Chemoradiation for Small Cell Esophageal Carcinoma: Report of 11 Cases from Multi-institution Experience

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Small cell carcinoma/Esophageal cancer/Chemoradiation.

Small cell esophageal carcinoma (SCEC) is a rare disease with aggressive behavior and poor prognosis. Because of the rarity of this disease, standard therapy has not yet been established. The objective of this retrospective study was to report the outcomes of SCEC treated with chemotherapy and radiotherapy from a retrospective study of 11 patients. We enrolled 11 SCEC patients who were treated with radiation therapy (more than 50 Gy) and chemotherapy between May 1996 and October 2007. Patients’ age ranged from 44 to 77 years (mean: 69 years). In all patients, pathological examination of the specimen obtained by biopsy revealed small cell carcinoma. All patients were treated with chemotherapy and radiation therapy. The mean follow-up time was 14.7 months, and the median overall survival time of all patients was 13.2 months (range: 4.2–43.6 months). The 1-year and 3-year overall survival rates were 63% and 24%, respectively, while the 1-year and 3-year progression-free survival rates were 45% and 14%, respectively. Five of seven patients with complete response (CR) developed recurrent disease. Recurrence sites were distant metastases in four patients and lymph node outside the radiation field in one patient. Chemoradiation should be considered as one of the important treatment options for the loco-regional control in the patients with SCEC.

INTRODUCTION

The esophagus is the most commonly involved site of extrapulmonary small cell carcinoma. Small-cell carcinoma has been described in the lung, esophagus, stomach, intestine, salivary gland, paranasal sinus, thymus, prostate, urinary bladder, breast, uterine cervix, endometrium, and skin.¹ In the gastrointestinal (GI) tract, 50% of tumors arise in the esophagus.² McKeown reported two cases of small cell esophageal carcinoma (SCEC), the first report of this disease,³ and since that time the incidence of SCEC has been estimated to range from 0.4% to 3.2% of all esophageal malignancy.⁴,⁵ SCEC is a rare disease with aggressive behavior and poor prognosis, and because of the rarity of this disease, standard therapy has not yet been established.

The clinical behavior of SCEC has a marked resemblance to that of small cell lung carcinoma (SCLC), with a high frequency of regional and distant spreading at diagnosis and early systemic relapse after local treatment. Small cell carcinoma is considered to be highly sensitive to radiotherapy and chemotherapy. Radiation therapy and surgery are used to manage loco-regional disease, and systemic chemotherapy is used to treat metastasis. The objective of this retrospective study was to report the outcomes of SCEC treated with chemotherapy and radiotherapy from a retrospective study of eleven patients.

MATERIALS AND METHODS

Patients

We enrolled eleven SCEC patients who were treated with radiation therapy (more than 50 Gy) and chemotherapy at Kyushu University Hospital, Kyushu Cancer Center, Kita-Kyushu Medical Center, and Saiseikai Fukuoka Hospital between May 1996 and October 2007. The characteristics of
the patients are shown in Table 1. Patient age ranged from 44 to 77 years (mean: 69 years). In all patients, pathological examination of the specimen obtained by biopsy revealed small cell carcinoma.

Pretreatment evaluation

The extent of disease in each patient was evaluated by physical examination, esophagography, esophagoscopy, and computed tomography (CT) of the neck, chest, and abdomen. Distant metastases were evaluated using CT, brain MRI or positron emission tomography (PET). Assignment of clinical staging was performed according to the criteria of the International Union against Cancer (UICC, 2002). By analogy with SCLC, we have defined limited disease (LD) as a tumor that could be covered reasonably within a single field, and extensive disease (ED) as one that involved distant metastases.

Treatments

The details of radiation and chemotherapy treatment of all patients are shown in Table 2. All patients were treated with chemotherapy and radiation therapy. In all patients, radiation therapy was performed using an external beam and delivered at a daily dose of 1.8–2 Gy, five times per week using 4, 6, or 10MV photon beams. The total dose ranged from 50 to 70 Gy (median 60.8 Gy). Eight patients were treated with prophylactic regional irradiation of 40–41.4 Gy. The chemotherapy regimen consisted of cisplatin (CDDP) and 5-fluorourasil (5-FU) in four patients, CDDP and UFT in one patient, carboplatin (CBDCA) and etoposide (VP-16) in three patients, CDDP and irinotecan hydrochloride (CPT-11) in two patients, and CDDP and VP-16 in one patient. In two ED patients with liver metastases before treatment, transarterial infusion with CDDP was performed for liver metastasis. Concurrent chemoradiotherapy was performed in eight patients.

