |
| Range | 60–483 | 30–246 | 0.12–1.03 | |
| $C_{max}$ (ng/mL) | | | | |
| Median | 183.8 | 205.2 | 1.22 | 0.04 |
| Range | 72.0–358.8 | 101.5–584.6 | 0.71–1.78 | |
| AUC (μg × min/mL) | | | | |
| Median | 66.0 | 65.7 | 1.03 | 0.15 |
| Range | 28.6–83.3 | 37.9–115.0 | 0.83–1.42 | |
| *Oxo* | | | | |
| $T_{max}$ (min) | | | | |
| Median | 120.0 | 118.0 | 0.51 | 0.0005 |
| Range | 90–243 | 58–122 | 0.26–1.01 | |
| $C_{max}$ (ng/mL) | | | | |
| Median | 26.2 | 35.0 | 1.51 | 0.041 |
| Range | 3.8–60.1 | 11.5–212.4 | 0.48–3.58 | |
| AUC (μg × min/mL) | | | | |
| Median | 7.5 | 9.2 | 1.39 | 0.21 |
| Range | 1.9–18.7 | 3.1–57.9 | 0.68–4.71 | |

5-FU, 5-fluorouracil; CDHP, 5-chloro-2,4-dihydroxypyridine; Oxo, potassium oxonate.



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44–62 months), local recurrence only, distant metastasis and both local recurrence and distant metastasis were observed in four, four and one patient, respectively. A total of nine patients died, five from local recurrence, three from disease progression of distant metastases and one from progression of residual neck lymph node. Estimated rates of 3-year locoregional PFS, PFS and OS were 75%, 48% and 62% respectively.

## Discussion

In this phase I study of S-1 in combination with CRT in patients with unresectable locally advanced SCCHN, MTD of S-1 was 80 mg/m$^2$ per day. S-1 at 60 mg/m$^2$ per day for 14 days with concurrent CRT was well tolerated, and provided promising activity in these patients. Administration of S-1 as a suspension via a feeding tube or by oral capsule can be considered therapeutically interchangeable.

S-1 contains CDHP, which inhibits DPD. As 50% of CDHP is excreted in the urine, renal dysfunction might directly affect the inhibitory effect on DPD and lead to increased 5-FU concentrations.[10] Although the current standard dosing regimen for cisplatin is a single intravenous infusion of 100 mg/m$^2$, this regimen has a higher incidence of renal toxicities than lower doses. We therefore selected divided doses of the CDDP to reduce renal toxicity.

The incidence and severity of both hematological and non-hematological toxicities increased in accordance with the increasing dose. At a dose level of S-1 80 mg/m$^2$, half experienced febrile neutropenia lasting more than 4 days and all developed grade 3 or 4 mucositis, indicating that the dose of S-1 80 mg/m$^2$ was intolerable. The MTD was therefore set at 80 mg/m$^2$ per day of S-1. Two patients treated with S-1 at 60 mg/m$^2$ experienced grade 3 diarrhea. One of these patients did not receive anti-diarrhea drugs until the development of grade 3 diarrhea and infection, which was regarded as a DLT. The second experienced grade 3 diarrhea following grade 3 febrile neutropenia. Because the administration of S-1 had finished 1 week previously, this diarrhea was not related to S-1 but to the neutropenia or antibiotic drugs, and was not regarded as a DLT. However, this patient experienced grade 3 febrile neutropenia for more than 4 days, which was regarded as a DLT. Three patients experienced grade 3 febrile neutropenia for more than 4 days at S-1 60 mg/m$^2$. In other words, four of 12 patients receiving S-1 at 60 mg/m$^2$ experienced a DLT. Another experienced febrile neutropenia lasting 2 weeks despite the use of granulocyte colony-stimulating factor and was subsequently diagnosed with myelodysplastic syndrome on bone marrow study, indicating that this patient was inappropriate for evaluation of the recommended dose of S-1 in combination with CRT.

In the present study, all four patients whose creatinine clearance was decreased to <60 mL/min after the first cycle of chemotherapy developed febrile neutropenia lasting more than 4 days, and two of these were treated at a dose level of S-1 60 mg/m$^2$. The higher incidence of febrile neutropenia in the present study is therefore likely related to decreased creatinine clearance. Grade 1 creatinine or creatinine clearance of more than 50 mL/min had to have occurred by the time of the next cycle, while dose modification according to creatinine clearance was not performed. Dose modification according to creatinine clearance could have reduced or prevented these toxicities. Based on these results, we are convinced of the need for dose modification according to creatinine clearance in the treatment with S-1. In this regard, recent studies of S-1 have indeed used dose modification according to creatinine clearance.[11,12]

Although a slightly higher incidence of DLT was observed at this level, suggesting that it was not suitable for consideration as the recommended dose (RD), these toxicities might have been reduced by dose modification according to creatinine clearance and appropriate anti-diarrhea medication. Furthermore, this dose level was well tolerated in the other eight patients, with acceptable toxicity. We therefore established S-1 at 60 mg/m$^2$ per day as the RD. The clinically appropriate dose of S-1 in combination with CRT can only be determined in phase II trials.

