Because tumor regrowth after SBRT is thought to occur at a rapid rate, close follow-ups should be mandatory for patients treated with SBRT.

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ORIGINAL ARTICLE

Carboplatin and etoposide combined with radiotherapy for limited-stage small-cell esophageal carcinoma: three cases and review of the literature

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Abstract
Purpose. Small-cell esophageal carcinoma (SCEC) is a rare disease for which standard therapy has not yet been established. We report the results of three cases of limited-stage SCEC treated with combination therapy using carboplatin (CBDCA) and etoposide (VP-16) and radiotherapy.
Materials and methods. The clinical stage according to the Japanese Classification of Esophageal Cancer 7th ed. was stage III in 2 cases and stage IVa in 1. These patients with limited-stage SCEC were treated at our institution with four cycles of CBDCA and VP-16, either concurrent with radiotherapy for the second two cycles ($n = 2$) or followed by radiotherapy after the last cycle ($n = 1$).
Results. A complete response (CR) was obtained for all three patients, resulting in a response rate of 100%. Two patients are alive at 16.4 and 22.5 months after initial treatment. One patient died with myeloid leukemia at 43.5 months after initial treatment. None of the patients had loco-regional recurrence. Brain metastasis was detected in one patient at 7 months after initial therapy and was treated with stereotactic radiotherapy combined with whole brain irradiation.
Conclusion. CBDCA and VP-16 in combination with radiotherapy should be considered an important treatment option for SCEC.

Key words Small-cell carcinoma · Esophageal cancer · Chemoradiotherapy · CBDCA · VP-16

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Introduction

The esophagus is one of the main sites of extrapulmonary small-cell carcinoma, although it has also been described in the lungs, stomach, intestine, salivary glands, paranasal sinus, thymus, prostate, urinary bladder, breast, uterine cervix, endometrium, and skin. Small-cell esophageal carcinoma (SCEC) accounts for less than 2% of all esophageal malignancies.[1] Standard therapy has not been established because of the rarity of the disease. Like small cell lung cancer (SCLC), SCEC is aggressive and has a poor prognosis. Radiation therapy and surgery are used to manage locoregional disease, and systemic chemotherapy is used for patients with metastasis. SCEC has histological and clinical characteristics similar to those of SCLC, so the same therapeutic strategies are recommended in the literature.[2]

Chemotherapy with CBDCA (carboplatin) and VP-16 (etoposide) is one of the effective regimens for SCLC. Therefore, we used this regimen combined with radiation therapy for limited-stage SCEC. We report the results of three cases of limited-stage SCEC treated with combination therapy using CBDCA plus VP-16 and radiotherapy.

Materials and methods

Patients

During the period from January 2002 to October 2008, a total of 391 patients with esophageal cancer received radiation therapy in our institution, including 3 (0.76%) patients with SCEC. All of the SCECs were diagnosed by pathological findings. The staging workup included chest radiography, barium esophagography, endoscopy, chest and abdominal computed tomography (CT), brain magnetic resonance imaging (MRI), and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). Staging was done according to the UICC TNM Classification of Malignant Tumors, Sixth Edition. The clinical characteristics are summarized in Table 1. We obtained informed consent from the patients for use of clinical data.

Case 1 was a 70-year-old man with mild dysphagia. The primary tumor was located in the middle third of the esophagus, and the tumor length was approximately 10 cm. The left main bronchus was compressed by the primary tumor, as seen on CT and during bronchoscopic examinations, which suggested direct invasion to the bronchus. There was no definite lymphadenopathy. The clinical stage was diagnosed as T4N0M0, stage III.

Case 2 was a 51-year-old woman. She had a performance status (PS) of 3 because of several neurological symptoms suggesting paraneoplastic panencephalitis. The primary tumor was located in the middle third of the esophagus and was widely in contact with the descending aorta, which suggested direct invasion. There were multiple lymph node metastases in the right supraclavicular node, subaortic node, and subcarinal node. The clinical stage was diagnosed as T4N1M0, stage III.

Case 3 was a 66-year-old woman. The type 2 tumor was located from the lower middle third of the esophagus to the esophagogastric junction (Fig. 1a). Multiple lymph node metastases were seen in the mediastinal region, cervical paraesophageal region, esophagogastric junction, and lesser curvature of the stomach region with FDG accumulation (Fig. 1b). The clinical stage was diagnosed as T3N1M0, stage III.

All three patients had limited-stage cancers. We defined the limited stage of the disease as a tumor that could be covered with a single target volume of radiotherapy, similar to the definition for SCLC. We used National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTACE) version 3 to classify adverse events.

Treatment

Table 2 summarizes the treatment used for each patient. The chemotherapy regimen was as follows: on day 1, CBDCA [area under the curve (AUC) was 5 mg/ml/min] was administered intravenously; and, on days 1, 2, and 3, VP-16 (100 mg/m^2) was administered. This regimen was repeated four times at 4-week intervals for all patients. The patient with PS 3 (case 2) received an 80% dose of chemotherapy for all cycles.

Radiotherapy was performed after four cycles of chemotherapy for case 1. For the other two cases, radiation therapy was combined concurrently after two cycles of

Table 1. Patient characteristics

Patient	Sex	Age (years)	PS	Finding type	Site of primary lesion	Tumor length (mm)	T status	N status	M status	Stage
1	M	70	1	2	Mt	100	4	0	0	III
2	F	51	3	2	Mt	30	4	1	0	III
3	F	66	1	2	Lt	100	3	1	0	III

PS, performance status; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus

Table 2. Treatment course and results of treatment

Patient	Treatment course (CT dose %)	RT total dose (Gy)	CT regimen	Response of all sites	Response of primary site	Survival time (months)	Distant metastasis site	Present status
1	CT → RT	61.4	CBDCA/VP	CR	CR	43.5	None	Dead of myeloid leukemia
2	CT → CCRT	61.4	CBDCA/VP	CR	CR	22.5	Brain	Alive with disease
3	CT → CCRT	61.4	CBDCA/VP	CR	CR	16.4	None	Alive with NED

CT, chemotherapy; RT, radiotherapy; CCRT, concurrent chemoradiation; CR, complete response; CBDCA/VP, carboplatin/VP-16 (etoposide); NED, no evidence of disease

