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Extrapulmonary Small-cell Carcinoma: a Single-institution Experience

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Background: Extrapulmonary small-cell carcinoma (EPSCC) has been recognized as a clinicopathological entity distinct from small-cell carcinoma (SCC) of the lung. This study aimed to review the clinical features, therapy and natural course of patients with EPSCC in Oriental single-institution series.

Methods: We retrospectively reviewed the medical records of patients with SCC between September 1995 and December 2002. Study eligibility required that patients had pathologically proven SCC in sites other than lung and normal radiological findings of the chest and normal sputum cytology or negative bronchoscopic findings.

Results: Twenty-four patients with EPSCC were identified and primary sites were various: uterine cervix in seven (29%), urinary bladder in five, colon or rectum in three, kidney in two and stomach, esophagus, pancreas, common bile duct, larynx, parotid gland, thymus in one each. Sixteen patients (66.7%) had limited disease (LD) and eight had extensive disease (ED). Patients with ED received mostly platinum-based chemotherapy, for which the response rate was 57%, but showed an aggressive natural history, with median overall survival (OS) of 9.2 months. Patients with LD were treated with a variety of therapeutic modalities. LD SCC of the cervix showed a favorable clinical course, with five patients being disease-free with a median follow-up of 28.4 months. Patients with LD SCC of sites other than cervix had an aggressive course with a median OS of 9.6 months.

Conclusion: EPSCC was identified in various sites, with the most common primary site being the uterine cervix. Regardless of the primary site or disease stage, EPSCC of sites other than cervix was usually a fatal disease with a discouraging outcome for various treatment modalities.

Key words: small-cell carcinoma – extrapulmonary – cervix

INTRODUCTION

Small-cell carcinoma (SCC) was first described in the lung (1) and represents ~20–25% of all bronchogenic carcinomas (2). On the other hand, extrapulmonary small-cell carcinoma (EPSCC) is a relatively rare disease, encompassing ~2.5–4% of all SCC (3,4). The primary site of occurrence of EPSCC has been described in a variety of organs, such as head and neck region, esophagus, stomach, pancreas, gallbladder, uterine cervix, kidney, urinary bladder and prostate (5–10). It has been increasingly recognized as a clinicopathological entity with biological behavior and prognosis distinct from small-cell lung carcinoma (SCLC) (11). The clinical course of these tumors is known to be aggressive in general, with early dissemination and frequent recurrences (3,12). Although chemotherapy seems to be an effective therapeutic modality as in SCLC, surgery and radiation therapy may also play an important role depending on the stage or primary site (12).

Although there have been a few sporadic reports about EPSCC, much remains to be uncovered about the clinical features, optimal treatment and natural history. Moreover, there are no available data about the development of EPSCC in Orientals. We performed this study to review the clinical features, therapy and natural course of patients with EPSCC in Oriental single-institution series.

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SUBJECTS AND METHODS

Patient Selection

We retrospectively reviewed medical records of patients proven with SCC between September 1995 and December 2002 at the Samsung Medical Center. A total of 613 cases of SCC were registered and 24 cases (3.9%) of EPSCC were identified. The histology of SCC was reviewed by two pathologists in the study institution. The histological criteria applied for the diagnosis of EPSCC were identical with those for SCC in the lung (1,13), namely the appearance of round to spindle-shaped small cells with dense nuclei, inconspicuous nucleoli and sparse cytoplasm. For equivocal cases according top the histological criteria, immunohistochemical examinations by the avidin–biotin complex method were performed to confirm the accurate diagnosis using antibodies to chromogranin A, synaptophysin or neuron-specific enolase (NSE) (DakoCytomation, Glostrup, Denmark). Three cases that were not distinctive in the histological examination expressed one or two of these neuroendocrine antigens (synaptophysin in one, NSE in one, chromogranin A and synaptophysin in one) and were included in this study. Patients with well-differentiated neuroendocrine tumor, mixed histological types and Merkel cell carcinoma of the skin were excluded. By definition, patients with EPSCC have a normal plain radiograph or CT scan of the chest and normal sputum cytology or negative bronchoscopic findings.

