Diseases of the Esophagus (2011) **24**, 258–264
DOI: 10.1111/j.1442-2050.2010.01133.x

DISEASES OF THE ESOPHAGUS

Original article

Small cell carcinoma of the esophagus: a multicentre Rare Cancer Network study

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SUMMARY. **Small cell carcinoma of the esophagus (SCCE) is a rare and aggressive malignant tumor with a poor prognosis. The aims of this retrospective study were to analyze the epidemiology, clinical characteristics, and treatment outcomes of these patients. Between 1994 and 2004, 24 patients with SCCE from several centers were reviewed for data on demographics, presenting symptoms, diagnosis, disease stage, type of treatment, and outcome. SCCE occurs in the sixth decade: median age (interquartile range [IQR]): 65 (59–69) years with a male predominance (63%). The most common complaining symptoms were rapidly progressive dysphagia (79%), weight loss (54%), and retrosternal/epigastric pain (46%). The tumor arises primarily in the middle (52%) or in the lower (35%) third of the esophagus. History of tobacco and alcohol exposure was present in 90% and 70% of case, respectively. Extensive disease was present in 13 cases (54%) at initial diagnosis.**

The overall median survival (IQR) was 11 (8–20) months for all 24 patients, and the 2-year overall survival was 25.1%. Four patients were alive more than 2 years after treatment. Chemotherapy increased the survival compared with symptomatic management in extensive disease (median survival [IQR]: 9.5 [6–14] vs. 6 [4–7] months, $P = 0.05$). In limited disease, concurrent chemo-radiotherapy was more effective than non-concurrent treatment (median survival [IQR]: 36 [14–93] vs. 11 [9–15] months, $P = 0.04$). Two patients were treated by surgery and chemoradiation therapy with a survival of 35 and 66 months. Chemotherapy is the cornerstone of treatment of SCCE in all stage. For limited disease SCCE, concurrent chemo-radiotherapy is the primary choice compared with sequential approach. The role of surgery was not assessable in our study.

KEY WORDS: **chemotherapy, esophagus, radiotherapy, small-cell carcinoma.**

INTRODUCTION

Small cell carcinoma (SCC) is an aggressive tumor most frequently described in bronchial tree, representing about 15% of all lung cancers. Extrapulmonary SCC is extremely rare and has been described mainly in the urinary bladder, prostate, salivary glands, pharynx, larynx, esophagus, stomach, pancreas, colon, rectum, skin, and cervix.[1–3]

SCC of the esophagus (SCCE) is the most frequently reported gastrointestinal site of extrapulmonary SCC. The incidence is usually reported between 0.4% and 2.8%[4–7] of all esophageal tumors; in Japanese populations, this increases up to 15%.[8] Since the first description of SCCE, more than 200 cases have been reported in the literature.[9] SCCE is characterized by a high metastatic potential and metastases are found in 31% to 90% of cases at initial diagnosis.[5,9–12] The management of SCCE is not well defined due to the small number of case reported in the literature. The aims of the study were to analyze the characteristics of recent cases of SCCE and, as possible, better define therapeutic options.

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METHODS

Twenty-four patients with SCCE from six institutions were recorded from the Rare Cancer Network register between January 2007 and January 2008. Patients reviewed for data on demographics, presenting symptoms, diagnosis, disease stage, type of treatment, and outcome. The inclusion criteria were a histological diagnosis of SCCE between 1994 and 2004. Where applicable in the case of retrospective studies, the protocol underwent local ethics board review.

For statistical analysis, continuous variables were expressed as median (interquartile range [IQR]). Differences between groups were examined by unpaired two-sided Student's *t*-test. The χ^2 were used in order to compare proportions. The Kaplan-Meier method was used to calculate survival curves, and the log-rank test was used to determine differences in survival rates. The statistical analyses were carried out using SPSS version 11.0 (SPSS Inc, Chicago, IL).