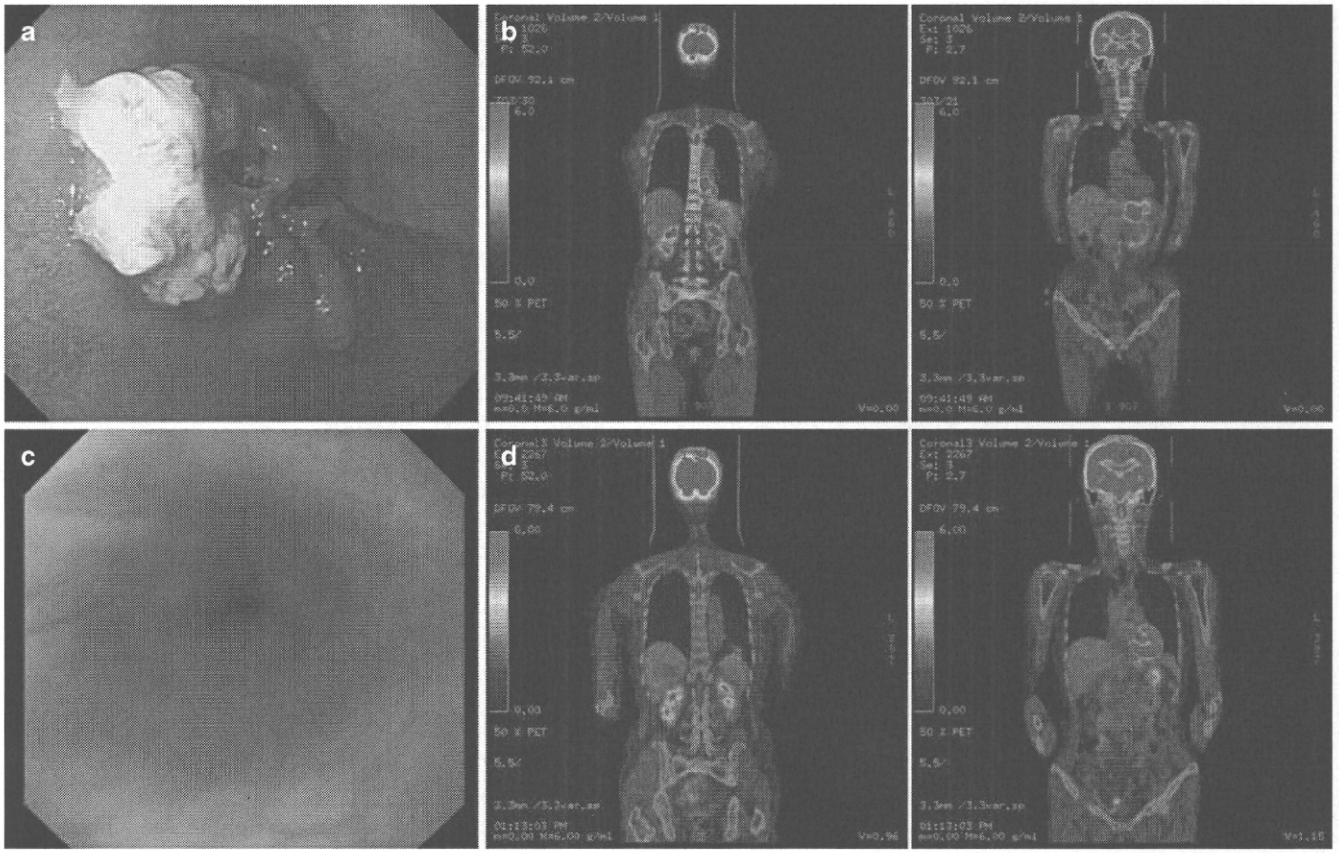

Fig. 1. Case 3, a 66-year-old woman. Lt T3N2M0. **a**, **b** Pretreatment. **a** Endoscopy shows that the type 2 tumor is located 32–42 cm from the dental arch. **b** Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET-CT). *Left* the FDG-accumulated tumor is seen from the lower third of the esophagus to the fundus of the stomach. *Right* lymph nodes in the cervical paraesophageal region, esophagogastric junction, and lesser curvature of the stomach region are positive. **c**, **d** Post-treatment. **c** Endoscopy shows no residual tumor. **d** FDG PET-CT reveals that FDG accumulation in the esophageal tumor and the lymph nodes has disappeared

chemotherapy. The positioning of the field and dosimetry were determined using CT and a three-dimensional (3D) treatment plan. An opposing T-shaped field—including prophylactic irradiation of the bilateral supraclavicular, whole mediastinal, and celiac nodes—was used in all patients (Fig. 2a). The field was changed to avoid the spinal cord after a total dose of 41.4 Gy, by conventional fractionation (1.8 Gy/day five times a week). The changed field (Fig. 2b) was used as a total dose of 20 Gy, by conventional fractionation (2 Gy/day five times a week). The total dose was 61.4 Gy.

Results

Response and survival

A complete response (CR) was obtained for all three patients, resulting in a response rate of 100% (Table 2). Case 1 had no local recurrence or metastasis for more than 40 months but died of acute myeloid leukemia (AML). In case 2, brain metastasis was found 7 months after the start of the initial therapy. The brain metastasis was controlled using stereotactic radiosurgery combined with whole-brain irradiation, and the patient is still alive without other recurrence. Case 3 had no recurrence for 16 months after the initial chemoradiotherapy (Fig. 1c,d).

Adverse reactions

The toxicity of this regimen is shown in Table 3. All patients had grade 2 esophagitis. The most severe adverse reaction was myelosuppression. Grade 4 leukocytopenia was observed in one patient, grade 3–4 anemia in two patients, and grade 4 thrombocytopenia in two patients. In one patient, the chemotherapy dose was reduced to 80% of the original dose beginning with the second course because of an adverse hematological reaction. Because the chemotherapy dose was reduced, the patient

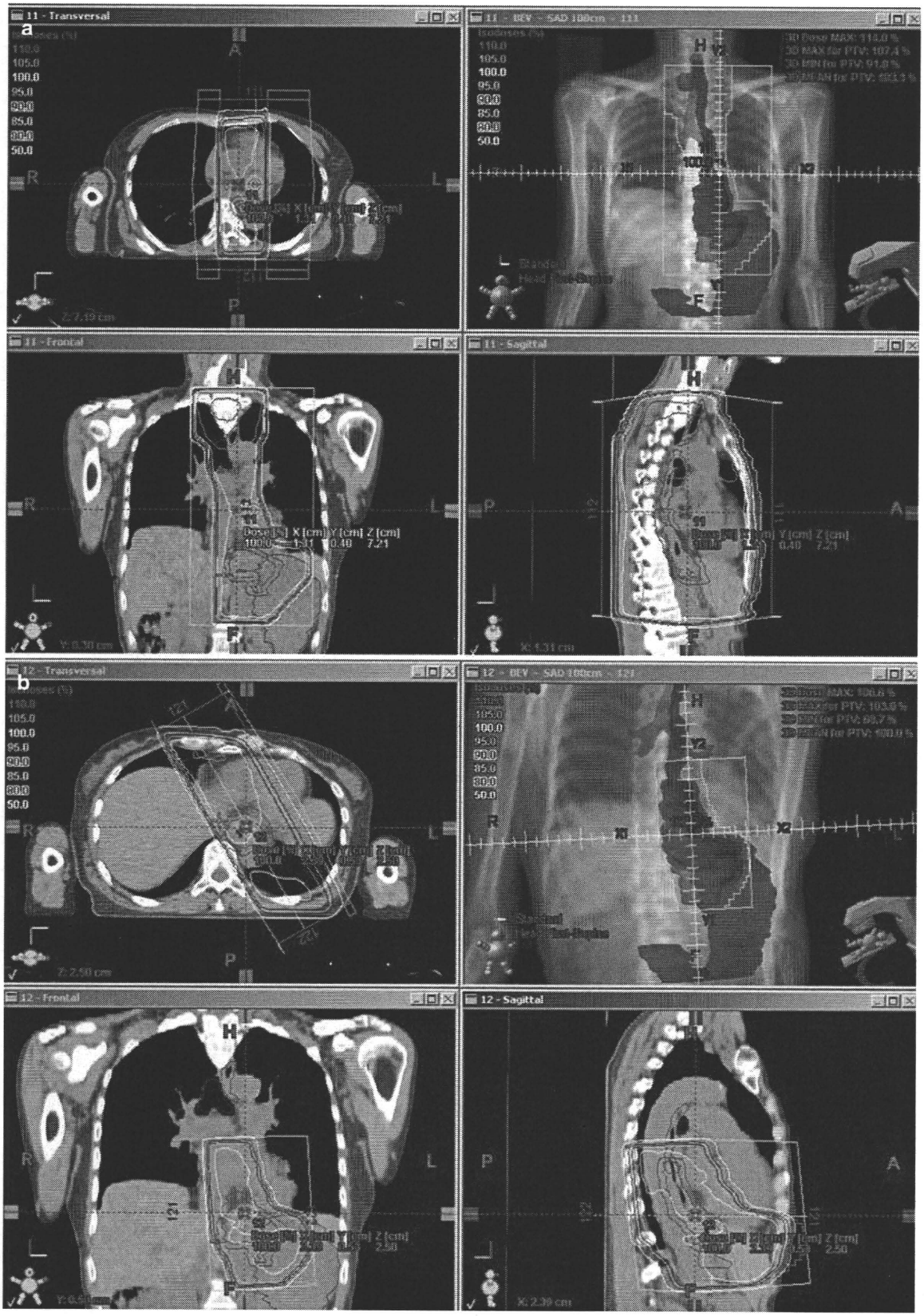

Fig. 2. Radiation field in case 3. **a** The first field, including the tumor and narrow supraclavicular, mediastinal, and celiac regions, received a total of 41.4 Gy. **b** The changed field received a total dose of 20 Gy to avoid the spinal cord. *A*, anterior; *P*, posterior; *R*, right; *L*, left; *H*, head; *F*, foot; *PTV*, planning target volume; *MAX*, maximum; *MIN*, minimum

Table 3. Adverse reactions

Patient	Esophagitis	Acute phase: hematological adverse reaction			Late phase
		Leukopenia	Anemia	Thrombocytopenia	
1	Grade 2	Grade 2	Grade 3	Grade 2	None
2	Grade 2	Grade 2	Grade 1	Grade 4	None
3	Grade 2	Grade 4	Grade 4	Grade 4	None

could still receive four courses. Grade 3–4 myelosuppression, which was seen in all three patients, was managed by granulocyte-colony stimulation factor (G-CSF) and platelet and/or red cell concentrates mannitol adenine phosphate (RC-MAP) transfusion. No patients had any other severe adverse reactions such as pneumonitis and pericarditis. There were no delays in delivering chemotherapy and radiotherapy because of adverse reactions.