Previous studies demonstrated a significant correlation between 5-FU plasma concentration, in particular 5-FU AUC, and therapeutic activity and toxicity.[13–17] Moreover, two phase I studies of S-1 showed a significant correlation between diarrhea grade and 5-FU AUC,[17,18] one of which additionally demonstrated a significant correlation between diarrhea grade and 5-FU Cmax.[18]

In the present study, pharmacokinetic analysis revealed that the Tmax of all parameters, including tegafur, 5-FU, CDHP and Oxo, were significantly lower on administration as a suspension, whereas the Cmax of tegafur, CDHP and Oxo were significantly higher than with oral capsules, indicating that the absorption of S-1 is higher in suspension. However, the Cmax for 5-FU and AUC of all parameters did not significantly differ by the administration route, indicating that the two routes can be considered therapeutically interchangeable.

In the present study, 18 of 21 patients achieved a complete response, while an additional two patients who had been pathologically diagnosed revealed no residual tumor on salvage neck dissection, with 3 years OS of 61.9%. Considering the small number of patients, these findings indicate that this regimen may provide promising activity in patients with unresectable locally advanced SCCHN.

Severe mucositis in locally advanced SCCHN patients receiving CRT frequently leads to dysphasia and weight loss. These patients may require adequate nutritional support to avoid treatment interruption, which can adversely impact the treatment outcome. However, although the relative benefits of prophylactic versus therapeutic PEG feeding tube placement are controversial, we are convinced that prophylactic PEG feeding tube replacement is indispensable to the completion of these high-intensity treatments. Although all PEG feeding tube replacements in this study were performed by pull techniques, few severe complications and no tumor seeding were observed. Furthermore, despite the high incidence of toxicities, all but one patient completed the CRT, indicating the likely usefulness of a prophylactic PEG feeding tube.

Feeding tube placement prior to CRT due to pre-existing dysphagia and advanced T stage are associated with prolonged feeding tube dependence.[19] In the present study, 71% of patients received nutritional support via a feeding tube, with a median feeding tube duration of 199 days and a 1-year feeding tube dependence of 14%. Additionally, one patient who achieved a complete remission subsequently experienced pharyngeal stricture after the completion of CRT, indicating that all patients should receive evaluation by a speech-language pathologist throughout the course of CRT, swallowing exercises, even though a feeding tube is in place, and rapid rehabilitation.

Concern has been expressed over the considerable ethnic differences in the tolerated doses of S-1. These relate to the varying efficiency rates of conversion of tegafur to 5-FU by CYP2A6 of the CYP450 enzyme system, now identified as the principal enzyme responsible for this conversion process.[20–23] A phase I study of S-1 plus CDDP in Western patients with advanced gastric carcinoma showed that the S-1 dose tolerated by Western patients is lower than that by Japanese patients, but that the AUC of FU appears higher in white rather than Japanese patients in a comparable dose range of S-1.[24] This is mostly attributed to different polymorphisms in the *CYP2A6* gene among Asians and whites. The RD of the present study is likely to be unsuitable for Western patients, and further study

to determine the RD of this combination for these patients is required.

In conclusion, S-1 at 60 mg/m$^2$ per day for 14 days was well tolerated with concurrent CRT with CDDP. Furthermore, no difference was seen in the pharmacokinetics of S-1 between administration as a suspension and orally as a whole capsule, indicating that these can be considered therapeutically interchangeable. Although these data are preliminary, activity was highly promising, and this approach warrants further investigation. A multicenter phase II study of this approach by the Japan Clinical Oncology Group (JCOG) is ongoing.[11]


## Acknowledgment

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## Disclosure Statement

The authors have no conflict of interest.

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HEAD AND NECK

# Salvage surgery for local recurrence after chemoradiotherapy or radiotherapy in hypopharyngeal cancer patients

**Shigenari Taki · Akihiro Homma · Nobuhiko Oridate · Seigo Suzuki · Fumiyuki Suzuki · Tomohiro Sakashita · Satoshi Fukuda**

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**Abstract** This retrospective study aimed to assess the role of salvage surgery for local recurrence in hypopharyngeal cancer (HPC) patients who had received radiotherapy (RT) or concomitant chemoradiotherapy (CRT) as an initial treatment. The local recurrence rate, salvage rate after local recurrence and overall survival rate were investigated in 104 HPC patients who received treatment between 1991 and 2005. Local recurrence in the primary site was observed in 41 patients (rate, 39.4%) of whom only 12 could undergo further salvage surgery. Disease control was achieved in seven of these patients (successful salvage rate, 17.1%). The 5-year overall survival rate was 40.6% in the RT/CRT patient group and successful salvage rates for T1, T2, T3 and T4 primary disease were 33.3% (1/3), 20.0% (4/20), 16.7% (2/12) and 0% (0/6), respectively. Severe postoperative complications such as pharyngocutaneous fistula were seen in six patients (50.0%). Prognosis of patients with locally recurring HPC after RT/CRT is poor at any primary T-stage and the incidence of postoperative complication is relatively high. This should be taken into consideration when the initial treatment plan is decided and the choice of salvage surgery for such recurrent cases should be carefully determined.