RESULTS

Patient's characteristics

The characteristics of the 24 SCCE are reported in the Table 1. The tumor occurs in the sixth decade: median age (IQR): 65 (59–69) with a male predominance and a male to female ratio of 1.66. All patients of our study were Caucasian. The most common complaining symptoms were rapidly progressive dysphagia (79%), weight loss (54%), and retrosternal/epigastric pain (46%). History of tobacco exposure was present in 90% of case: median consumption

Table 1 Small-cell carcinoma of the esophagus patients' characteristics

Case	Age	Sex	PS	Location	Size (cm)	Stage	Stage	Location	Treatment	Survival (Months)
1	79	M	1	Upper	6	IV	ES	Liver, mediastinal adenopathy, bone	Vindesine, VP16	19
2	44	M	0	Middle	5	IV	ES	Thyroid, pulmonary	CDDP, 5-FU, VP16	15
3	78	F	3	Middle	NS	IV	ES	Liver, mediastinal adenopathy	Symptomatic	NS
4	65	M	1	Middle	5	II B	LS		CDDP, VP16, ERT non concomitant	9
5	71	M	3	Middle	8	IV	ES	Brain, mediastinal adenopathy	Symptomatic	8
6	68	M	1	Middle	7	IIA	LS		Gastroesophagectomy, carboplatin, VP16, ERT concomitant	35, alive
7	90	F	2	Middle	6	IV	ES	NS	Symptomatic	7
8	60	M	1	Middle	5	III	LS		Cyclophosphamide, doxorub, VP16, ERT non concomitant	13
9	58	M	2	Upper	6	IV	ES	Lung	Symptomatic	9
10	59	M	1	Middle	6	IV	ES	Supraclavicular adenopathy	Cyclophosph, adriamycin, VP16, ERT non concomitant	6
11	65	M	2	Lower	NS	IV	ES	Liver	Symptomatic	NS
12	75	M	1	Lower	5	III	LS		CDE	NS
13	69	F	2		NS	IV	ES	NS	CDE, ERT non concomitant	NS
14	64	F	1	Lower	7	IV	ES	Liver	CDE	8
15	65	M	1	Upper	4	IV	ES	Liver	Endoxan, adriamycin, etoposide	6
16	68	M	1	Lower	8	IV	ES	Mediastinal adenopathy	CDDP, VP16, ERT non concomitant	11
17	65	F	0	Lower	4	IIA	LS		CDDP, VP16, ERT non concomitant	18
18	61	F	0	Middle	2	IIA	LS		Esophagectomy, carboplatin, VP16	66, alive
19	60	F	0	Middle	4	IIA	LS		CDDP, VP16	4, LFU
20	23	M	2	Lower	8	IV	ES	Liver	Symptomatic	1.5
21	56	M	1	Middle	8	IIB	LS		CDDP-VP16, ERT concomitant	24
22	71	F	0	Lower	6	IIB	LS		CDDP-VP16, ERT concomitant	11
23	50	M	0	Middle	NS	IIB	LS		CDDP-VP16, ERT concomitant	108, alive
24	59	F	0	Lower	NS	III	LS		CDDP-VP16, ERT concomitant	48

CDDP, cisplatin; CDE, cyclophosphamide-doxorubicin-etoposide; ERT, external radiation therapy; ES, extensive stage; FU, fluoro-uracil; LFU, lost of follow-up; LS, limited stage; NS, not stated; PS, performance status; VP-16, etoposide.

(IQR): 40 (20–50) pack-years and alcohol exposure in 70% of case: median consumption (IQR): 3 (2–5) drinks per day. At initial diagnosis, extensive disease was present in 13 cases (54%) and limited stage in 11 cases (46%). Paraneoplasic syndromes were not observed in our series.

Serum neuron-specific enolase (NSE) and serum carcinoembryonic antigen (CEA) were within normal value when they were measured, in four and five cases, respectively.

Tumor location and metastatic sites

In most cases, the tumor was located in the middle (52%) or in the lower (35%) third of the esophagus. The tumor length was greater than 5 cm in 58% of cases.

SCCE was associated with metastatic dissemination at initial diagnosis in 54% of cases. The most frequent metastatic sites were the liver (60%) and the lung (20%). Mediastinal adenopathy were seen in 40%. Metastasis was observed in the bone, brain, supraclavicular adenopathy, or in the thyroid in one case, respectively.