Discussion

Small-cell esophageal carcinoma is a rare disease. Following the initial two cases reported by McKeown in 1952,[3] there have been fewer than 300 cases of the disease in the medical literature.[4] SCEC accounts for only 0.8%–2.4% of all esophageal malignancies,[5] or 1.2% of all esophageal malignancies in the Japanese population.[1]

Standard therapy has not been established because of the rarity of the disease. As in the case of SCLC, the SCEC behaves aggressively and exhibits widespread metastasis at diagnosis. Therefore, limited-stage SCEC is rare, although all three of our patients had limited-stage cancer. Several retrospective reviews have reported that SCEC has a poor prognosis. In a literature review of 230 patients with SCEC, the median survival for patients with local disease was 8 months, and that for patients with extensive disease was only 3 months.[6]

Many studies have emphasized that systemic chemotherapy is the key to treating SCEC. Nemoto et al. presented a retrospective series including 24 patients with limited-stage SCEC and reported that patients who did not receive chemotherapy did not survive for more than 2 years, and the use of chemotherapy was a significant prognostic factor.[7] Many investigators have recommended that SCEC should be managed in a manner similar to SCLC. Combination therapy with cis-diaminedichloroplatinum (CDDP) and VP-16 has been widely used as a standard chemotherapy regimen for SCLC. Okamoto et al. reported that a carboplatin (CBDCA) plus VP-16 regimen could be an alternative regimen for elderly or high-risk patients.[8] One benefit of using CBDCA is that it does less harm to the kidneys than CDDP, so it does not require hydration. Therefore, we have been using CBDCA and VP-16 combined with radiation therapy for the treatment of limited-stage SCEC, which we have encountered three times. All of our patients experienced a grade 3–4 adverse hematological reaction during treatment. However, we were able to use four cycles of chemotherapy in all of these cases, including an elderly patient and a patient with poor PS owing to the fact that we added supportive therapy with G-CSF and RC-MAP or platelet transfusion. Recently, Chin et al. reported that the combination of CPT-11 and CDDP was also effective in patients with SCEC,[2] and the CPT-11 plus CDDP combination is one of the standard regimens for SCLC in Japan.[9] Nonetheless, there have been few reports on the treatment of SCEC using this chemotherapy.

Several reports have shown that good local control rates can be obtained by radiotherapy. Nemoto et al.[7] reported an excellent local control rate (92%) for irradiated patients treated with 60–70 Gy (median 65 Gy). In our three patients, who received radiotherapy of 61.4 Gy combined with chemotherapy, a complete response was obtained in all cases as an initial response. Furthermore, none of the patients had a locoregional recurrence during the follow-up period (16–43 months). In the report by Chin et al., 7 of 12 cases initially treated with CPT-11 plus CDDP without radiotherapy suffered from locoregional recurrence. In contrast, Yamashita et al. reported that nine patients with limited-stage SCEC were treated with concurrent chemoradiation using CDDP and VP-16, and two of the nine cases suffered from locoregional recurrence.[10] In their report, the total dose of radiotherapy was 50 Gy. The optimal radiation dose has not been discussed in the literature to date; but given the good locoregional control of our cases and those of Nemoto et al.,[7] we suggest that a radiation dose of 60 Gy or more is adequate for definitive radiation therapy. Further studies are needed to establish the fractionation schedule and the proper timing of the combination with chemotherapy. We performed concurrent chemoradiation therapy beginning with the third cycle

in two patients, whereas Yamashita et al.[10] began with the first cycle. We thought that it would be possible to reduce the field size by using two cycles of chemotherapy alone.

Several authors have suggested that surgery is a possible choice of treatment for SCEC.[11,12] Hosokawa et al.[13] reported five patients who underwent radical esophagectomy alone, and only one patient survived more than 24 months. When surgery was associated with chemotherapy, longer survivals were achieved. Also, in the report by Nemoto et al.,[7] all three long-term survivors (>5 years) underwent surgery followed by radiation therapy of 45–50 Gy and chemotherapy. In the present study, we were not able to determine which treatment was better because the number of patients was small and surgery tended to be performed during the early stage. However, Hudson et al.[14] reported that the median survival of six patients with limited-stage disease who were treated with combined modality therapy using platinum-based combination chemotherapy and radical radiotherapy was 24.4 months (9–104 months). They concluded that such combination therapy might allow a nonsurgical approach to management, avoiding the morbidity of esophagectomy.

Small-cell esophageal cancer is a systemic disease. In Nemoto et al.'s report, metastasis developed in more than half of the patients despite the use of chemotherapy.[7] The most frequent sites were bone and liver, followed by lymph nodes, brain, and lungs. In the present study, only one of three patients had metastasis, which was in the brain at 7 months after initial treatment. The brain metastasis was controlled by radiation therapy. It is known that prophylactic cranial irradiation (PCI) improves the survival rate for patients with SCLC in a complete response.[15,16] However, it is difficult to determine the role of PCI in the treatment for SCEC because of the rarity of this disease. Similar to SCLC, PCI may also be considered for SCEC patients showing a complete response after the initial chemoradiotherapy.

Among the present cases, one patient (case 1) died with AML at 40 months after the completion of initial chemoradiotherapy. AML is well known to be one of the secondary malignancies induced by chemoradiotherapy that includes VP-16. Therefore, we cannot deny the possibility that the AML of this patient was secondary AML induced by the initial chemoradiotherapy. In a previous study,[17] about 1.3% of patients treated with chemotherapy including VP-16 suffered from AML. At the follow-up examination after the initial therapy, we need to pay careful attention not only to the occurrence of pulmonary and cardiovascular toxicities but also to that of secondary malignancies.

Conclusion

Although only a small number of patients with SCEC were included in this report, our results suggest that the combination of CBDCA and VP-16 with radiation therapy should be considered an important treatment option for SCEC. Because a prospective trial cannot be envisaged owing to the rarity of SCEC, multi-institutional studies are needed to obtain a sufficiently large population for investigation and optimization of local therapy for this disease.

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Case Report

A Case of Radiation Fibrosis Appearing as Mass-Like Consolidation after SBRT with Elevation of Serum CEA

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We report a case of radiation fibrosis appearing as mass-like consolidation, which was difficult to distinguish from local recurrence. A 72-year-old woman was diagnosed as having primary lung cancer (cT1N0M0 stage IA) in the right upper lobe and was treated with SBRT of 48 Gy in 4 fractions. After 12 months, mass-like consolidation appeared around the irradiated area, and after 13 months, it had increased in size. FDG-PET revealed high uptake (SUV max = 5.61) for the consolidation. CT-guided biopsy was performed, but we could not confirm the diagnosis. Considering her poor respiratory function and her age, short-interval follow-up was performed. After 15 months, the consolidation enlarged at the dorsal side, and carcinoembryonic antigen (CEA) became elevated (14.6 ng/mL). Serum KL-6 (436 U/mL) and SP-D (204 ng/mL) were also elevated. However, after 16 months, serum CEA slightly decreased. The consolidation gradually retracted on follow-up CT images. CEA, KL-6, and SP-D were also decreased by degrees. After 40 months, there is no evidence of local recurrence.

1. Introduction

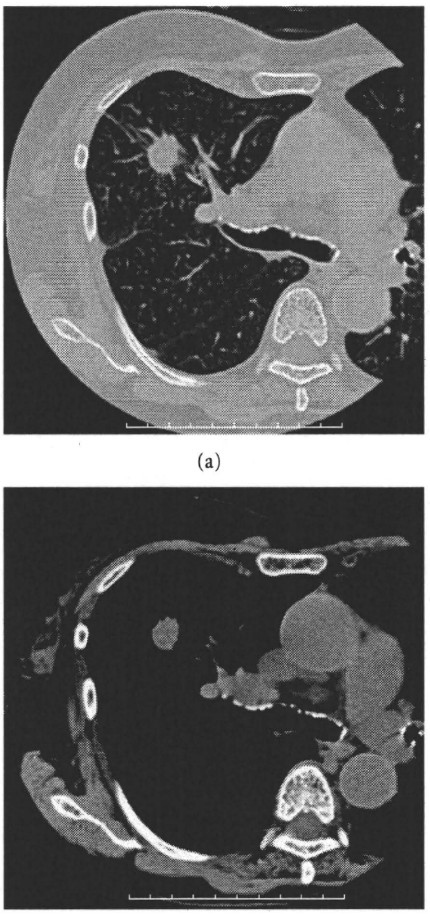
Stereotactic body radiotherapy (SBRT) is an effective therapy for early-stage lung cancer. In some cases after SBRT, dense consolidation is observed over or around the tumors on follow-up computed tomography (CT). Sometimes, it appears as mass-like consolidation, in which case it is difficult to distinguish radiation fibrosis from local recurrence, though it is important from a clinical point of view to make this distinction.

We experienced a case of radiation fibrosis appearing as mass-like consolidation with elevation of serum carcinoembryonic antigen (CEA), which was difficult to distinguish from local recurrence. In this paper, we present this case along with a review of the literature.