**Keywords** Chemoradiotherapy · Hypopharyngeal cancer · Radiotherapy · Salvage surgery

## Introduction

Despite improvements in surgery, radiotherapy and chemotherapy, hypopharyngeal cancer has one of the worst prognoses of head and neck malignant diseases. Recent studies have documented the effectiveness of concomitant chemotherapy with radiation (CRT) for both survival benefits and organ preservation in head and neck cancer [1]. The addition of concomitant treatments, such as single or multi-agent chemotherapy, molecular-targeted agents [2, 3] and superselective arterial infusion [4], as an adjuvant to radiotherapy is becoming more prevalent and its survival benefit is now comparable to that of definitive surgery [5, 6]. Consequently, the role of surgical treatment is shifting to salvage therapy after the primary treatment based on radiotherapy. However, recurrent diseases tend to be more invasive and salvage surgery is often technically difficult and offers a poor prognosis [7]. Functional sacrifice due to surgical salvage of the primary site and postoperative complications often diminish the quality of life, so the decision to perform salvage surgery for locally recurring head and neck cancer remains controversial.

In this study, we assessed the role of salvage surgery in hypopharyngeal cancer by retrospectively analyzing patient outcomes of salvage surgery for local recurrence after RT/CRT as a primary treatment.

## Patients and methods

We used medical records to retrospectively analyze 104 patients with previously untreated resectable HPC who

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S. Taki (✉) · A. Homma · N. Oridate · S. Suzuki · F. Suzuki · T. Sakashita · S. Fukuda
Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan
e-mail: taki-s@hakochu-hp.gr.jp

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**Table 1** Patient characteristics

| Characteristics | No. patients (%) |
|---|---|
| Gender | |
| Male/female | 97/7 (93.3/6.7) |
| Age (years) | |
| 30–50 | 10 (9.6) |
| 51–70 | 72 (69.2) |
| 71+ | 22 (21.2) |
| T-stage | |
| I | 8 (7.7) |
| II | 17 (16.3) |
| III | 18 (17.3) |
| IV | 61 (61.5) |
| Primary tumor location | |
| Pyriform sinus | 83 (79.8) |
| Posterior wall | 12 (14.5) |
| Postcricoid region | 9 (8.7) |

received RT or CRT at Hokkaido University Hospital, Sapporo, Japan, for 14 years from 1991 to 2005. Patient characteristics are shown in Table 1. Most patients were male ($n = 97$, 93.3%) with an age range from 38 to 86 years (median 63 years) and a median follow-up time of 21 months (mean 27.8 months). No unresectable cases were included in this study.

All pathological findings were of squamous cell carcinoma. Seventeen patients had T1 primary tumors, 46 had T2, 27 had T3 and 14 had T4. The rates for lymph node metastasis were 52.9% with T1, 63.0% with T2, 85.2% with T3 and 85.7% with T4 (Table 2). The local recurrence rate, salvage rate after local recurrence and overall survival rate for these patients were investigated. Survival rate was analyzed by using the Kaplan–Meier's estimate.

Table 3 shows the initial treatment breakdown of patients. Of the 104 patients, 32 received conventional RT of 62–70 Gy alone and 72 received RT with concomitant chemotherapy. These regimens consisted of weekly treatment with carboplatin (AUC = 1–2), i. v. docetaxel (10 mg/m$^2$) or a daily low dose of cisplatin (4 mg/m$^2$). Patients who were treated with weekly cisplatin (100–120 mg/m$^2$) received this by arterial infusion. When the local or regional recurrence was detected during the follow-up after initial treatment of RT or CRT, appropriate surgical treatment such as laryngopharyngectomy or neck dissection was conducted depending on recurrent tumor state.

As a reference, we also analyzed the outcomes of the patients who were initially treated with definitive surgery ($n = 58$) during the same period (surgery group). In this group, the patient distribution of primary disease consisted of 2 patients of T1 tumor, 23 of T2, 23 of T3 and 11 of T4.

**Table 2** Patient distribution of RT/CRT patient group by T and N classification

| T/N | N0 | N1 | N2a | N2b | N2c | N3 | Total (%) |
|---|---|---|---|---|---|---|---|
| T1 | 8 | 5 | 1 | 3 | 0 | 0 | 17 (16.3) |
| T2 | 17 | 7 | 4 | 14 | 4 | 0 | 46 (44.2) |
| T3 | 4 | 2 | 1 | 13 | 8 | 0 | 27 (26.0) |
| T4 | 2 | 4 | 0 | 5 | 2 | 0 | 14 (13.5) |
| Total (%) | 31 (29.8) | 18 (17.3) | 6 (5.8) | 35 (33.7) | 14 (13.5) | 0 (0) | 104 (100) |

**Table 3** Patient distribution of RT/CRT patient group by initial treatment method

| Treatment | No. patients (%) |
|---|---|
| RT alone (62–70 Gy) | 32 (30.8) |
| CRT (65–71 Gy) | 72 (69.2) |
| Regimens of concomitant chemotherapy | |
| Carboplatin (AUC = 1–2 IV)/week × 4–7 cycles | 27 (26.0) |
| Docetaxel (10 mg/m$^2$ IV)/week × 2–5 cycles | 24 (23.1) |
| Cisplatin (4 mg/m$^2$ IV)/day × 16 cycles | 5 (4.8) |
| Cisplatin (100 mg/m$^2$ IA)/week × 3–5 cycles | 14 (13.5) |
| Others | 2 (1.9) |

## Results

### Survival

For the 37 of the 104 patients, any of recurrent disease had not been detected after initial treatment of RT or CRT during the follow-up period. They were able to have oral intake without feeding tube support and no patient had tracheostoma. The local recurrence in the primary site was observed in 41 patients (local recurrence rate, 39.4%) of whom only 12 could undergo further salvage surgery and the remaining 29 could not receive salvage surgery (Fig. 1). The 5-year overall survival rate of all patients was 40.6% for the all 104 patients (Fig. 2). Salvage surgery for recurrent primary disease achieved preservation of the larynx in four patients, one by endoscopic mucosal resection and three partial resections because of early detection of local recurrence. The remaining eight patients required laryngopharyngectomy. Eleven of the 12 patients who underwent salvage surgery needed to receive unilateral or bilateral neck dissection.