Histology and immunohistochemistry

In 54% of cases (13/24), the histological type was pure SCCE, differentiated and pure SCCE, undifferentiated/anaplastic, in 38% of cases (9/24). Mixed tumors with squamous differentiation were present in 8% of cases (2/24).

In reported immunohistochemistry, one or more marker of epithelial cellular origin was present in all reported cases (13/13) and at least one marker of neuroendocrine differentiation (synaptophysin, NSE, chromogranin A, cluster differentiation 56 [CD56]) was present in 13 of the 14 reported cases.

Treatment

Six patients (25%) received only symptomatic management: endoscopic esophageal prothesis, brachytherapy or palliative external radiation therapy. Eighteen patients received chemotherapy alone (n = 6) or chemotherapy associated with radiotherapy or surgery (n = 12). All patients treated by chemotherapy received etoposide in combination with other drugs. The combination of etoposide/cisplatin was the most frequently used (9/18). Eleven patients were treated with external radiation: the total radiation dose was 45 Gray (Gy) in eight cases (1.8 Gy/day, five times a week), 50 Gy in two cases (2.5 Gy/day, five times a week) and 24 Gy in one case (4 Gy/day, six consecutive days). For the two patients treated by surgery, one was treated by gastroesophagectomy with a R0 resection (free margin and 23 lymph nodes negative for tumor) followed by adjuvant chemotherapy and the other one was treated by partial esophagectomy with a R2 resection (positive margin and four lymph nodes negative for tumor) followed by salvage concurrent chemo-radiotherapy, with survivals of 66 and 35 months, respectively.

Outcome

The overall median survival was 11 months (8–20, IQR) for all 24 patients and the actuarial 2-year overall survival rate was 25.1%. The median survival was significantly better in limited disease compared with extensive disease of SCCE: 30 (12–53) versus. 8 (6–12) months (IQR), P = 0.002 (Fig. 1a). In extensive disease, chemotherapy increases median survival in comparison with symptomatic management alone: 9.5 (6–14) versus 6 (4–7) months (IQR), respectively, P = 0.05 (Fig. 1b). In limited disease, most patients (9/11) were treated with chemotherapy in combination with local therapy (esophagectomy in two cases, radiation therapy for the others). In limited disease treated by chemo-radiotherapy, concurrent administration of both therapies was more effective than sequential treatment: 36 (14–93) versus 11 (9–15) months (IQR), P = 0.04 (Fig. 1c). All complete responses to treatment (8/11) were observed in limited disease of SCCE and seven of them received chemotherapy in association to local therapy. Four of them were alive more than 2 years after complete response.

DISCUSSION

SCCE usually occurs in male patients, with a reported male to female ration of 1.57.[9] The tumor occurs in the sixth to eighth decade. The most common symptoms were rapidly progressive dysphagia and weight loss, as seen in the classical types of esophageal cancers.[9] In most cases, the tumors are located in the middle and the lower third.[9] Although the risk factors are not well-defined, they seem to be similar to squamous cell esophageal cancer (history of alcohol consumption and smoking).[6,7,9] At initial diagnosis, metastases are reported in 31% to 90% of cases.[5,9–12] Similar clinical characteristics were observed in our population.

The natural history of this subset seems different from SCC of the lung (SCLC). Paraneoplasic syndromes in SCLC have been well reported but extrapulmonary SCC, including SCCE, does not produce identifiable paraneoplasic syndromes.[13] Similarly, paraneoplasic syndromes were not observed in our patient series. Brain metastases, which are common with SCLC, are rare with SCCE. Only one patient developed brain relapse in this series and none of the patients received prophylactic cranial irradiation.