2. Case Report

A 72-year-old woman was diagnosed as having primary lung cancer (cT1N0M0 stageA) of the right upper lobe (Figure 1). Because her respiratory function was not sufficient for her to undergo surgical resection, she was treated with SBRT. Irradiation was performed with a 4-MV and 10-MV linear accelerator. Forty-eight Gy in 4 fractions was prescribed at the isocenter with multiple static ports. The isodose distribution of SBRT is shown in Figure 2. Serum CEA was elevated to 14.7 n/mL, but serum KL-6 (230 U/mL) and SP-D (72.8 ng/mL) were not elevated before SBRT. She was a heavy smoker, and her Brinkman index was 900 (20 × 45 years).

Follow-up CT scans were performed 2, 6, 9, and 12 months after SBRT. On CT images 2 months after treatment, irregularly shaped patchy consolidation, which was considered radiation pneumonitis, appeared in the irradiated field (Figure 3(a)). After 6 and 9 months, the patchy consolidation was retracted, which was considered to be typical radiation fibrosis (Figures 3(b), 3(c)), and serum CEA gradually decreased. However, after 12 months, mass-like consolidation appeared around the irradiated area (Figure 3(d)), and after 13 months, it had increased in size.



(a)

(b)

FIGURE 1: CT images before SBRT showing a solitary lung tumor in the right upper lobe.

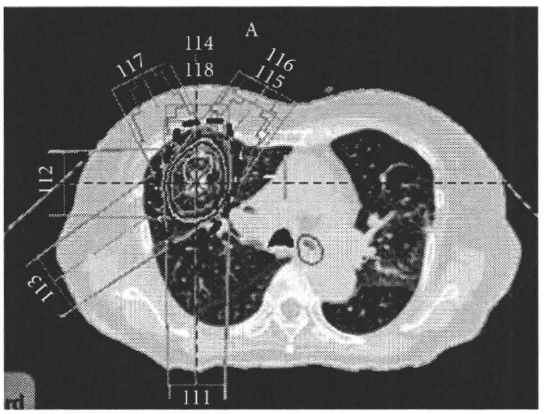
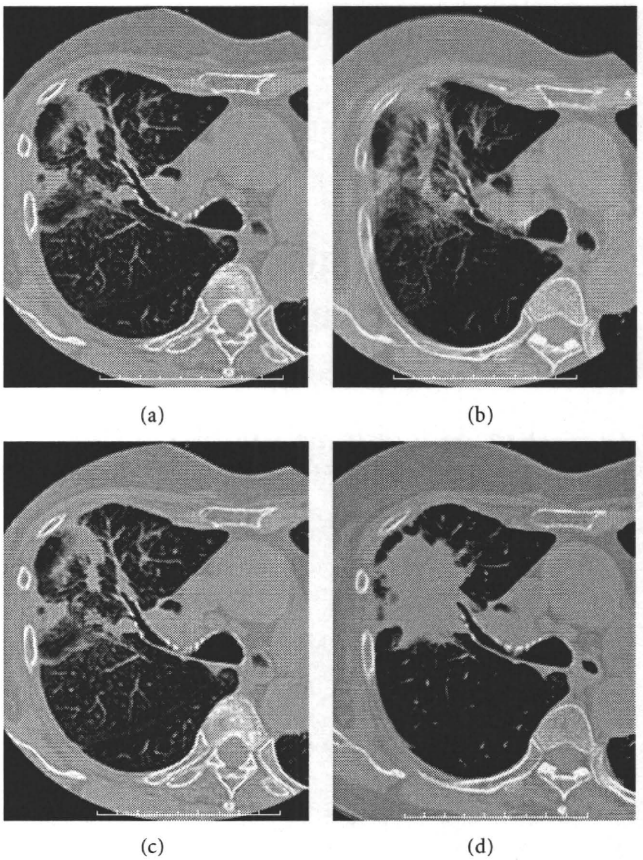


FIGURE 2: Dose distribution of treatment plan. The dashed line indicates the 50% isodose curve.

Because ecstatic air-containing bronchi were not observed within the consolidation, and the 3b branch of the right lung was displaced on CT images, the possibility of local recurrence was considered. At this time, serum CEA, KL-6, and SP-D were not elevated compared with the previous values. FDG-PET revealed high uptake (SUVmax = 5.61)



(a) (b)

(c) (d)

FIGURE 3: Serial CT images after SBRT. (a), (b), (c) CT images at 2, 6, and 9 months after SBRT show irregularly shaped patchy consolidation in the irradiated area. (d) CT images at 12 months after SBRT showing the appearance of mass-like consolidation in the irradiated area.

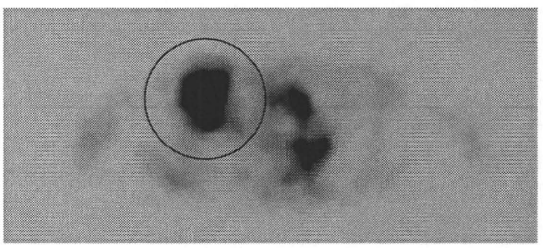
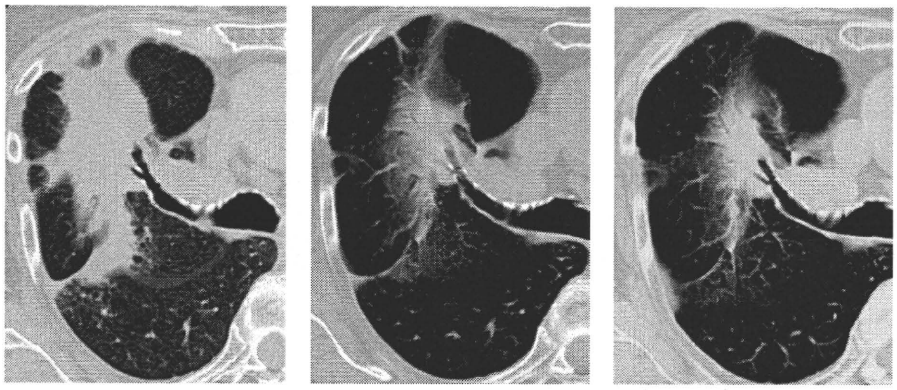


FIGURE 4: FDG-PET at 13 months after SBRT. High FDG uptake (SUVmax = 5.61) was observed for the consolidation.

for the consolidation (Figure 4). CT-guided biopsy was performed. The result of cytology was class II, and histologically cancer cells were not detected. Because there was no definite evidence of malignancy, and considering her poor respiratory function and her age, short-interval follow-up was performed.

After 15 months, the consolidation enlarged at the dorsal side, and serum CEA was elevated to 14.6 ng/mL. Serum KL-6 and SP-D were also elevated to 436 U/mL and 204 ng/mL, respectively. However, after 16 months, serum CEA started to decrease slightly. Furthermore, the consolidation gradually



(a) (b) (c)

FIGURE 5: Serial CT images. (a) CT images at 15 months after SBRT show the mass-like consolidation enlarged at its dorsal side. (b), (c) CT images at 18 and 27 months after SBRT show that the mass-like consolidation gradually retracted.

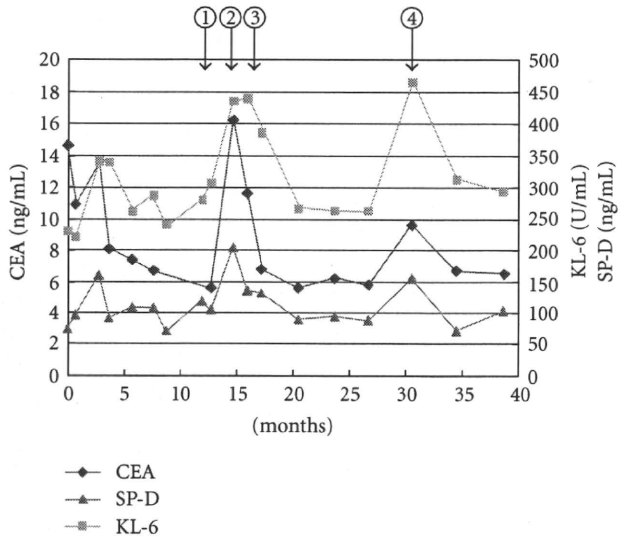


FIGURE 6: Serial changes of serum CEA, KL-6, and SP-D. (1) At 12 months after SBRT, mass-like consolidation appeared in the irradiated area. (2) At 15 months, the mass-like consolidation enlarged at the dorsal side and serum CEA increased accompanied by KL-6 and SP-D. (3) At 16 months, serum CEA was slightly decreased. (4) At 31 months, minimal lung opacities suggesting pneumonia in the left lower lobe were observed on CT images, but no significant change was seen in the irradiated area.

retracted on follow-up CT images (Figure 5). CEA, KL-6, and SP-D decreased by degrees (Figure 6), although transient re-elevation was observed after 31 months, accompanied by the development of pneumonia in the left lower lung. At 40 months after the completion of SBRT, she is alive without local recurrence.