Of the 41 patients, recurrences were seen in 30 patients with tumors of the pyriform sinus, five of the postcricoid region and six of the posterior wall. Salvage surgery was performed on nine (30.0%) patients with recurrences in the pyriform sinus, two (40.0%) in the postcricoid region, and one (16.7%) in the posterior wall (Table 4). Successful salvage rates for each subsite were 16.7% for the pyriform sinus, 40.0% for the postcricoid region, and 0.0% for the

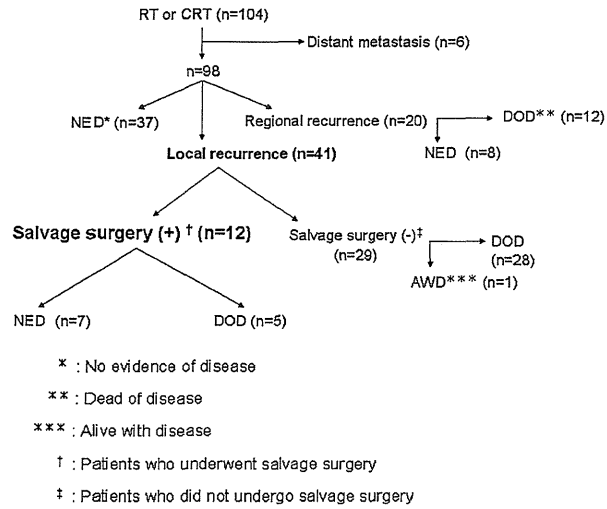


**Fig. 1** Treatment course of 104 patients treated with RT or CRT

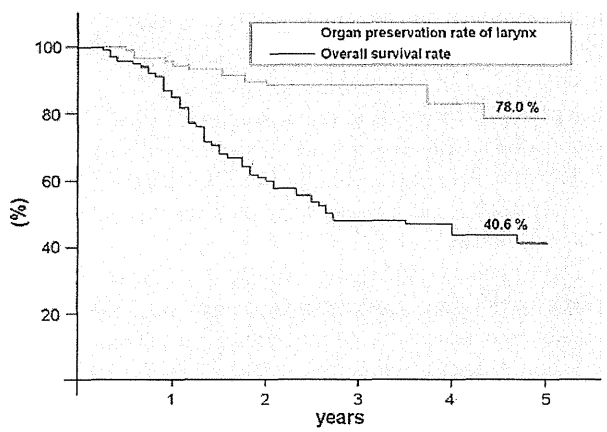


**Fig. 2** The graph shows the 5-year overall survival rate and the 5-year organ preservation rate of larynx of RT/CRT group patients ($n = 104$)

**Table 4** Successful salvage rate at each subsite

| Subsites (no. patients) | No. local recurrences | No. salvage surgeries (%) | No. successfully salvaged (%) |
|---|---|---|---|
| Pyriform sinus (83) | 30 | 9 (30.0) | 5 (16.7) |
| Postcricoid region (9) | 5 | 2 (40.0) | 2 (40.0) |
| Posterior wall (12) | 6 | 1 (16.7) | 0 (0.0) |
| Total (104) | 41 | 12 (29.3) | 7 (17.1) |

posterior wall. Disease control was achieved in seven patients who underwent salvage surgeries (successful salvage rate, 17.1%). Table 5 shows successful salvage rates for each T-stage.

Survival curves after local recurrence are shown in Fig. 3. The 5-year Kaplan–Meier overall survival rate after

**Table 5** Successful salvage rate at each T-stage

| T-stage (no. patients) | No. local recurrences | No. salvage surgeries (%) | No. successfully salvaged (%) |
|---|---|---|---|
| T1 (17) | 3 | 1 (33.3) | 1 (33.3) |
| T2 (46) | 20 | 8 (40.0) | 4 (20.0) |
| T3 (29) | 12 | 3 (25.0) | 2 (16.7) |
| T4 (12) | 6 | 0 (0.0) | 0 (0.0) |
| Total (104) | 41 | 12 (36.4) | 7 (17.1) |

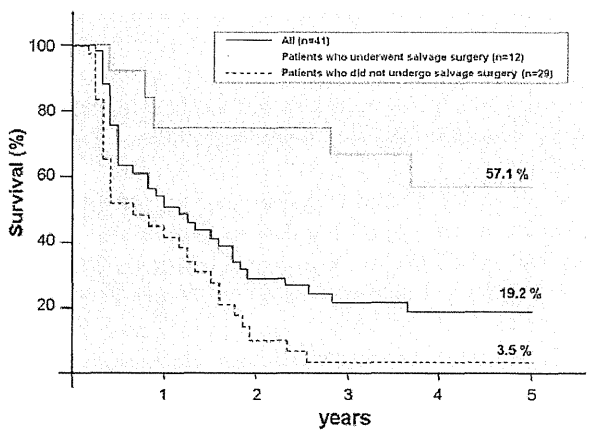


**Fig. 3** Comparison of survival curves after detection of local recurrence with or without salvage surgery

recurrence was 19.2% among 41 patients, and overall survival rates were 57.1% with salvage surgery ($n = 12$) and 3.5% among those who could not receive salvage surgery ($n = 29$).