It has been reported that NSE, which is found in neuroendocrine cells, is a good marker for the diagnosis of SCLC.[14–16] Furthermore, levels of serum NSE correlate with the extent of the disease and the

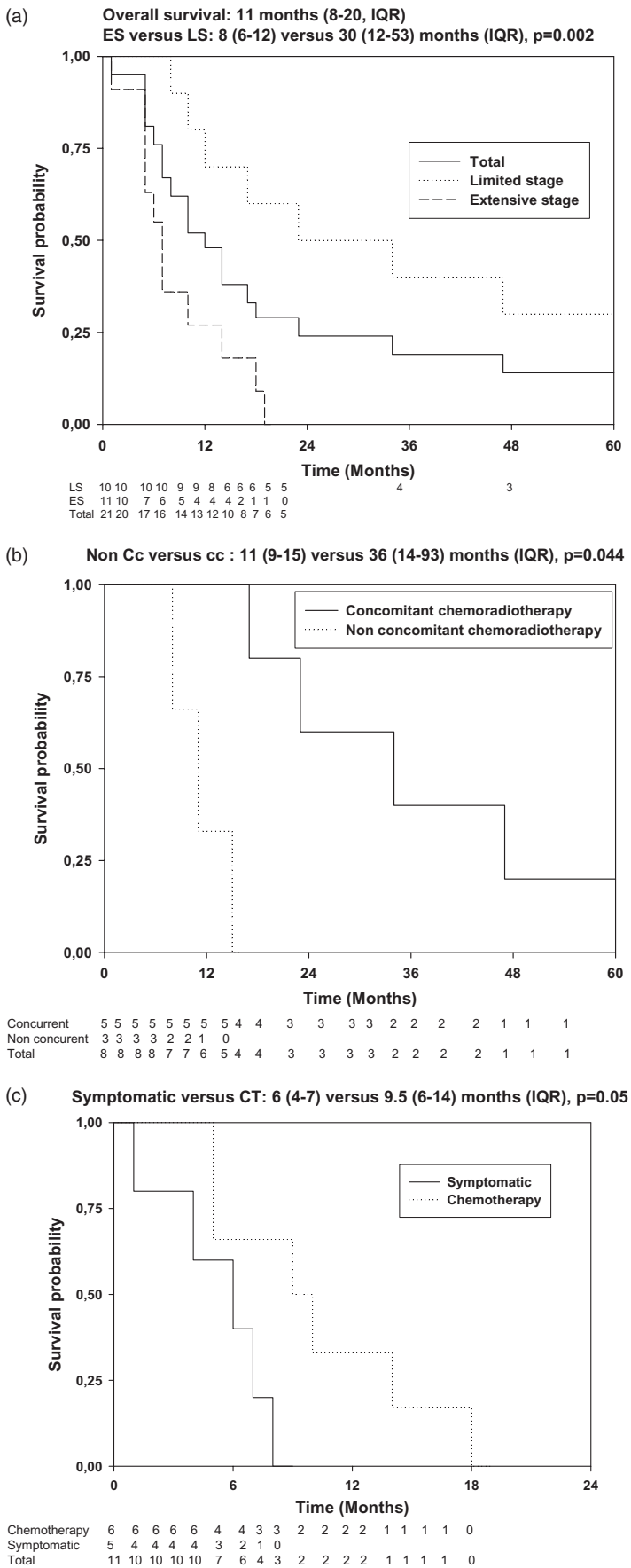

Fig. 1 Survival probability of small-cell carcinoma of the esophagus, depending on the stage (1a), depending on the type of treatment according to the stage (limited stage, 1b; extensive stage, 1c). ES, extensive stage; LS, limited stage; IQR, interquartile range.

response to the treatment in SCLC.[15,16] In SCCE, NSE is rarely reported in the literature and its expression is variable.[17,18] When reported, NSE remained within normal limits in our series.

