Extrapulmonary Small Cell Carcinoma- A Medical Center's Experience

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Background: To review the biologic behavior, therapy and natural courses of patients with extrapulmonary small cell carcinoma (EPSCC) in a medical center.

Methods: We used the computer assisted search for patients diagnosed with EPSCC registered from July 1986 through April 2005. The eligible patients had pathologically proven SCC in sites other than the lung and normal chest radiographs, computed tomography of the chest, sputum cytology, and /or negative bronchoscopic findings.

Results: Twenty patients with EPSCC were identified and 12 patients (60%) had limited disease (LD). For the patients with LD receiving systemic chemotherapy, the response rate was 73% (36.5% complete response (CR), 36.5% partial response (PR). However, most of the patients experienced rapid systemic recurrence, with a median disease free survival (DFS) of 8 months. Patients with extensive disease (ED) received mostly etoposide-cisplatin (EP) based chemotherapy, for which the response rate was 50%. The median overall survival (OS) of the patients with LD and ED was 22 months and 3 months. The patients with EPSCC of the head and neck region showed a favorable clinical course, with a median OS of 43 months. Patients with EPSCC of sites other than the head and neck region had aggressive courses with a median OS of 15.5 months.

Conclusion: Integrated chemoradiotherapy with surgery for patients with LD generates realistic survival results. EP-based chemotherapy should be the current chemotherapy regimen of choice for patients with ED. Patients with EPSCC of sites other than the head and neck region was usually had poor overall outcomes.

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Key words: Extrapulmonary small cell carcinoma, limited disease, extensive disease.

Small cell carcinoma (SCC) of lung, which was first described by Barnard,[1] accounts for 20% of all bronchogenic carcinomas.[2,3] Extrapulmonary small cell carcinoma (EPSCC), which was first reported by Duquid and Kennedy,[4] is a relatively rare disease and represents about 2-4% of all SCC.[5] One thousand new cases are estimated every year in the United States.[6] The primary site of EPSCC has

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been described in a variety of organs, such as head and neck region, esophagus, stomach, pancreas, gallbladder, uterine cervix, kidney, urinary bladder and prostate.[3] SCC of the lung is an aggressive tumor with early dissemination and frequent recurrences. EPSCC has been recognized as a clinicopathological entity distinct from SCC of the lung.[7] Although there have been a few sporadic reports of EPSCC, most of the clinical features, optimal treatment, and natural history remain to be uncovered. The purpose of this study was to review the biologic behavior, therapy and natural course of patients with EPSCC in a medical center.

METHODS

Patient selection

We used the computer assisted search for patients proven to have EPSCC from July 1986 through April 2005 at the Chang Gung Memorial Hospital (CGMH)-Kaohsiung Medical Center. The records of 20 patients with EPSCC were retrieved and evaluated. The histological criteria applied for the diagnosis of EPSCC were identical with those for the pulmonary counterparts,[1,8] namely the appearance of round to spindle-shaped small cells with dense nuclei, inconspicuous nucleoli and sparse cytoplasm. Mitotic rates were normally high, and necrosis was generally present.[7] Immunohistochemical staining for neuroendocrine markers, including chromogranin, synaptophysin, and CD 56, and for keratin expression are usually positive.[9-11] By definition, patients with EPSCC have normal chest radiographs, normal computed tomography of the chest, negative sputum cytology, and/or negative bronchoscopic study.

Staging

Patients were staged utilizing a two-stage system. Limited disease (LD) was defined as a tumor localized to the organ of origin and the locoregional lymph nodes that were easily encompassed within one radiation therapy portal. Any evidence of the disease beyond that was classified as extensive disease (ED).[7]

Data analysis

Survivorship was estimated as a function of time since the diagnosis using the Kaplan-Meier Survivorship Analysis.[12] Survival was measured from the time of diagnosis to the date of death or the latest follow-up examination. Clinical responses including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were classified according to World Health Organization criteria.[13] Disease free survival was measured from the date of CR to the date of disease recurrence.

RESULTS

Table 1 displays the characteristics and clinical courses of 20 patients with EPSCC.

Patient population

The records of 20 patients with EPSCC were evaluated in the study. There were 10 men and 10 women. The median age at diagnosis was 56 years (range, 30-85 years). The primary sites varied including uterine cervix in seven patients (35%), head and neck region in five, urogenital system in four, gastrointestinal system in three, thymus in one. Twelve patients (60%) had LD and eight patients (40%) had ED.