In the surgery group, primary disease could be controlled by partial resection of pharynx preserving larynx for three patients. Total laryngopharyngectomy with or without reconstruction was done for 55 patients. Five-year overall survival rate of the surgery group was 45.2%. Of these, radiotherapy was performed on 37 patients preoperatively and 2 postoperatively. The survival rates for each T-stage were 100% for T1, 48.2% for T2, 56.2% for T3 and 28.3% for T4, respectively. There was no statistical difference of survival rates for each T-stage between RT/CRT group and surgery group.

*Postoperative complications*

Postoperative complications were seen in six patients (50.0%). Pharyngo-cutaneous fistulas occurred in two of the eight patients who underwent laryngopharyngectomy (25%). A fistula closed without surgery after 2 months but the other needed surgical reconstruction to close. Prolonged wound healing in the neck without fistula also occurred in 2 of the 11 patients, including those patients

who underwent neck dissection. The aspiration pneumonia occurred on one patient who received the partial resection of hypopharynx and he finally underwent glottic closure. Peritonitis in the donor site of the free jejunum graft was also observed in one patient.

## Discussion

HPC has one of the worst prognoses of all head and neck tumors and a low survival rate, making the choice of treatment difficult. Recent changes in CRT have contributed to improvements in functional organ preservation, but successful locoregional control does not always increase survival rates. It has been reported that the feasibility of salvage therapies following tumor recurrence is generally low [7, 8].

In our series, the local recurrence rate of HPC was 43.7% in patients with T2–4 disease after treatment with RT/CRT, and 17.6% in those with T1 disease. When the recurrence became unequivocal, most T3 and T4 patients were considered unsuitable to receive surgical salvage. Only two of 18 patients (11.1%) who experienced local recurrence with an initial diagnosis of T3 or T4 achieved long-term survival after salvage surgery, with 15 of the 18 not even having the chance to undergo salvage surgery. All T4 patients died within 19 months after the local recurrence was detected.

Even in those with early stage (T1 or T2) tumors, disease control was successful in only 6 of 23 (26.1%) with local recurrence. In total, 70.7% of locally recurrent HPC patients were unable to receive salvage surgery. In addition, the chance for salvage surgery was more limited in patients with tumors in the primary posterior wall because of difficulties in early detection. However, the statistical analysis did not indicate a significant difference because of the low frequency of posterior wall and postcricoid tumor types. Therefore, the initial T-stage and tumor subsite are important factors that affect the indication of HPC salvage surgery.

Laryngeal cancer, by contrast, offers more chance to undergo salvage surgery for recurrence. Leon et al. [9] reported that 25 of 34 patients (73.5%) received salvage surgery for local or locoregional recurrence, and their 5-year survival rates ranged from 43 to 45% for T3 or T4 laryngeal cancer (compared with 19.2% for HPC in our data). Stoeckli et al. also reported performing salvage surgery for 39 of 44 recurrent laryngeal cancer patients, compared with 15 of the 33 recurrent HPC cases [10]. Although the hypopharynx and larynx are adjacent to each other, the results of salvage treatment are so distinct that the treatment strategy for these two cancers should not be the same. These differences should be considered when deciding on the primary treatment plan.

Some studies report an acceptable frequency of postoperative complications such as pharyngo-cutaneous fistulas after CRT [8, 9]. Even with high-dose intra-arterial infusion of cisplatin, Proctor et al. [11] found that postoperative complications were not significantly worse than those encountered during primary surgery. On the other hand, Clark et al. [12] showed that irradiation increased the incidence of postoperative pharyngo-cutaneous fistula from 24 to 38%, while Wakisaka et al. [13] noted that although the frequency of pharyngo-cutaneous fistula after RT or CRT was not high, fistula closure tended to be delayed. In the present study, we experienced severe postoperative complications including pharyngo-cutaneous fistulas in 25% of patients who underwent laryngopharyngectomy. Such complications could severely diminish the quality of life for patients.

As the treatment outcomes for the survival of CRT are not superior to those of definitive surgery, the latter should remain a treatment option for patients pursuing a higher chance of survival rather than organ preservation. The CRT survival rate of the present study was 40.6%, while that of the definitive surgery group ($n = 58$) was 45.2% during the same period of comparison in our institute. This difference was not statistically different (Wilcoxon's rank test). CRT has become increasingly popular over the past decade, but it is difficult to make great improvements to successful salvage by advances on surgical technique. On this basis, we recommend surgical salvage for local failure of HPC in patients with good performance status and potentially resectable recurrent tumors; this decision should be made after careful consideration and unless there are no other options for such patients.

## Conclusion

To assess the role of salvage surgery for failure cases of HPC who underwent RT/CRT as an initial treatment, we retrospectively analyzed the outcomes of salvage surgery for such recurrent cases. We demonstrated that it is difficult to salvage locally recurrent HPC, especially at more advanced T-stages or when tumors recur on the posterior wall. The limited effects of surgical salvage for recurrent HPC need to be addressed when choosing the initial treatment plan for HPC.