Staging

The stages of disease were evaluated in a similar fashion to those with SCC of the lung – whether or not the known tumor can be encompassed within a tolerable radiation therapy port (3,11). Thus, a tumor confined to the primary site, with or without regional lymph node involvement, was classified as limited disease (LD), whereas spread of disease beyond locoregional boundaries was considered extensive disease (ED).

Data Collection and Statistical Analysis

The following clinical data were collected from medical records of the 24 study patients: demographic findings, past medical history, ECOG performance status (PS), primary sites, stage of the tumor, treatment modalities and survival. Patient follow-up was performed through office visits or telephone interview.

Demographic and clinical data were described with medians, frequencies and percentages. Clinical response – complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) – was classified according to World Health Organization criteria (14). Survival was measured from the time of diagnosis to the date of death or the latest follow-up. Time-to-failure (TTF) was measured from the date of treatment to the date of progression or death. Overall survival (OS) was estimated using the Kaplan–Meier method.

RESULTS

Table 1 shows the clinicopathological characteristics and clinical course in each of the 24 patients.

Demographic Characteristics

The patients consisted of 13 males (54%) and 11 females, with a median age of 53 years (range, 26–80 years). Ten of the 24 patients (42%), of whom nine were male, had a smoking history. The majority of patients (79%) had a relatively good performance status (ECOG, 0–1) at the time of diagnosis. One patient with SCC of thymus showed ectopic adrenocorticotropic hormone (ACTH) syndrome, with a serum ACTH level of 310 pg/ml (normal value, <60 pg/ml).

Primary Site and Staging

In our series, uterine cervix was the most common primary site, comprising 29% (seven cases) of all EPSCC patients. Five cases (20.8%) were detected in urinary bladder, three cases (12.5%) in colon or rectum and two cases (8.3%) in kidney. One case was detected in each of the following organs: stomach, esophagus, pancreas, common bile duct (CBD), larynx, parotid gland and thymus. The 16 patients (66.7%) were classified as LD and the remaining eight patients as ED at initial staging work-up.

Treatment and Outcome

Among eight patients with ED EPSCC, five whose primary site was colon, rectum, stomach or pancreas received a combination of etoposide (oral or intravenously) and platinum as the primary chemotherapy. One with SCC of the thymus received combination chemotherapy consisting of cyclophosphamide, doxorubicin and cisplatin. Another patient with SCC of the kidney received a Taxol plus cisplatin regimen. The overall response rate was 57% (CR in one, PR in three), with a median TTF of 6.4 months (range, 1.5–8.7 months). The remaining one patient refused palliative chemotherapy. Salvage chemotherapy was administered in three patients and PR was obtained for one with renal SCC. Seven patients died of disease or unknown cause, with a median overall survival (OS) of 9.2 months (range, 2.4–16.1 months).

The 16 patients with LD EPSCC were primarily treated with a variety of therapeutic modalities. Two patients with SCC of the cervix were sequentially treated with neoadjuvant chemotherapy, radical surgery and adjuvant radiotherapy and/or chemotherapy. Eight patients received radical surgery followed by adjuvant chemotherapy (in five) or radiotherapy (in two) or both (in one). Five patients received only local treatment modality (radical surgery in four, radiotherapy in one). The remaining one patient underwent concurrent chemoradiation therapy. The chemotherapeutic regimens used usually included platinum in combination with other agents (5-fluorouracil, Taxol, ifosfamide, etoposide, methotrexate, gemcitabine, vin-

Table 1. Clinicopathological characteristics and clinical course in 24 patients with extrapulmonary small-cell carcinoma