Response evaluation

For measurable disease, responses were evaluated according to the World Health Organization (WHO) criteria. Response for all sites was as follows: complete response (CR) was consistent with disappearance of all visible tumors including distant metastasis, while partial response (PR) was assigned if all visible tumors were reduced by at least 50%. Progressive disease (PD) was consistent with an increase in the tumor area by 25% or developing distant metastasis. Response for the primary tumor was also evaluated according to the criteria of the Japanese Society for Esophageal Disease. Briefly, CR for a primary tumor was consistent with the disappearance of all visible tumors, including ulceration, and a negative biopsy result on esophagoscopy that lasted more than four weeks. PR was assigned if the primary tumor was reduced by at least 50% on esophagography and reduction lasted for four weeks. PD was consistent with an increase in the tumor area by 25%. Responses were evaluated using esophagography, esophagoscopy, and CT of the chest and abdomen. Distant metastases were evaluated using CT, brain MRI or PET. Common Terminology Criteria for Adverse Events v.3.0 (CTCAE) was used to evaluate observed toxicity.

Statistical analysis

The survival time was calculated from the date of treatment initiation to that of death from any cause or to the last

Table 1. Patient characteristics

<table>
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<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>PS</th>
<th>Finding type</th>
<th>primary site</th>
<th>Tumor length (mm)</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Stage</th>
<th>LD or ED</th>
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<td>0</td>
<td>1</td>
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Abbreviations: Ut = upper thoracic esophagus; Mt = middle thoracic esophagus; Lt = lower thoracic esophagus; LD = limited disease; ED = extended disease
date of confirmation of survival. We estimated survival curves using the Kaplan-Meier method.

**RESULTS**

The response for all sites was CR in seven patients, PR in three patients, and PD in 1 patient. The response rate (RR) for all sites was 91%. The RR of primary esophageal lesions was 82% (nine of 11 patients). The summary of results of treatment is shown in Table 2. One patient with PD of all sites (patient 10) developed distant metastasis in the liver and bone during therapy. Two patients (patients 3 and 5) were still alive at the last follow-up, and one patient showed no evidence of disease.

The mean follow-up time was 20 months, and the median overall survival time of all patients was 13.2 months (range: 4.2–43.6 months). The 1-year and 3-year overall survival rates were 63% and 24%, respectively (Fig. 1), and the 1-year and 3-year progression-free survival rates were 45% and 14%, respectively (Fig. 2). Five of seven patients with CR response developed recurrent disease. Recurrence sites were distant metastases in four patients and lymph node outside the radiation field in one patient. Local recurrence was not observed. Distant metastatic sites were the liver in two

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**Table 2. Treatment course and results of treatment**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment course</th>
<th>RT total dose (Gy)</th>
<th>RT initial field*</th>
<th>CT regimen</th>
<th>Response of all sites</th>
<th>PD site</th>
<th>OST (month)</th>
<th>Present status</th>
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<td>small</td>
<td>CDDP/5-FU</td>
<td>PR</td>
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<td>23.4</td>
<td>Dead of disease</td>
</tr>
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<td>50.4</td>
<td>large</td>
<td>CDDP/VP</td>
<td>CR</td>
<td>DM</td>
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<td>CR</td>
<td>DM</td>
<td>24</td>
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</tr>
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<td>large</td>
<td>CBDCA/VP</td>
<td>CR</td>
<td>none</td>
<td>18</td>
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<tr>
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<td>CDDP/5-FU</td>
<td>CR</td>
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<td>CDDP/CPT-11</td>
<td>CR</td>
<td>DM</td>
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</tr>
<tr>
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<td>small</td>
<td>CDDP/CPT-11</td>
<td>PR</td>
<td>DM</td>
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<td>PR</td>
<td>DM</td>
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<tr>
<td>10</td>
<td>CCRT</td>
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<td>large</td>
<td>CDDP/5-FU</td>
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<td>LN</td>
<td>18.1</td>
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</tr>
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</table>