Treatment and outcomes

The 12 patients with LD were primarily treated with multimodality therapy including operation, radiotherapy, and chemotherapy. For those receiving systemic chemotherapy, the overall response rate was 73% (36.5% CR in four, 36.5% PR in four). Most of the patients showed rapid systemic recurrence and the median disease free survival (DFS) was 8 months (95% Confidence interval, CI, 4.08~11.92 months). Among the eight patients with ED, six patients received chemotherapy and/or radiotherapy. The primary chemotherapy was a combination of etoposide and cisplatin (EP). Three of six patients (50%) had DFS of 2, 7.5, and 10.5 months, respectively. The remaining two patients refused chemotherapy. The salvage radiotherapy was administered in these two patients and progressive disease (PD) was obtained. The median overall survival (OS) of the LD and ED was 22 months (95% CI, 17.22~26.78 months) and 3 months (95% CI, 0~16.86 months) (Fig. 1), respectively. All of the patients with EPSCC of the head and neck region were LD and showed favorable clinical courses with three patients (60%) being alive

Table 1. The Characteristics and Clinical Course in 20 Patients with EPSCC

NO.	Location	Gender	Age	Stage	OP	C/T	R/T (cGy/fx)	Response	DFS (Mon)	OS (Mon)	CS
1	Soft palate (L)	M	43	LD	-	EP(4),FP(1);EP(4)	6800/34	CR	6	43	DOD
2	Hypopharynx	M	54	LD	-	EP(4)	5040/28	CR	57	>61	ANED
3	Nasopharynx	M	49	LD	-	CAV(4),EP(4), FBP(1)	-	PR	-	13	DOD
4	Nasal (R)	M	71	LD	+	-	6800/34	CR	21	>21	ANED
5	Sinonasal (L)	M	64	LD	+	EP(4)	6480/36	CR	8	>13	ANED
6	Thymus	M	66	ED	-	ADOC(3),CEP(3)	4400/22	CR	2	12	DOD
7	Esophagus	M	70	ED	-	EP(8),I(1)	4680/26	CR	7.5	20	DOD
8	Esophagus	M	43	ED	-	FLP(1)	1080/6	PD	-	0.8	DOD
9	Pancreas	F	40	LD	-	EP(4),FP(1);IP(4)	5580/31	PR	-	20	DOD
10	Prostate	M	71	ED	-	EP(1)	-	PD	-	3	DOD
11	Bladder	M	85	LD	+	M(7)	-	PR	-	>4	ANED
12	Kidney (L) & Bladder	F	66	LD	+	VAC(2)	3250/16	PD	-	7	DOD
13	Kidney (L)	F	61	LD	+	GP(1)	-	*	6	>6	ANED
14	Uterine cervix	F	30	LD	+	EP(5)	5040/28	PD	-	15.5	DOD
15	Uterine cervix	F	68	ED	+	-	1080/6	PD	-	2	DOD
16	Uterine cervix	F	52	ED	+	EP(6)	4500/35	CR	10.5	>13	ANED
17	Uterine cervix	F	47	ED	-	EP(1)	2500/10	PD	-	0.5	DOD
18	Uterine cervix	F	48	LD	-	FP(3);EP(7)	4320/24	PR	-	28	DOD
19	Uterine cervix	F	44	LD	+	EP(6),AIP(1), VAC(1)	6360/32	CR	5	22	DOD
20	Uterine cervix	F	65	ED	-	-	4500/25	PD	-	23	DOD

Abbreviations: L: left; R: right; C/T: chemotherapy; R/T: radiotherapy; OS: overall survival; DFS: disease free survival; CS: current status; EP: etoposide, cisplatin; FBP: 5FU,bleomycin,cisplatin; CAV: cisplatin, adriamycin, vincistine; DOD: died of disease; FLP: 5FU, leucovorin, cisplatin; M:mitomycin C bladder irrigation; ANED: alive with no evidence of disease; I: ifosfamide; AIP: adriamycin, ifosfamide, cisplatin; ADOC: epirubicin, cisplatin, vincristine, cyclophosphamide; GP: gemcitabine, cisplatin; P: cisplatin; CR: complete response; PR: partial response; PD: progressive disease; LD: limited disease; ED: extensive disease.
* alive with no evidence of disease after operation.

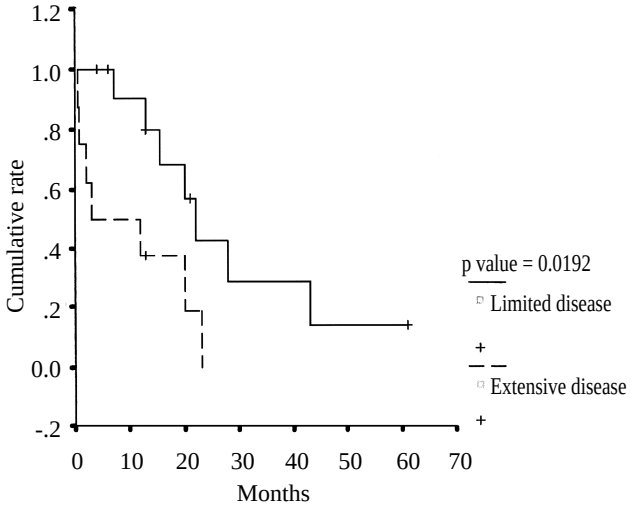

Fig. 1 Survival curves for 20 patients with EPSCC. According to the extent of disease (Limited disease and Extensive disease).

with no evidence of disease. The median OS was 43 months (95% CI, 0~86.61 months), which was longer than that of the other sites (Fig. 2). Patients with EPSCC of sites other than the head and neck region had aggressive courses with a median OS of 15.5 months (95% CI, 7.69~23.31 months).