No.	Age (years)	Gender	Smoker	PS	Primary site	Stage	Treatment	Response	Site of failure	TTF (months)	Status	OS (months)
1	37	F	No	0	Cervix	LD	BOMP#2 + Op + BOMP#3	–	Lung	8.2	DOD	20.4
							VIP#4, TP#4	PR, PD				
2	36	F	No	1	Cervix	LD	VIP#3 + Op + RT (40 Gy) + VIP#3	–	–	–	NED	66.7
3	47	F	No	1	Cervix	LD	Op + adj RT (40 Gy)	–	–	–	NED	28.4
4	37	F	Yes	1	Cervix	LD	Op + adj ITP#6	–	LN	7	AWD	19.3
							pRT to pelvis (30 Gy)	–				
5	33	F	No	1	Cervix	LD	Op + adj FP#3 + adj RT (40 Gy)	–	–	–	NED	18
6	33	F	No	1	Cervix	LD	Op + adj FP#3	–	–	–	NED	36.7
7	74	F	No	2	Cervix	LD	RT (52 Gy)	CR	–	–	NED	37.7
8	78	F	No	1	Bladder	ED	–	–	U	U	DOD	15.3
9	64	M	No	1	Bladder	LD	Op + adj CMV#1	–	–	4.4	DOT	4.5
10	50	M	No	1	Bladder	LD	Op + adj VIP#6	–		–	NED	98.5
11	72	M	Yes	1	Bladder	LD	Op	–	Liver, LN	4	DOD	10.6
							VIP#4, TC#2	PD, PD				
12	63	M	Yes	1	Bladder	LD	Op + adj GP#3	–	LN	5.4	DOD	16.7
13	42	M	Yes	1	Colon	ED	EP#6	CR	Peritoneal seeding	8.7	DOD	16.1
							ToP#1, pRT to LN (30 Gy)	PD				
14	49	F	No	1	Rectum	ED	Oral EP#2	PD	Ovary	1.5	DOD	7.2
15	36	M	No	1	Rectum	ED	EP#6	PR	Liver	7	DOD	13.1
							To#2	PD				
16	61	M	Yes	1	Kidney	ED	TP#6	PR	Adrenal gland	6.4	AWD	11.4
							VIP#4	PR				
17	51	F	No	1	Kidney	LD	Op	–	Liver	2.0	DOD	2.2
18	57	M	Yes	1	CBD	LD	Op + adj RT (50 Gy)	–	Liver, LN	5.7	DOD	9.6
19	57	M	No	1	Parotid	LD	Op	–	Liver	2.4	LOF	2.5
20	70	M	Yes	2	Esophagus	LD	Op	–	–	0.7	DOT	0.8
21	64	M	Yes	2	Stomach	ED	Oral EP#6	PR	Brain	8.2	DOD	9.2
							pRT to brain (30 Gy)					
22	55	F	No	3	Pancreas	ED	Oral EC#4	PD	Bone	3.5	DOD	4.0
23	80	M	Yes	2	Thymus	ED	CAP#3	SD	–	2.4	DOU	2.4
24	26	M	Yes	1	Larynx	LD	CCRT (Oral EP + RT) (60 Gy)	CR	Skin	7.5	DOD	25
							ToP#3, IT#3	PD, PD				

Abbreviations: adj, adjuvant; AWD, alive with disease; BOMP, bleomycin/vincristine/methotrexate/cisplatin; CAP, cyclophosphamide/adriamycin/cisplatin; CCRT, concurrent chemoradiotherapy; CMV, cisplatin/methorexate/vinblastine; CR, complete response; DOD, died of disease; DOT, died of treatment-related complication; DOU, died of unknown cause; EC, etoposide/carboplatin; ED, extensive disease; EP, etoposide/cisplatin; F, female; FP, 5-fluorouracil/cisplatin; GP, gemcitabine/cisplatin; Gy, gray; IT, ifosfamide/paclitaxel; ITP, ifosfamide/paclitaxel/cisplatin; LOF, lost to follow-up; LD, limited disease; LN, lymph node; M, male; NED, no evidence of disease; Op, operation; OS, overall survival; PD, progressive disease; PR, partial response; pRT, palliative radiotherapy; PS, ECOG performance status; RT, radiotherapy; SD, stable disease; TC, paclitaxel/carboplatin; To, topotecan; ToP, topotecan/cisplatin; TP, paclitaxel/cisplatin; TTF, time-to-failure; VIP, etoposide/ifosfamide/cisplatin; U, unknown.