Abbreviations: CT = chemotherapy; RT = radiotherapy, CCRT = concurrent chemoradiation; TAI = transarterial infusion; CR = complete response; PR = partial response; PD = progressive disease; DM = distant metastasis; LN = lymph node; OST = overall survival time; NED = no evidence of disease

*large/small; with/without prophylactic irradiation

**Fig. 1.** Overall survival curve: 1-year and 3-year overall survival rate were 63% and 24%.

**Fig. 2.** Progression-free survival curve; 1-year and 3-year progression-free survival rate were 45% and 14%.
patients, brain in two patients, bone in one patient, and pancreas in one patient.

Toxicity is summarized in Table 3. Grade 3/4 neutropenia was observed in four patients (36%), grade 4 thrombocytopenia was observed in two patients (18%). And grade 3/4 anemia was observed in two patients (18%). Regarding non-hematologic adverse reactions, grade 3 radiation pneumonitis was observed in one patient (9%). Other adverse reactions were mild, with no treatment-related deaths observed.

**DISCUSSION**

Small-cell esophageal cancer (SCEC) is a rare disease with aggressive behavior and poor prognosis. The SCEC tumor is aggressive, and most patients present with disseminated disease. The prognosis of this tumor is generally unfavorable, with median survival ranging from 3.1 to 15.5 months.9–11 Surgical resection, radiotherapy and multi-drug chemotherapy have been used either alone or in combination to treat SCEC, but the overall prognosis is still disappointing, regardless of treatment modality. Because of the rarity of this disease, the most effective treatment for SCEC has not yet been established.

Small cell carcinoma is considered to be highly sensitive to radiotherapy and chemotherapy. Since SCEC has similar histological and clinical characteristics to small cell lung cancer (SCLC), the same therapeutic strategies for both malignancies are recommended in the literature.12–15 SCEC is a systemic disease, so chemotherapy is considered to play a more important role in the combined therapy. In a study involving eight patients, Isolauri et al. suggested that the survival was better for the patients receiving chemotherapy (range: 4–8 months) compared with the patients treated with surgery alone (range: 9–30 days).16 Law et al. reported a median survival of 16.7 months (range: 2.8–72 months) for patients receiving systemic treatment compared to 2.2 months (range: 4 days to 9.1 months) in the other cases.10 Nichols et al. reported that 50% of patients with SCEC were insensitive to multi-drug combination chemotherapy with/without sequential radiation.5 and Nishimaki et al. also reported that chemotherapy with a single-drug protocol could not prolong patient survival.17 Nemoto et al. reported that survival rates were significantly better in the 14 patients who were treated with chemotherapy (median survival time: 24 months) compared with six patients who were not treated with chemotherapy (median survival time: 5 months) (p = 0.0061).13

Hudson et al. concluded that combined modality therapy using platinum-based combination chemotherapy and radical radiotherapy might allow a non-surgical approach to management, avoiding the morbidity of esophagectomy.19 They reported that the median survival time of all patients (n = 16) was 13.2 months and that the median survival time of patients with LD (n = 6) was significantly longer than those with ED (n = 9) (24.4 versus 9.1 months, P = 0.034). Additionally, Yau et al. managed all patients non-operatively with chemotherapy and/or radiotherapy, and the overall median survival time was 8 months (range: 2–62 months).20 The survival was 4–62 months for patients with LD (n = 4), whereas it was 2–10 months for patients with ED (n = 6) at initial diagnosis. They concluded that satisfactory palliation could be achieved with chemoradiation for patients with limited disease.

Chemotherapy for squamous cell esophageal cancer usually consists of platinum plus 5-FU regimens. However, the recommended chemotherapy for SCLC is the platinum plus VP-16 or CPT-11 regimen. CDDP and VP-16 or CPT-11 are the standard regimen for SCLC in Japan.21 Recently, the authors of two studies have suggested that the combination of CPT-11 or VP-16 and platinum such as that used to treat SCLC seems to be effective therapy for SCEC with an acceptable toxicity profile.22,23 Regarding SCEC, Yamashita et al. reported that 9 LD patients treated with concurrent chemoradiation using a CDDP plus VP-16 regimen showed a median survival time of 10.8 months (range: 4.2–42.8 months) and a 3-year overall survival rate of 55.6%.22 Chin et al. reported that 12 patients treated with chemoradiation using a CDDP plus CPT-11 regimen with/without radiation or surgery showed a median survival time of 417 days (range: 97–1626 days), and 3 of 12 patients were alive for over 40 months.24 CDDP plus VP-16 or CPT-11 may be an effective regimen for SCEC as well as SCLC. However, further analysis is needed to determine the optimal chemotherapy regimen for SCEC.