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頭頸部癌 36(1)：89-92, 2010

# 中・下咽頭癌に対するplanned neck dissectionにおけるリンパ節転移残存状況に関する検討

米澤宏一郎[1) ] 岩江信法[1)] 長谷川稔文[1)]
小松弘和[1)] 副島俊典[2)] 辻野佳世子[2)]
太田陽介[2)] 藤井収[2)]

**要 旨**

当院では2001年12月以降，中・下咽頭癌に対して，Platinum + 5FUの導入化学療法後，T1/T2症例とT3の導入化学療法奏功例を主な対象として同時併用化学放射線療法を根治目的で施行し，N2以上のリンパ節転移陽性症例に対してはさらにplanned neck dissectionを積極的に施行してきた。当初患側のレベルⅠ～ⅤまたはⅡ～Ⅴ領域の郭清を行ってきたが，郭清リンパ節の病理組織学的検討で，初回治療前の画像検査で転移が疑われた領域以外にはviable cellの残存を認めないことが分かった。planned neck dissectionでは，郭清範囲を治療前転移陽性レベル周辺に限局して縮小できる可能性があるものと思われた。

**キーワード**：同時併用化学放射線療法，計画的頸部郭清術，中咽頭癌，下咽頭癌，腫瘍残存リンパ節

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**Investigation of residual cancer node levels in planned neck dissection after concurrent chemoradiotherapy for oropharyngeal and hypopharyngeal cancer:**

Kouichiro Yonezawa[1)], Shigemichi Iwae[1)], Toshifumi Hasegawa[1)], Hirokazu Komatsu[1)], Toshinori Soejima[2)], Kayoko Tsujino[2)], Yosuke Oota[2)] and Osamu Fujii[2)]

[1)] Department of Head and Neck Surgery, Hyogo Cancer Center

[2)] Department of Therapeutic Radiation, Hyogo Cancer Center

***Summary***

We investigated four patients with oropharyngeal cancer and 12 patients with hypopharyngeal cancer who underwent planned neck dissection (PND) after concurrent chemoradiotherapy (CCRT) from December 2001 to January 2005. We performed neck dissections in levels Ⅰ to Ⅴ or Ⅱ to Ⅴ. But we found that there was no residual cancer in the initially negative neck level. We conclude that we can limit the excision in the initially positive level in planned neck dissection.

**Key words**：Concurrent chemoradiotherapy (CCRT), Planned neck dissection (PND), Oropharyngeal cancer, Hypopharyngeal cancer, Residual cancer nodes

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## はじめに

当院では中・下咽頭癌に対して，原則としてまずPlatinum + 5FUの導入化学療法を施行し，その4週後にT1，T2症例の一部に放射線療法，その他の症例には根治手術を行ってきた。2001年12月以降は同時併用化学放射線療法(concurrent chemoradiotherapy: CCRT) とCCRTでの制御が困難と思われるN2以上のリンパ節転移陽性症例に対するplanned neck dissection (PND) を積極的に施行している。今回我々は，初回治療前に把握していた転移陽性リンパ節と，PNDでviable cellの残存が病理組織学的に確認されたリンパ節を，所属レベル単位で比較して検討した。郭清範囲縮小の妥当性の可能性とあわせて文献的考察を加え報告する。

[1)] 兵庫県立がんセンター頭頸部外科
[2)] 兵庫県立がんセンター放射線治療科
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**別刷請求先**：〒673-8558 兵庫県明石市北王子町13-70
兵庫県立がんセンター頭頸部外科
岩江 信法

表 1 化学療法 ICT, CCRT に共通

| 70歳未満 | | 70歳以上 | |
|---|---|---|---|
| Ccr ≧ 80ml/min | | Ccr ≧ 80ml/min | |
| CDDP 80mg/m² | day1 | CDDP 60mg/m² | day1 |
| 5FU 1000mg/body | day1-5 | 5FU 800mg/body | day1-5 |
| Ccr < 80ml/min | | Ccr < 80ml/min | |
| CBDCA | day1 | CBDCA | day1 |
| 5FU 1000mg/body | day1-5 | 5FU 800mg/body | day1-5 |

## 対象および方法

導入化学療法（induction chemotherapy: ICT）は CDDP 80mg/m² day1, 5FU 1000mg/body day1～5 を施行した。70歳以上の症例では CDDP 60mg/m² day1, 5FU 800mg/body day1～5 に減量し，腎機能低下が認められる場合は，CDDP の代わりに CBDCA（AUC 4～5）を用いた（表1）。原則として ICT 奏功症例を CCRT の対象としたが，非奏功例でも強く希望する場合には対象に含めた。また治療方針が当初から CCRT で確定している症例の一部で ICT を省略した。CCRT の際には，放射線治療開始日にあわせて同内容の化学療法を1クールのみ同時併用した。放射線治療は全頸部に 45.0～50.4Gy/25～28Fr 照射後，原発巣と転移陽性リンパ節に 26.0～20.0Gy/13～10Fr を追加照射し，総線量約 70Gy とした。CCRT による粘膜炎や皮膚炎などの急性期反応の沈静化を待ち，なおかつ原発巣再発が無いことを確認した後，6～10週目を目途に PND を予定したが，状況に応じて手術時期を遅延した。T4 any N 症例および T1-3 N0-1 症例では，CCRT 終了後 PND を施行せずに経過観察とした（図1）。