3. Discussion

On CT images, parenchymal consolidation with a straight lateral margin and air bronchograms is typical for radiation fibrosis, whereas a homogeneous opacity without air bronchograms and with a convex border is strongly suggestive of recurrent tumor in the irradiated lung [1]. In addition, the filling in of bronchi within radiation fibrosis is abnormal and usually represents local recurrent malignancy or a superimposed infection [2]. Koenig et al. firstly described as mass-like radiation fibrosis related to 3-D conformal radiotherapy [3]. Mass-like radiation fibrosis in their cases was accompanied by volume loss and bronchiectasis. However, in our case, neither volume loss nor bronchiectasis was observed at the presence of mass-like consolidation. Therefore, it was difficult to differentially diagnose this mass-like consolidation as radiation fibrosis from local recurrence. Aoki et al. [4] reported patchy consolidation or discrete consolidation in 74% of cases during the first 6 months after SBRT. In SBRT, the shape of the dose distribution with a lower dose tended to become large and irregular, while a higher dose could be concentrated uniformly on the tumor. Matsuo et al. [5] reported that mass-like consolidation appeared in 27 (68%) of 40 tumors treated with SBRT. Of these 27 mass-like consolidations, 24 were radiation-induced lung injuries (RILI) and 3 were local recurrences. According to the previous reports mentioned above, it is not uncommon for mass-like consolidation to appear after SBRT. In conventional radiation therapy, the shape of the dose distribution of irradiated lungs is simple, and the boundary between the nonirradiated and irradiated lung is usually distinct [4]. In contrast, in SBRT, multiple non coplanar portals with various directions were used. And the dose distribution usually has a 3-D shape and concentrates around the tumor. Therefore, radiation fibrosis after SBRT can appear in a 3-D shape, and is sometimes observed as mass-like lesions. In our case, also, the consolidation after SBRT had a 3-D shape, and was observed in approximately 50% or more of the isodose area.

Matsuo et al. [5] also reported that mass-like consolidations appeared at a median of 5 months (range, 2 to 9 months) after SBRT. The time to the appearance of the mass-like consolidations after SBRT was 2 to 9 months (median,

5 months) in RILI cases and 4 to 7 months (median, 7 months) in local recurrence cases. There was no significant difference in the time to appearance between RILI and local recurrence. According to their report, the size of the mass-like consolidations did not increase in any RILI cases after 12 months or later. In our case, however, the mass-like consolidation appeared at 12 months after SBRT, and had increased in size at 13 months. Radiation fibrosis can appear as mass-like consolidation even 12 months or more after the completion of SBRT.

In our case, serum CEA was also elevated in addition to the mass-like consolidation. The CEA elevation and the late appearance of the mass-like consolidation made it very difficult to differentially diagnose this condition as RILI from local recurrence. Several authors have reported that CEA elevation is observed in patients with various pulmonary inflammations such as acute pneumonia, chronic bronchitis, bronchial asthma, especially in cases with mucoid impaction, and idiopathic interstitial pneumonia [6–9]. In our case, after 31 months, transient and slight re-elevation of serum CEA was seen, accompanied by the elevation of serum KL-6 and SP-D. CT examination at this time revealed minimal lung opacities, suggesting the presence of pneumonia in the left lower lobe, but no significant change in the irradiated area. This finding also suggested that the transient CEA elevation after SBRT was related to inflammatory changes of the lung in this case. The serum CEA level of smokers has been reported to be higher than that of nonsmokers [9]. CEA secretion from pulmonary epithelial cells has been considered to be influenced by smoking [10]. This patient was a heavy smoker, and serum CEA did not decrease to its normal level after SBRT. The elevation of the serum CEA level before SBRT may have been caused not only by the tumor but also by heavy smoking.

Serum KL-6 and SP-D are useful serum markers of inflammatory lung diseases, typically interstitial pneumonia [11]. It has also been reported that KL-6 and SP-D can become elevated in some cases of adenocarcinoma [12]. In our case, however, serum KL-6 and SP-D levels were not elevated before SBRT. Also, serial changes of these serum marker levels were almost synchronous with the radiological change of the consolidation after SBRT and that following pneumonia in the left lower lung. Therefore, the changes in the serum KL-6 and SP-D levels after SBRT were considered to reflect the severity of the pulmonary inflammation rather than the progression of cancer.

4. Conclusion

We experienced a case of radiation fibrosis appearing as mass-like consolidation after SBRT with the elevation of serum CEA, which was difficult to distinguish from local recurrence. If it is difficult to make a definitive diagnosis by further examination including FDG-PET and histological examination, short-interval follow-up should be recommended.

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Concurrent Chemoradiotherapy with S-1 for T2N0 Glottic Squamous Cell Carcinoma

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Early glottic carcinoma/Squamous cell carcinoma/Chemoradiotherapy/S-1.

In this study, we evaluated the feasibility, efficacy and toxicity of concurrent chemoradiotherapy with S-1 (tegafur-gimeracil-oteracil potassium) for T2N0 glottic carcinoma. A total of 23 patients with T2N0 glottic carcinoma received chemoradiotherapy with S-1. Radiotherapy consisted of five daily fractions of 2 Gy per week, to a total median dose of 70 Gy. S-1 was administered 65 mg/m^2 per day for 4 weeks, beginning on the day therapy was started, followed by 2 weeks off the drug and twice a day until the end of radiotherapy. Initial local control rate of the primary tumor was achieved in all patients. The median follow-up period for all patients was 38 months. The 3-year local control rate was 95.4%. Regarding adverse reactions, grade 3 mucositis upon clinical examination, mucositis upon functional/symptomatic examination, dysphagia, hepatic toxicity and anemia were observed in 13, 2, 2, 1 and 1 patients, respectively. This chemoradiotherapy did not result in grade 4 acute toxicity or severe late toxicity. Chemoradiotherapy with S-1 was feasible, well tolerated and effective. This therapy is suggested as a possible regimen for improving local control of T2N0 glottic carcinoma.

INTRODUCTION

Definitive radiotherapy is indicated as the primary treatment for early glottic carcinoma. Radiotherapy has the advantage of preserving laryngeal structure and function in the majority of patients. The 5-year local control rates with radiotherapy alone range from 81% to 94% for T1N0 glottic carcinoma and from 67% to 80% for T2N0 glottic carcinoma (T2N0GC).[1–4] In cases of T2N0GC, local control with RT alone could be improved upon. To improve the local control rate of T2N0GC, clinicians have begun to perform concurrent chemoradiotherapy (CCRT).[5–8] Among chemotherapeutic agents, S-1 is an oral antitumor agent that consists of tegaful and may act as a radiosensitizer. Preclinical and clinical studies have demonstrated the radiosensitizer potency of S-1.[9–12]

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In our institution, CCRT with S-1 has been used for patients with T2N0GC since 2003. In the present study, we reviewed the clinical outcome of CCRT with S-1 for T2N0GC and evaluated the feasibility, efficacy and toxicity of this regimen.

MATERIALS AND METHODS

The records of 29 patients treated consecutively with definitive radiotherapy to T2N0 glottic squamous cell carcinoma as a primary treatment modality for larynx preservation, according to the International Union Against Cancer (UICC, 1997) TNM classification system between February 2003 and July 2008 were reviewed. Six patients were excluded from analysis because they could not received concurrent chemoradiotherapy with S-1, due to renal failure (n = 4), liver dysfunction (n = 1) or poor performance status (n = 1). All patients were men, and the median age was 64 years (range 52–78 years). Performance status was between 0 and 1, according to Eastern Cooperative Oncology Group criteria. Radiotherapy was delivered five days a week using a once-daily fractionation of 2.0 Gy; the median total radiation dose was 70 Gy (range: 62–70 Gy). Three patients, who discontinued at 62 Gy, 66 Gy and 68 Gy, respectively, refused further radiotherapy. Four patients underwent radio-

therapy with a 6-MV photon beam and 19 patients with a 4-MV photon beam. Parallel-opposed lateral fields were used and a median field size was 36 (ranging from 28 to 42 cm^2). Appropriate wedge filters were used to improve dose homogeneity. S-1 was administered 65 mg/m^2 per day for 4 weeks, beginning on the day therapy was started, followed by 2 weeks off the drug and then twice a day until the end of radiotherapy. A metachronous malignant tumor of another primary organ was observed in 6 patients. Gastric cancer was observed in 2 patients, mesopharyngeal cancer in 1, esophageal cancer in 1, colon cancer in 1 and thyroid cancer in 1. No synchronous malignant tumors were detected. All patients were treated on an inpatient basis. Initial responses were evaluated with transnasal laryngoscopy four weeks after completion of the concurrent chemoradiotherapy.