cristine, vinblastine, bleomycin). We did not administer prophylactic cranial irradiation for patients in CR. There were two treatment-related deaths (sepsis, post-operation acute myocardial infarction). LD SCC of the uterine cervix showed a favorable clinical course, with five patients being in a disease-free state with a median follow-up of 28.4 months. Patients with LD SCC of sites other than cervix had an aggressive natural history, with a median TTF of 4.4 months and a median OS of 9.6 months.

For all 24 patients with EPSCC, the median overall survival was 15.3 months (range, 0.7–98.5 months), with a 3-year survival rate of 30% (Fig. 1).

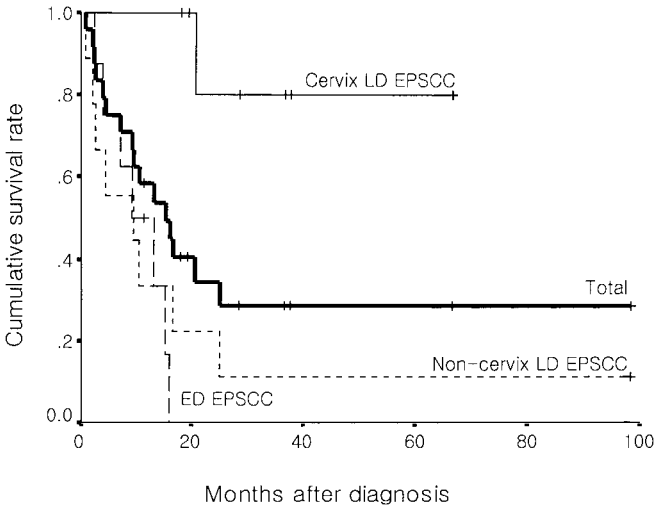

Figure 1. Kaplan–Meier plots for the 24 patients with EPSCC. Overall survival is presented in total and according to the disease stage and site (cervix or non-cervix) in cases of limited disease. EPSCC, extrapulmonary small-cell carcinoma; LD, limited disease; ED, extensive disease.

DISCUSSION

Since the first report was published on EPSCC that occurred in mediastinal glands (15), this histological subtype has been recognized in all sites of the body except the central nervous system (3). The primary sites frequently involved are cervix, esophagus, colon and rectum, head and neck and urinary bladder, with the most common site being variable according to institution (3,5,11,12,16). In this review with 24 patients, the most common site was uterine cervix (58.3%) in women and urinary bladder (41.6%) in men. Other primary sites were variable, including esophagus, stomach, colon or rectum, pancreas, CBD, larynx, parotid gland, kidney and thymus. It appears that EPSCC of sites other than cervix mainly affects patients of middle age or older, with 76% of the patients being older than 50 years. Approximately 40% of the affected patients (70% of the male patients) had a history of smoking. Although other reports suggest that cigarette smoking is associated with EPSCC, particularly in the head and neck region and esophagus (11,17), no definite correlation between smoking and EPSCC could be postulated in this retrospective study.