The histology of SCCE is similar to SCLC, consisting of round of spindle-shaped cells with scanty cytoplasm, hyperchromatic nuclei, inconspicuous nucleoli, and structural and immunohistochemical evidence of neuroendocrine differentiation.[19] The diagnosis of SCC is primarily made on light microscopy. Although electron-microscopical, immunohistochemical, and molecular-biological findings have considerably increased the understanding of the pathogenesis and progression of malignant tumors, routine pathological-anatomical diagnostics are still decisively based on light-microscopical evaluation of tissue samples.[20] It is now accepted that SCC is of endodermal origin derived from pluripotential basal epithelial cell, explaining the coexistence of small cell, squamous, and glandular elements in the same lesions.[17] The incidence rate of mixed differentiation ranged between 31% and 35%.[9,17] However, the actual rate of incidence may be higher, because the entire specimen is rarely analyzed, explaining the incidence of 10% in our series.

In immunohistochemistry, virtually all SCC are immunoreactive for keratin, epithelial membrane antigen, or other epithelial markers because of their epithelial cellular origin. Because of their neuroendocrine differentiation, SCC can be immunoreactive to NSE, chromogranin A, CD56, gastrin releasing peptide or insulin growth factor-1 (IGF)-1. One or more markers of neuroendocrine differentiation can be found in approximately 75% of SCC and a complete negative neuroendocrine staining doesn't exclude the diagnosis.[21] Although the neuroendocrine markers is absent on biopsy on one of our case, he was therefore considered as a SCCE.

Regarding the treatment, chemotherapy is now recognized as the primary treatment for extrapulmonary SCCs,[22] both in limited disease[9,23] as well as in extensive disease SCCE[6,7] although our results are of borderline significance for extensive disease. Moreover, the advantage in survival is modest although the tumor response to chemotherapy in extensive disease SCCE is significant.[6,7] There is no consensus about the optimal combination chemotherapy to be used. Cisplatin, etoposide, and 5-fluorouracil have been reported to be active agents against SCCE[24] and the combination of cisplatin/etoposide is the most frequently prescribed by analogy with SCLC.[25]

For limited disease SCCE, studies on limited disease SCLC have showed the advantage to use concurrent chemo-radiotherapy[26,27] but our study is the first to shows the survival benefit of concurrent chemo-radiotherapy for limited disease SCCE.

To date, the question of local therapy for limited disease remains controversial.

Table 2 summarizes 14 published English language studies with a focus on therapy. In the largest published clinical experience focusing on SCCE (126 patients), Lv *et al*.[28] show that there is no significant difference between outcomes in patients treated with surgery, chemotherapy with or without radiation versus radiochemotherapy and that chemotherapy but not surgery was independent prognostic factor in a multivariate analysis. Our study is not able to respond to the question about the role of surgery in limited disease SCCE but this role is controversial in the literature for a number of reasons. First, the long-term survival advantage for patients treated by surgery, chemotherapy, and radiation may reflect a selection bias of a more aggressive therapy for fitter patients who have a better pretreatment prognosis. Second, parallel data from limited disease of SCLC indicate that chemoradiation therapy can cure a small subgroup of patients without surgery.[36] Third, parallel data from Cooper *et al*.[37] with locally advanced esophageal carcinoma showed that 26% of patients lived more than 5 years after treatment by chemoradiation without surgery. In our experience, four patients (17%) with an overall survival higher than 2 years, including the two patients treated by surgery, although R0 resection was present in only one case. Fourth, patients surviving their malignancies may experience quality of life issues following esophagectomy.[38]

However, surgery must be considered as an important part of a multimodal management in limited disease SCCE[11,23,39] because of the potentially curative effect of surgery and the absence of randomized control trial comparing concomitant chemoradiation therapy alone versus associate to surgery in limited disease.

There are no available data regarding the optimal radiation schema for SCCE. Current treatment is adapted from the SCLC. In SCLC, local recurrence is observed in approximatively half of the patients receiving a total dose of 40 to 50 Gy irradiation[40] but seems to be reduced by high-dose twice-daily thoracic radiation therapy.[41] In a randomized Phase III trial, Turrisi *et al*.[36] have demonstrated improved survivals with twice daily radiotherapy concurrent initiation of chemotherapy in patients with limited stage SCLC in comparison to once daily treatments. A number of investigators have reported improved outcomes with dose escalation to 60 to 70 Gy outside the setting of a randomized clinical trial.[23] However, given the potential morbidity of high dose thoracic radiotherapy, particularly in the esophagus, in conjunction with the very high rate of systemic metastases in SCC, no clear consensus yet exists in the radiotherapy community regarding the relative efficacy of escalation. In the setting of SCCE, the risk of malignant tumor obstruction from persistent disease after irradiation must be weighed against the possibility of radiation induced