The estimated overall survival rate and local control rate were calculated using the Kaplan-Meier method. Toxicity was assessed during and after treatment, using the Common Terminology Criteria for Adverse Events, version 3.0.

RESULTS

The follow-up period for all patients was 6–68 months (median: 38 months) and follow-up period was relatively short. The overall treatment time of all patients was 50–102 days (median: 59 days). Twelve patients interrupted radiotherapy, and the most common causes were mucositis pain (42%) and evaluation of the effect of treatment (42%). S-1 was administrated to all patients for over 4 weeks. Because of toxicities (grade 3 anemia, grade 3 hepatic toxicity and grade 3 mucositis upon functional/symptomatic examination), S-1 administration was interrupted in 3 patients. Initial local control of the primary tumor was achieved in all patients. One patient experienced local recurrence and underwent total laryngectomy 8 months after completion of CCRT. The estimated curve of local control is shown in Fig. 1. The 3-year overall survival rate, 3-year cause-specific survival rate and 3-year local control rate of all patients were 100%, 100% and 95.4%, respectively. One patient died of thyroid cancer 38 months after treatment; however, local control of this patient's glottic carcinoma was maintained.

The treatment-related acute toxicities are summarized in Table 1. Regarding non-hematological toxicity, grade 3 mucositis upon clinical examination was observed in 13 patients. Grade 3 mucositis upon functional/symptomatic examination and dysphagia were each observed in 2 patients. Grade 3 hepatic toxicity was observed in 1 patient. Regarding hematological toxicity, grade 3 or greater toxicity was not observed except in one patient with grade 3 anemia. This CCRT did not result in severe treatment-related late toxicity.

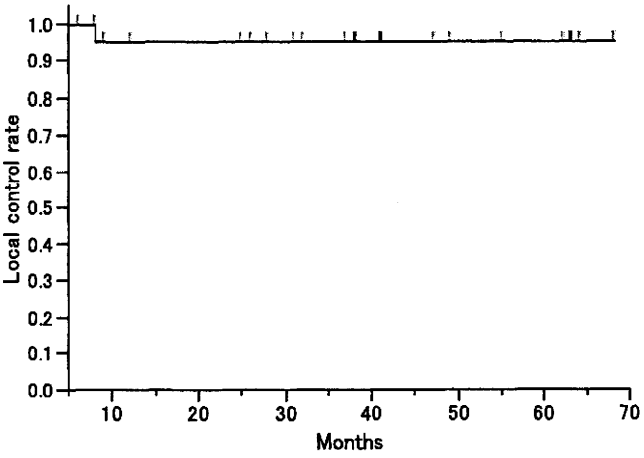

Fig. 1. Local control rate of 23 patients

Table 1. Acute toxicity

	Grade*			
Parameter	1	2	3	4
Hematological				
Leukocytopenia	4	2	0	0
Neutropenia	2	3	0	0
Anemia	14	1	1	0
Thrombocytopenia	2	1	0	0
Nonhematological				
Dermatitis	19	2	0	0
Mucositis (clinical exam)	3	7	13	0
Mucositis (functional/symptomatic)	11	9	2	0
Dysphagia	11	9	2	0
Hepatic toxicity	15	1	1	0
Diarrhea	5	3	0	0

*Common Terminology Criteria for Adverse Events (version 3.0, 2003)

DISCUSSION

In most institutions, early glottic carcinoma is treated with conventional radiotherapy as primary treatment for laryngeal preservation. A standard course of radiation for early glottic cancer usually consists of a total of 60–70 Gy administrated in single daily fractions over 6 weeks. For early glottic carcinoma, the published dose-response curves for local control appear to be shallow in the dose range between 60 Gy and 70 Gy.[13,14] Although Akine *et al.* documented that local control rates have a tendency to increase as the total radiotherapy dose increases in the range of 57.5 Gy to 72.5 Gy,[15]

treatment with conventional radiotherapy alone for local control of T2N0GC is thought to be improved upon; the 5-year local control rate ranged from 67% to 80%. To improve the local control rate, clinicians have performed CCRT for T2N0GC and CCRT has been reported to be effective. Itoh *et al.* reported that administration of low-dose cisplatin and 5-fluorouracil resulted in an initial local control rate of 91.0% and ultimate laryngeal preservation by cordectomy in all cases.[5] Akimoto *et al.* documented that administration of cisplatin (CDDP) alone, CDDP plus docetaxel or docetaxel alone resulted in a 5-year disease-free survival rate of 91.8%. Niibe *et al.* reported that administration of UFT resulted in a 3-year local control rate of 90.1%.[7] Nishimura *et al.* documented that administration of carboplatin and UFT resulted in a 5-year larynx preservation survival rate of 93.3%.[8] In the present study, the initial local control rate was 100% and the 3-year local control rate 95.4%, which are nearly the same as of the rates of previous studies. Beam energy, field size, daily fraction size, prolonged overtreatment time, impaired cord mobility, anterior commissure involvement and low pretreatment hemoglobin level have been reported as important prognostic factors for local control.[16,17] There were no poor prognostic factors applied to the recurrent case in our study.

Among chemotherapeutic agents, S-1 is an oral antitumor agent consisting of tegaful, 5-chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxonate in a molar ratio of 1:0.4:1. Tegaful is a prodrug of 5-fluorouracil (5-FU), and CDHP and potassium oxonate prolong a higher concentration of 5-FU in the bloodstream and diminish the toxicity of 5-FU.[18] Although CCRT with S-1 is not considered the standard therapy for head and neck cancer, preclinical and clinical studies have demonstrated the radiosensitizing potency of S-1 and, in this study, S-1 was administered as a radiosensitizer. Harada *et al.* documented that S-1 greatly enhanced radiosensitivity by suppressing the activation of Akt/PKB.[9] Zeng *et al.* reported that S-1 enhanced radiation-induced apoptosis of endothelial cells by suppressing hypoxia-inducible factor-1(HIF-1) activity, resulting in increased radiosensitivity.[10] In clinical data, Niibe *et al.* documented that administration of S-1 resulted in a 3-year local control rate of 100% in the 24 T2N0GC patients treated with CCRT using S-1.[7] Tsukuda *et al.* reported that in CCRT with S-1 for locally advanced squamous cell carcinoma of the head and neck, pathologically, complete response rates were 93% in stage III and 54% in stage IV tumors.[12] The potency of S-1 as a radiosensitizer has also been demonstrated in other solid tumors, with response rates of 24% for pancreatic cancer,[19] 74% for esophageal cancer[20] and 22% for lung cancer.[21]

With regard to adverse reactions to S-1 for head and neck cancer, Harada *et al.* documented that administration of S-1 for 2 weeks followed by 1 week of rest or 4 weeks followed by 2 weeks resulted in grade 3 toxicity rates for mucositis, liver dysfunction, leukocytopenia, neutropenia and anemia of 15%, 7%, 11%, 11% and 4%, respectively.[11] Tsukuda *et al.* reported that administration of S-1 for 2 weeks followed by 1 week of rest resulted in grade 3 toxicity rates for mucositis, leukocytopenia and neutropenia of 20%, 6% and 12%, respectively.[12] Tsuji *et al.* documented that administration of S-1 for 2 weeks followed by 2 weeks of rest resulted in grade 3 toxicity rates for mucositis, dysphagia and dermatitis of 5%, 5% and 19%, respectively.[22] As previously indicated, in the past studies, CCRT for head and neck cancer with S-1 has been reported to be performed with tolerable adverse events. In the present study, with administration of S-1 for 4 weeks followed by 2 weeks of rest, although grade 3 mucositis upon clinical examination was observed in 13 patients (57%), the grade 3 toxicity rate of mucositis upon functional/symptomatic examination and dysphagia were only 8% and 8%, respectively. Grade 3 toxicity rates of anemia and liver dysfunction were 4% and 4%, respectively, and no grade 4 toxicity was observed. Harada *et al.* documented that a 2-week application followed by a 1-week rest regimen for oral squamous cell carcinoma reduced adverse reactions and enhanced therapeutic effects, compared with a 4-week application followed by a 2-week rest regimen.[11] The optimal schedule of CCRT with S-1 for T2N0GC has not yet been established, so it is important to take the balance between treatment effect and toxicity into account. We need to determine the optimal schedule of CCRT with S-1 for T2N0GC.

Although there are several shortcomings of this retrospective study, including the small patient number and a relatively short follow-up period, we find that concurrent chemoradiotherapy with S-1 for T2N0GC is feasible, well tolerated and effective. This therapy is suggested as a possible regimen to improve the local control of T2N0GC.