Patients with EPSCC can be clinically staged by a method similar to those with SCC of the lung (3,11). In general, patients with ED in any site are treated initially with systemic combination chemotherapy (3,5,12). The chemotherapeutic regimens are similar to those employed in SCLC (3,12). The combination of etoposide and cisplatin (EP) is one of the most frequently used regimens, with a response rate of 69% in one study (12). Radiation therapy also has an effective palliative role in many sites. In this study, eight patients (33.3%) had ED, the primary sites being rectum, colon, stomach, pancreas, thymus, kidney and urinary bladder. Seven patients, except one who refused chemotherapy, received platinum-based chemotherapy, the response rate of which was 57% (CR in one, PR in three), with a median TTF of 6.4 months (range, 1.5–8.7 months). The overall survival of patients with ED EPSCC was poor, with a median of 9.2 months (range, 2.4–16.1 months), and the natural history seems to resemble closely that of ED SCLC with early and rapid dissemination. Therefore, clinical trials using new regimens that include topoisomerase I inhibitors or taxanes are warranted to improve treatment outcome.

For the majority of patients with LD EPSCC, radical surgery or definite radiotherapy has been frequently employed (3, 8,18). Because of the unfavorable prognosis, multimodality therapy has become increasingly used, including chemotherapy and radiotherapy and possibly surgery depending on the extent of disease or primary site (3–7,11). However, the best way to integrate these modalities and the role of adjuvant therapy remains to be defined. Of our nine patients with non-cervix LD EPSCC, six had locoregional disease with direct extension to the adjacent structures or metastasis to the regional lymph nodes and the remaining three had local disease confined to the organ of origin. These patients received various treatments: operation alone in four (including two who had local disease), radical surgery followed by adjuvant chemotherapy or radiotherapy in four and concurrent chemoradiotherapy in one. There seemed to be a trend that surgery followed by adjuvant chemotherapy showed a better outcome than operation alone. Regardless of the primary site, however, these patients generally showed an aggressive clinical course like patients with ED EPSCC, with a median OS of 9.6 months (range, 0.7–98.5 months). This unfavorable outcome might be partly associated with two early treatment-related deaths (sepsis, acute myocardial infarction) and a small number of patients and a large proportion of locoregional disease in this study. Taking this factor into consideration, however, this outcome was thought to be inferior to that of LD SCLC (19,20). One study on 54 patients with LD EPSCC reported an unfavorable outcome (median disease-free survival of 5–6 months) with local therapy alone (11). In view of the poor overall outcome, one needs to consider the use of adjuvant chemotherapy in appropriate situations if surgery or radiotherapy is to be employed. In addition, concurrent chemoradiotherapy, which is the standard treatment in LD SCLC, seems to be worth trying in LD EPSCC.

SCC confined to the uterine cervix showed a favorable clinical course compared with that at other sites. The seven patients with cervix SCC received individualized treatment including radiation alone or a variety of combinations of radical surgery, radiotherapy and chemotherapy. Five patients are still in disease-free state with a median follow-up of 36 months (range, 18–66.7 months). Some studies with early-stage (stages 1 and 2) SCC of the cervix have reported a favorable outcome with local modalities of treatment (21,22). In this review, one patient who received radiotherapy alone is disease-free at 37.7 months. Like its pulmonary counterpart, however, SCC of the cervix tends to metastasize early and follow an aggressive course (8,17,23). This suggests that it should be considered as a systemic disease, hence the use of adjuvant chemotherapy following radical surgery and/or radiotherapy is to be encouraged for patients with LD SCC of the uterine cervix (8). Further, in view of the successful outcome in a recent study (24),

the concurrent chemoradiotherapy may be another treatment option which warrants further investigation.

In conclusion, EPSCC was identified in various sites, with the most common primary site being the uterine cervix. SCC confined to the uterine cervix showed a relatively good outcome with a combination of radical surgery and other treatment modalities. However, EPSCC of sites other than cervix was a fatal disease with a discouraging outcome with various treatment modalities regardless of the extent of disease or primary site. Based on this retrospective review, it seems difficult to provide adequate answers regarding the optimal treatment of EPSCC. Clinical trials using new regimens which include topoisomerase I inhibitors or taxanes are warranted in attempts to improve the treatment outcome of ED EPSCC and concurrent chemoradiotherapy, which is the standard treatment in LD SCLC, needs to be investigated in LD EPSCC.

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