Table 2 Previous studies with SCCE including surgical cases

Study	*n*	1-year or median survival	Comments
Lv *et al.*[28]	126	52% and 12.5 months, respectively	No significant difference between surgery, chemotherapy plus or not radiation versus chemoradiationtherapy; chemotherapy but not surgery was independent prognostic factor in a multivariate analysis.
Ku *et al.*[29]	25	19.8 months	Of the six long-term survivors (survival >5 years), only 1 had received surgery; all received chemotherapy and radiation.
Sun *et al.*[30]	73	51%	The four patients who survived more than 10 years had received postoperative chemotherapy.
Yun *et al.*[31]	21	Not reported; 2-year survival: 29%	Three patients lived greater than 1 year with chemotherapy and radiation; two lived greater than 4 years with esophagectomy, chemotherapy, and radiation.
Koide *et al.*[32]	10	Not reported	All nine patients with limited disease received surgery and chemotherapy. Five patients lived >18 months.
Hosokawa *et al.*[6]	14	7.7 months	All five patients who underwent only esophagectomy developed 'early relapse.' Among nine patients who received chemotherapy with or without radiation, 'two have survived more than 2 yr.'
Nemoto *et al.*[23]	20	44%	Three long-term survivors, who lived longer than 5 years, received surgery, chemotherapy, and radiation. No significant difference between surgery and chemotherapy versus radiation and chemotherapy for limited disease.
Pantvaidya *et al.*[33]	18	6 months	The only long-term survivor (48 months) had received chemotherapy, surgery, and radiation.
Lam *et al.*[34]	20	3.4 months	Long-term survivors include one patient who underwent a palliative resection with no chemotherapy and lived 1.8 years; another who underwent a 'curative' resection, chemotherapy, and radiation and then lived 6 years; another who received chemotherapy and radiation and lived 1.4 years; and a fourth who received only a curative resection and lived 2 years.
Bennouna *et al.*[7]	10	15.5 months	Long-term survivors include one patient who received chemotherapy and radiation and lived 19 months; another who received chemotherapy and radiation and lived 18 months; another who received chemotherapy and radiation and lived 19 months; a third who received only surgery and died at 13 months; and a fourth who received surgery, chemotherapy and radiation and remained alive at last report at 18 months.
Nishimaki *et al.*[35]	13	31% and 10 months, respectively	Long-term survivors include one patient who received chemotherapy and surgery and lived 106 months; another who received surgery and chemotherapy and lived 64 months; and a third who underwent a 'palliative' resection with no chemotherapy and lived 34 months.
Craig *et al.*[11]	16	Not reported	Seven patients underwent surgery. One also received postoperative chemotherapy and remained alive at the time of report at 96 months. Another died at 34 months after surgery and adjuvant laser therapy.
Law *et al.*[13]	11	3.1 months	Five patients had surgery, but the authors conclude, 'Small cell carcinoma of the esophagus should be regarded as a systemic disease, and multimodality therapy, including chemotherapy, should be used.'
Nichols *et al.*[5]	11	7.5 months	Two patients underwent surgery followed by chemotherapy in both and whole brain radiation in one. One of these patients lived for 8 months (still alive at time of report), and one was lost to follow-up.

strictures when doses are escalated beyond 60 Gy or alternative dose fractionation patterns are employed. Our patients were treated with a definitive radiation therapy of 45 Gy to 50 Gy in most cases but only 24 Gy in one case.

In conclusion, chemotherapy is the cornerstone of treatment of SCCE in limited and extensive stage disease. This study shows a survival advantage favoring concurrent chemo-radiotherapy for limited disease SCCE compared with a sequential approach. In limited stage, addition of surgery to radiochemotherapy remains controversial but there are insufficient data to exclude surgery from multimodal management.

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