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Regular Paper

Concurrent Chemoradiotherapy with S-1 as First-line Treatment for Patients with Oropharyngeal Cancer

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Concurrent chemoradiotherapy/S-1/Oropharyngeal cancer.

Purpose: S-1 is an oral fluoropyrimidine. The purpose of this study was to review the clinical outcomes of S-1 with concurrent radiotherapy for patients with oropharyngeal cancer. **Materials and Methods:** Between 2002 and 2007, 38 patients with oropharyngeal cancer treated concurrently with S-1 and definitive radiotherapy were reviewed. The clinical stage was Stage I in 4 patients, Stage II in 7, Stage III in 7, and Stage IV in 20. S-1 was administered orally twice daily for 4 consecutive weeks followed by a 2-week drug withdrawal. The initial dose of S-1 was 65 mg/m^2/day. All patients were treated using three-dimensional conformal radiotherapy with a median total dose of 65.1 Gy (range, 60.0–71.0 Gy). Clinical outcomes and major acute toxicities were analyzed based on medical records and clinical follow-up. **Results:** With a median follow-up time of 33 months, the 3-year estimates of local-regional control, distant metastases-free survival, disease-free survival, and overall survival for all patients were 75%, 80%, 65%, and 80%, respectively. The 3-year estimates of local-regional control according to stage were 100% for Stages I and II, 86% for Stage III, and 56% for Stage IV. The rate of ≥ Grade 3 acute mucositis was 32%, and the rate of ≥ Grade 3 hematological toxicities was 8%. No other severe toxicities were observed. **Conclusions:** Concurrent chemoradiotherapy with S-1 was found to be effective, especially for early disease. The treatment-related toxicities were acceptable, and the incidence of myelotoxicity was low. Further study must be carried out to compare with other chemotherapy regimens.

INTRODUCTION

The treatment of oropharyngeal cancer has traditionally been surgery alone, radiotherapy alone, or a combination of both. There is little evidence to suggest that either primary surgery or radiotherapy is superior in terms of disease control or survival. Radiotherapy is preferred at many institutions because of the presumed lower morbidity and better functional and cosmetic outcomes compared with surgical treatment.[1)] Recently, many randomized trials have shown that chemoradiotherapy (CRT) improves locoregional control and survival in treating locally advanced head and neck cancer.[2–7)] In the 2006 German meta-analysis of 32 trials, 5-fluorouracil (5-FU) as a single drug and cisplatin as a single drug or in combination with 5-FU was found to exhibit the largest benefit.[8)]

At our institution, patients with cancer of the oropharynx have been initially treated with concurrent CRT to preserve organ function as much as possible. At a radiation dose of 40–45 Gy, the primary disease is evaluated clinically and/or by imaging. If complete response is achieved at the primary site, CRT is continued with neck dissection planned for residual neck disease after completion of CRT. If persistent primary disease is obvious, surgery is performed. The chemotherapy regimen used in the CRT has generally utilized 5-fluorouracil (5-FU) as a single agent. CRT with 5-FU has been shown to provide better therapeutic results than radiotherapy alone.[9)] We have developed a combination therapy including 5-FU, vitamin A, and radiotherapy (FAR therapy) for head and neck cancer, and the effectiveness of the FAR

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therapy has been reported.[10–12]

S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is a novel oral fluoropyrimidine that combines tegafur, a metabolically activated prodrug of 5-fluorouracil (5-FU), with 5-chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo).[13] CDHP enhances the pharmacological actions of 5-FU by potently inhibiting its degradation, and Oxo reduces the incidence of gastrointestinal toxicities by suppressing the activation of 5-FU in the gastrointestinal tract. In a pharmacokinetic study of S-1, plasma 5-FU concentrations were shown to be almost equivalent to those obtained with continuous venous infusion of 5-FU.[14] In the late phase II trials in patients with advanced or recurrent head and neck cancer in Japan,[15] S-1 alone showed an overall response rate of 28.8% and a response rate at the primary lesion of 48.1%. In addition to the high response rates, the incidences of adverse effects were shown to be low. In the late Phase II clinical trials of S-1 alone in 449 patients, the incidences of ≥ Grade 3 adverse reactions were less than 10%, except for neutropenia (11.1%).[16] These data led us to use S-1 concurrently with radiotherapy instead of 5-FU for patients with head and neck cancer.

The purpose of this study was to present the Kyushu University Hospital experience with concurrent CRT with S-1 in treating oropharyngeal cancer and to compare our findings with previous literature on this topic.

MATERIALS AND METHODS

Between 2002 and 2007, 45 patients with newly diagnosed oropharyngeal cancer without distant metastases were started on concurrent CRT with S-1 at the Kyushu University Hospital. After a radiation dose of 40–45 Gy, when an evaluation of the primary disease was performed, 7 of these 45 patients underwent surgery because of residual tumor at the primary site. Thirty-seven patients with complete response and one with unresectable residual tumor at the primary site continued CRT to a total dose of ≥ 60 Gy. These 38 patients who received definitive radiotherapy with S-1 were included in the present analysis.

The patient characteristics are shown in Table 1. Thirty-four (89%) of the patients were men, and the median age was 61 years (range, 37–82 years). Thirty-six patients (95%) had squamous cell histology. The primary sites were the lateral wall in 26 patients, the superior wall in 6, the posterior wall in 4, and the anterior wall in 2. Twenty-eight patients had a T1-2 primary and 10 patients had a T3-4 primary. Twenty-six patients (68%) were node positive. The stage distribution according to the International Union Against Cancer 2002 classification was as follows: 4 Stage I (10%), 7 Stage II (18%), 7 Stage III (18%), and 20 Stage IV (54%).

S-1 was administered orally twice daily for 3 or 4 consecutive weeks followed by a 2-week drug withdrawal from the beginning to the end of radiotherapy. The initial dose of S-1 was 65 mg/m^2 according to a phase I study of concurrent radiotherapy with S-1;[17] patients with a body surface area (BSA) of more than 1.5 m^2 received 100 mg daily, those with a BSA of 1.25 m^2 or more but less than 1.5 m^2 received 80 mg daily, and those with a BSA of less than 1.25 m^2 received 50 mg daily. If patients had renal dysfunction, their initial daily dose was reduced from 100 mg to 80 mg or from

Table 1. Patients' characteristics

Characteristics	No. of patients
Gender	
Male	34
Female	4
Performance Status	
0	16
1	21
2	1
Histology	
Squamous cell carcinoma	36
Adenosquamous cell carcinoma	1
Mucoepidermoid carcinoma	1
Subsite	
Lateral wall	26
Superior wall	6
Posterior wall	4
Anterior wall	2
2002 UICC* T-stage	
T1	9
T2	19
T3	4
T4	6
2002 UICC* N-stage	
N0	12
N1	6
N2	19
N3	1
2002 UICC* Stage	
I	4
II	7
III	7
IV	20

*UICC = International Union Against Cancer.

80 mg to 50 mg according to the level of creatinine clearance. If patients developed toxicities, their daily dose was reduced or S-1 administration was discontinued on the physicians' recommendation. The initial dose of S-1 was 120 mg in one patient, 100 mg in 20 patients, 80 mg in 16 patients, and 60 mg in one patient.

All patients received external beam radiotherapy. Three-dimensional conformal radiotherapy was delivered through a linear accelerator with a 4 MV X-ray. Conventional fractionation was used with a daily dose of 1.8–2.0 Gy, 5 times per week. Initial radiation fields generally encompassed the primary tumor, the bilateral neck, and the supraclavicular fossae. Lateral two fields with or without a single anterior field were used. After the dose of 40–45 Gy, the primary lesion and the lymphadenopathy were boosted with reduced field to a total dose of 60–70 Gy.

The overall survival, local control rate, regional control rate, local-regional control rate, and rate of distant metastases were calculated using the Kaplan-Meier method. The survival and local-regional control rates were calculated from the first day of radiotherapy to the date of the event. The statistical significance of differences between the survival curves was assessed with the log-rank test. A p value less than 0.05 was considered to be significant. Acute and late toxicity was assessed using the Common Terminology Criteria for Adverse Events, version 3.0.

RESULTS

Treatment outcomes

All patients completed the scheduled radiotherapy course. The radiotherapy ranged from 60.0 to 71.0 Gy (median, 65.1 Gy). Thirty-four patients (89%) had a treatment break longer than 3 days to allow for evaluation of the primary disease at a dose of 40–45 Gy and/or due to acute mucositis. The median treatment time of radiotherapy was 9.1 weeks (range, 6.0–12.0 weeks). The administration of S-1 was discontinued in 2 patients, with one showing elevated serum creatine values and the other developing nausea. The dose of S-1 was reduced during treatment in 2 patients due to Grade 2 thrombocytopenia. Neck dissection was performed within 3 months of the completion of treatment in 10 of the 12 patients who had suspected persistent disease in the neck, as assessed clinically or by imaging. However, only one of these 10 patients had pathologically viable carcinoma cells.