PND 施行当初（中咽頭癌症例1, 2, 下咽頭癌症例1, 2）はレベルⅠ～Ⅴを郭清範囲としていた。その後は原則としてレベルⅡ～Ⅴを郭清範囲とし，もしレベルⅠへの転移や他領域からまたがる進展（中咽頭癌症例3, 下咽頭癌症例9）を認めていればレベルⅠ領域の郭清を追加した。N2c 症例で一側のリンパ節転移が単発性かつ最大径が 3 cm 以下の場合（下咽頭癌症例6, 7, 10）は，同側の郭清を省略した。なお頸部リンパ節転移の有無の評価には CT, MRI および超音波検査を用いたが，検査により評価が異なる場合は特に超音波検査を重視して総合的に判断した。

上記の郭清範囲で PND を施行した中咽頭癌症例（2001年12月から2004年7月の間に初回治療を開始したもの）は4例4側，下咽頭癌症例（2001年12月から2005年6月の間に初回治療を開始したもの）は12例13側であった。これら計16例17側を対象として検討をおこなった。

摘出リンパ節は最大割面で切り出しを行い，H-E 染色で viable cell 残存の有無および角化物や壊死物，石灰化，線維化，異物反応などの癌細胞の転移があったことを示唆する所見の有無を確認した。

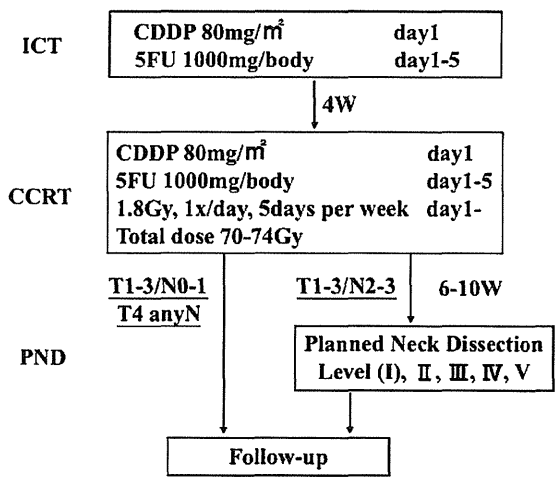


図 1 当院の ICT/CCRT/PND

## 結 果

PND を施行した中咽頭癌4例，下咽頭癌12例の年齢，性別，亜部位，TN 分類，初回治療前転移把握レベル，治療効果，郭清範囲，病理組織学的腫瘍瘢痕残存レベル，病理組織学的 viable cell 陽性レベル，レベル別リンパ節検索個数を示す（表2，表3）。

中咽頭癌では4症例4側中の2側（50%），下咽頭癌では12症例13側中の9側（69%）に viable cell の残存を認めた。viable cell は初回治療前に転移を把握していたレベルの全てあるいは一部に限局しており，その他のレベルに viable cell を認めなかった。viable cell が認められなかったレベルでも，角化物や壊死物，石灰化，線維化，異物反応などの癌細胞の転移があったことを示唆する腫瘍瘢痕の所見は大部分の症例で確認されたが，すべて治療前に転移を把握できていた範囲内であった。

下咽頭癌では，治療前レベルⅡ転移陽性が 11/13（85%）と最も多く，次いでレベルⅢ転移陽性が 10/13（77%）であった。PND 後の viable cell の残存状況は，治療前の転移陽性状況と比較すると，レベルⅡが 6/11（55%），レベルⅢが 5/10（50%），レベルⅣが 2/7（29%），レベルⅤが 3/4（75%）であった。

表 2　中咽頭癌 PND 施行症例頸部リンパ節転移状況

| 症例 | TN | 治療前転移把握レベル | 治療効果 ICT/CCRT | 郭清範囲 | 病理組織学的腫瘍癒痕残存 | 病理組織学的 viable cell 陽性 | レベル別リンパ節数 viable cell 陽性／提出リンパ節 |
|---|---|---|---|---|---|---|---|
| 1. 60男 | 側壁T2N2b | II, III, IV, V | NC/PR | I, II, III, IV, V | II | II, III, IV, V | I (0/5), II (1/6), III (2/2), IV (1/4), V (1/7) |
| 2. 78男 | 前壁T2N3 | II | NC/PR | I, II, III, IV, V | II | なし | I (0/4), II (0/3), III (0/3), IV (0/10), V (0/7) |
| 3. 61男 | 後壁T1N3 | I, II, III, IV, V | −/PR | I, II, III, IV, V | I | なし | I (0/7), II (0/1), III (0/0), IV (0/3), V (0/7) |
| 4. 69男 | 前壁T2N2b | II, III, IV | NC/PR | II, III, IV, V | なし | IV | II (0/3), III (0/7), IV (1/9), V (0/29) |