SCEC is extremely aggressive and exhibits early metastatic dissemination much like that seen in SCLC. The authors of several previous reports suggested that SCEC is a systemic disease, so metastasis developed in early stages of the disease.11,13,16–20 The most frequent sites of distant metastases were the bone and liver, followed by the lymph node, brain, and lung. In our two ED patients, liver metastases were found initially. We performed transarterial infusion with CDDP for liver metastasis in these two patients and achieved

<table>
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<th>Table 3. Severe adverse reactions</th>
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<tr>
<td>Hematologic adverse reactions</td>
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<tr>
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</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
</tbody>
</table>

Non-hematologic adverse reactions

- Radiation pneumonitis: 1/0
- Esophagitis: 0/0
- Nausea: 0/0

 Furthermore, the authors of two studies have suggested that SCEC is a systemic disease, so metastasis developed in early stages of the disease.11,13,16–20 The most frequent sites of distant metastases were the bone and liver, followed by the lymph node, brain, and lung. In our two ED patients, liver metastases were found initially. We performed transarterial infusion with CDDP for liver metastasis in these two patients and achieved
good response. Transarterial infusion can be effective for liver metastases. In our two patients, brain metastases were observed after initial treatment. Prophylactic cranial irradiation (PCI) prolonged the survival time in patients with LD and ED SCLC in CR cases. It is very difficult to determine the role of PCI in the treatment for SCEC by randomized prospective study because of the rarity of this disease.

The standard dose and timing of radiation therapy for SCEC has not been established. In our study, all of the 11 patients achieved CR or PR of the primary region and no patient had local recurrence following treatment with 50–70 Gy (median 60.8 Gy) of irradiation. However, Yamashita et al. reported that 2 of 9 patients suffered from loco-regional recurrence in the irradiation field with 50 Gy of irradiation.22) and Chin et al. reported that 7 of 12 patients initially treated with CPT-11 plus CDDP without radiotherapy suffered from loco-regional recurrence.23) Therefore, radiotherapy is considered to have an important role in loco-regional control of SCEC. In the treatment of SCLC, local recurrence is observed in approximately half of the patients receiving 40–50 Gy of irradiation,26) but recurrence tends to be reduced by higher radiation doses.27) Considering the excellent local control in our series, most of which were treated with 60 Gy or higher doses, high dose irradiation may be effective for local control of SCEC. The recommended radiation therapy for SCLC patients is early and concurrent radiation with an accelerated hyperfractionated (AHF) regimen.28) However, the AHF regimen is difficult to use for SCEC treatment because of the large field size consisting of a long part of the esophagus. The optimal dose, radiation field, fractionation schedule, and timing of the combination with chemotherapy remained to be established.

Surgical resection is often performed for LD-SCEC as well as radiation therapy. Sun KL et al. reported that, in the 73 patients treated with surgical resection for SCEC including 60 patients received chemotherapy after operation, 1-, 3- and 5-year survival rates of patients were 50.7%, 13.7% and 8.2%, respectively.29) In our study, 1-year and 3-year overall survival rates were 63% and 24%, respectively. Additionally, chemoradiation achieved good response of primary lesions and a local recurrence was not observed in our study. SCEC is considered a systemic disease rather than local disease because of high incidence of distant metastases as well as SCLC. Considering the high local control achieved by radiotherapy combined with chemotherapy, chemoradiation may be an effective treatment option comparable to surgical resection for LD-SCEC. Also for ED-SCEC, a combination use of radiotherapy with chemotherapy should be an useful palliative treatment against esophageal stenosis due to primary tumor.

In conclusion, chemoradiation should be considered as one of important treatment options for patients with SCEC. Although the incidence of SCEC is low, it is necessary to try to do clinical trials to obtain evidences of high level.

REFERENCES