The median follow-up time was 33 months (range, 3.4–78.3 months). Of the 38 patients, 17 patients with early disease (T1-2 and N0-1) had no locoregional recurrences. Of the remaining 21 patients with advanced disease (T1-2 and N2-3 or T3-4 and any N), 8 (33%) developed locoregional recurrences. The characteristics of these patients with local and regional failures are summarized in Table 2. There was one isolated local recurrence at the primary site at the 7-month follow-up. Three patients developed recurrences at the primary site and the neck at 4, 7, and 15 months after treatment. Four additional patients developed nodal recurrences. Two of the 8 patients with locoregional failure underwent surgery, and successful salvage was achieved. At the last contact, 5 of the 8 patients with locoregional failure had died of disease, 2 who had undergone surgery were alive without disease, and one patient who had received chemotherapy was alive with disease.

Distant metastases developed in one of the 17 patients with early disease, and in 5 of the 21 patients with advanced disease. Four of these 6 patients with distant failure had disease control above the clavicles. The site of distant metastases was the lung in 4 patients, the bone in one patient, and the mediastinal lymph node in one patient. At the last contact, 2 of the 4 patients with distant metastases and locoregional control had died of disease, one with mediastinal lymph node metastasis who had received chemoradiotherapy was alive without disease, and one who had received chemotherapy was alive with disease.

The 3-year rates of local-regional control by disease stage were as follows: Stage I, 100%; Stage II, 100%; Stage III, 86%; Stage IV, 56%; and overall, 75% (Fig. 1). The 3-year

Table 2. Characteristics of patients who developed local-regional recurrences

Patient	Primary site	Stage	Site of failures	Time to first failure (months)	Salvage therapy	Clinical status
1	Tonsil	T3N0	Local	7.2	None	Died of disease
2	Posterior wall	T2N2c	Local, regional	15.2	Surgery	Alive without disease
3	Base of tongue	T4bN2c	Local, regional, distant	3.8	Chemotherapy	Died of disease
4	Soft palate	T4bN2b	Local, regional, distant	7.1	Chemotherapy	Died of disease
5	Tonsil	T3N2b	Regional	31.3	Surgery	Alive without disease
6	Tonsil	T2N2b	Regional	25.2	Chemotherapy	Alive with disease
7	Base of tongue	T4aN2c	Regional	10.8	None	Died of disease
8	Tonsil	T2N2c	Regional, second primary	4.6	None	Died of disease

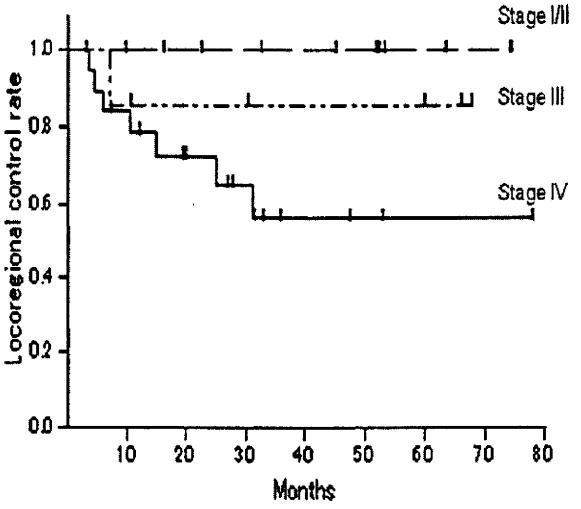

Fig. 1. Kaplan-Meier estimate of locoregional control probabilities by Stage.

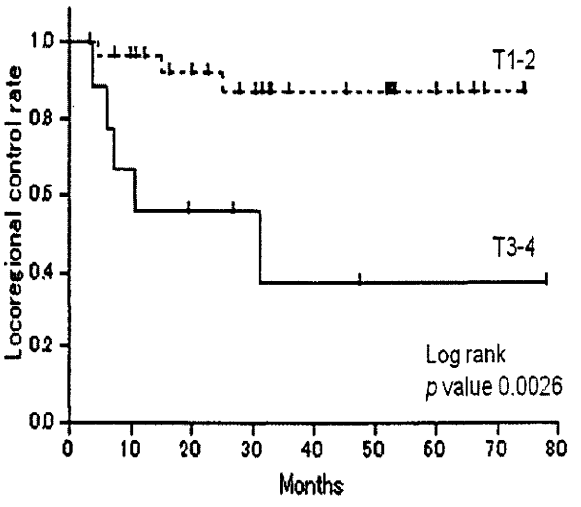

Fig. 2. Kaplan-Meier estimate of locoregional control probabilities by T-stage.

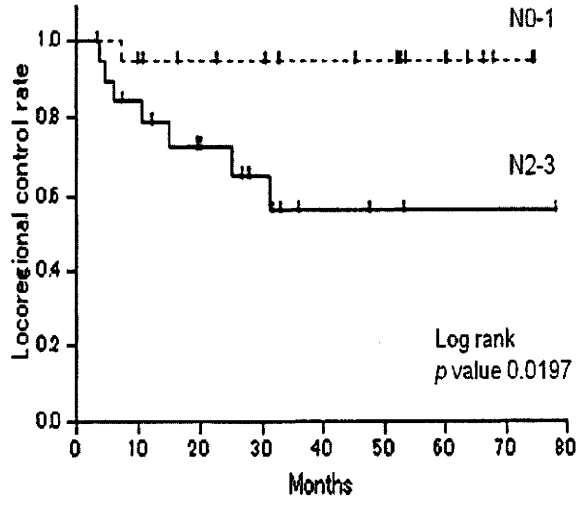

Fig. 3. Kaplan-Meier estimate of locoregional control probabilities by N-stage.

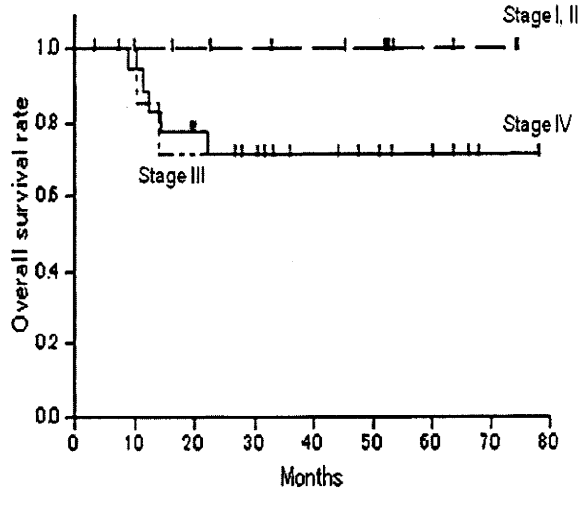

Fig. 4. Kaplan-Meier estimate of overall survival by Stage.

rates of ultimate local-regional control, including patients successfully treated with salvage therapy after a local-regional recurrence, were as follows: I, 100%; II, 100%; III, 86%; IV, 71%; and overall, 83%. T-stage (T1-2 vs. T3-4) and N-stage (N0-1 vs. N2-3) were significantly associated with local-regional control in the univariate analysis. The 3-year local-regional control rate for patients with T1-2 disease was 87% compared with 37% for patients with T3-4 disease (p = 0.0026) (Fig. 2). The 3-year local-regional control rate for patients with N0-1 disease was 94% compared with 56% for patients with N2-3 disease (p = 0.0197) (Fig. 3). Overall treatment time (< 9.0 weeks vs. ≥ 9.0 weeks, p = 0.2480) and total radiation dose (< 65.0 Gy vs. ≥ 65.0 Gy, p = 0.2152) were not associated with local-regional control. The 3-year rates of distant metastases by disease stage were as follows: Stage I, 0%; Stage II, 0%; Stage III, 13%; Stage IV, 29%; and overall, 18%. The 3-year overall survival rates by disease stage were as follows: Stage I, 100%; Stage II, 100%; Stage III, 71%; Stage IV, 71%; and overall, 79% (Fig. 4).

Acute and late toxicity

The acute toxicity of chemoradiotherapy by site and grade is detailed in Table 3. The incidence of acute mucositis higher than Grade 2 was 31%. Four of the 38 patients (11%) needed either a nasogastric feeding tube or total parenchymal nutrition during treatment. The rate of Grade 3 leukopenia was only 5.2%. No other severe acute toxicities were observed.

Late complications were scored according to the Radiation