治療効果（ICT/CCRT）は，リンパ節に対する評価のみを記す。

表 3　下咽頭癌 PND 施行症例頸部リンパ節転移状況

| 症例 | TN | 治療前転移把握レベル | 治療効果 ICT/CCRT | 郭清範囲 | 病理組織学的腫瘍癒痕残存 | 病理組織学的 viable cell 陽性 | レベル別リンパ節数 (viable cell 陽性数／提出リンパ節数) |
|---|---|---|---|---|---|---|---|
| 1. 79男 | ps T2N2a | II | −/NC | I, II, III, IV, V | II | II | I (0/0), II (1/8), III (0/6), IV (0/1), V (0/5) |
| 2. 57男 | psT2N2b | II, III | −/PR | I, II, III, IV, V | II, III | II | I (0/0), II (1/7), III (0/5), IV (0/6), V (0/1) |
| 3. 54男 | psT3N2b | II, III, IV | NC/PR | II, III, IV, V | II | II, III | II (2/3), III (1/2), IV (0/3), V (0/3) |
| 4. 66男 | psT1N2a | II | −/PR | II, III, IV, V | II | なし | II (0/5), III (0/2), IV (0/3), V (0/6) |
| 5. 56男 | psT3N2b | II, III | PR/CR | II, III, IV, V | II | III | II (0/9), III (2/3), IV (0/6), V (0/6) |
| 6. 57男 | psT3N2c | 右：II, III, IV, V<br>左：III | −/CR | II, III, IV, V<br>施行せず | III, IV, V | なし | II (0/3), III (0/12), IV (0/14), V (0/36) |
| 7. 64男 | pwT3N2c | 右：II, III<br>左：II | PR/NC | II, III, IV, V<br>施行せず | II | II | II (1/1), III (0/6), IV (0/5), V (0/8) |
| 8. 85男 | psT2N2b | II, III, IV, V | NC/PR | II, III, IV, V | II, III, IV, V | II, III, IV, V | II (6/7), III (9/10), IV (7/7), V (8/8) |
| 9. 56男 | psT2N3 | III | −/PR | I, II, III, IV, V | II | III | I (0/2), II (0/4), III (2/2), IV (0/4), V (0/2) |
| 10. 57男 | pcT3N2c | 右：II, III, IV<br>左：II | PR/CR | II, III, IV, V<br>施行せず | II, IV, V | なし | II (0/6), III (0/3), IV (0/5), V (0/7) |
| 11. 80女 | pwT3N2c | 右：II, III, IV, V<br>左：II, III, IV, V | NC/PR<br>NC/PR | II, III, IV, V<br>II, III, IV, V | II, III, IV, V<br>III, IV, V | II, V<br>III, IV, V | II (1/3), III (0/1), IV (0/1), V (3/4)<br>II (0/1), III (6/9), IV (4/5), V (3/4) |
| 12. 66男 | psT3N2a | II | −/NC | II, III, IV, V | II, III, IV, V | なし | II (0/7), III (0/2), IV (0/8), V (0/3) |

治療効果（ICT/CCRT）は，リンパ節に対する評価のみを記す。

## 考　察

1986年にMendenhall[1]等が始めて報告したPNDについては，その必要性や合併症に関する議論が賛否両論存在する。Kailash[2]等は放射線治療でcomplete responseが得られた症例に対してはPET検査での経過観察を推奨している。Ojiri[3]等，Anamaria[4]，後のMendenhall[5]等も放射線治療後のCTで残存が疑われる症例にのみ頸部郭清を行うことを提案している。ただし，これらの検討の対象としている疾患は中咽頭癌，下咽頭癌，喉頭癌をすべて含んだものであり，原発部位ごとの十分な検討はなされていないのが現状である。また，放射線療法を単独で施行した症例とCCRT症例では結果が異なることも考えられる。我々が以前に行った中咽頭癌・下咽頭癌症例に対するCCRT後に施行したPNDの検討では，比較的高率にviable cellの残存を認めた。また超音波検査や穿刺吸引細胞診を用いても転移残存リンパ節を評価することが困難であったため，積極的にPNDを施行すべきとの結論に至っている[6]。

今回の検討でも，中咽頭癌で50%，下咽頭癌では69%と，比較的高率にviable cellの残存が認められた。しかし，初回治療前の検索で転移が認められたレベル以外には病理組織学的にviable cellの残存や腫瘍瘢痕を認めなかった。

PNDの必要性については，CCRTの治療効果とあわせて症例毎に慎重に検討すべきであろう。また諸家の報告を参考にする場合は，その治療内容が各々の施設で施行している内容と乖離していないか十分に注意をするべきである。しかし一定以上の治療強度があれば，CCRT後のPNDでは治療前に把握されていたリンパ節転移陽性レベルを十分に郭清すればよいものと推測される。中咽頭癌ではレベルⅡ～Ⅲ，下咽頭癌ではレベルⅡ～Ⅳの領域を郭清範囲とし，転移があれば転移陽性領域を追加するのが妥当であろう。中咽頭癌症例に限定した検討ではあるが，Ilana[7]等の報告でも治療前にレベルⅠ，Ⅴに転移を認めていなければPNDの郭清範囲をⅡ～Ⅳに縮小しても頸部制御率を低下させないとあり，我々の検討結果を支持している。今後はさらに予後や合併症を含めてその妥当性を検討する必要があるものと思われた。

## まとめ

1）中・下咽頭癌に対するCCRT後のPNDにおけるviable cell残存の有無を，リンパ節のレベル毎に検討した。

2）初回治療前の検索で転移が認められたレベル以外には病理組織学的にviable cellの残存や腫瘍瘢痕を認めなかった。

3）中咽頭癌ではレベルⅡ～Ⅲ，下咽頭癌ではレベルⅡ～Ⅳの領域を郭清し，転移があれば転移陽性レベルを追加するのが妥当であると思われた。

4）郭清範囲の縮小や省略の可能性については，さらに検討する必要があるものと思われた。

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