DISCUSSION

The EPSCC was recognized in all sites of the body except for the central nervous system. The primary sites frequently involved are the uterine cervix, esophagus, colon and rectum, head and neck region, urinary bladder and kidney, with the most common site varying according to the institution.[3,6,7,11,14-16] In our study, the most common site was the uterine cervix and then the head and neck region. EPSCC mainly affects middle aged patients or older, with more than 70% of the patients being older than 50

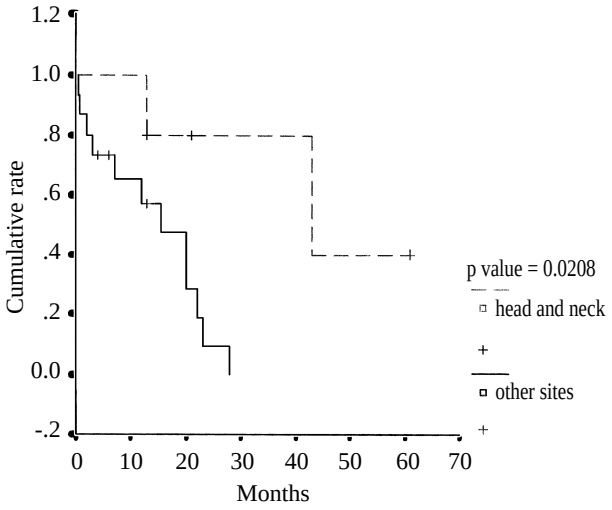

Fig. 2 Survival curves for 20 patients with EPSCC. According to the sites of disease (head and neck vs other sites).

years.[3,7] In our study, 60% of the patients were older than 50 years. Excluding the uterine cervix and non-bladder genitourinary system, EPSCC was more common in men than in women. The extent of disease at the time of diagnosis was similar between the two genders, with 30% of the men versus 40% of the women having extensive disease. In the largest series from the Mayo Clinic, Galanis et. al demonstrated that 75% of patients with LD-EPSCC were treated with surgery alone and had recurrence with a median disease free survival of 6 months.[7] For the most of the patients with LD-EPSCC, radical surgery or definite radiotherapy was frequently employed.[3,6,17,18] Because most patients with local therapy have rapid systemic recurrence, multimodality treatment has become increasingly applied, including surgery combined with different chemotherapy regimens and/or radiotherapy.[6,14,19-22] In general, patients with ED-EPSCC are treated initially with systemic combination chemotherapy. Cisplatin/ etoposide/cyclophosphamide/ doxorubicin represented the backbone of most of the treatment combinations used.[11] Some of the other agents used, such as mitomycin C, methotrexate, and streptozotocin, clearly lacked significant activity in this disease.[11,23,24] The overall response rate in ED, using cisplatin-based or CAV/ACE (cyclophsphamide/ doxorubicin with vincristine or etoposide) chemotherapy, was around 70% to 90%.[11] The combination of etoposide and cisplatin (EP) is one of the most frequently used regimens, with a response rate of 69% in one study.[15] EP-based chemotherapy regimens were employed in the majority of our ED-EPSCC. Three of six patients (50%) had DFS at 2, 7.5, and 10.5 months, respectively. Patients with LD had significantly better survival (P = 0.0192) as compared with the patients with ED (Fig. 1). EPSCC confined to the head and neck region showed a more favorable clinical course as compared with that at other sites (P = 0.0208). The reason is that a conspicuous symptom for which patients may seek attention earlier. Three patients are still alive with no evidence of disease. The median overall survival was 43 months (95% CI, 0~86.61 months) (Fig. 2).

The sites and median overall survival of EPSCC varied in three reported medical centers (Mayo Clinic, Samsung Center, and Chang Gung Memorial Hospital) (Table 2).[3,7] The most common site of EPSCC in our study was the uterine cervix, and that of the other two medical centers was the uterine cervix and gastrointestinal system. The median OS of GYN-EPSCC in our study and that from the Mayo Clinic were shorter than that of Samsung. The reason was that all the patients with uterine cervix EPSCC in the Samsung center had LD. The median OS of

Table 2. The Median Overall Survival in the three Reported Medical Centers

Sites	Patients No(%)			Median overall survival (months)		
	KS-CGMH	Samsung	Mayo clinic	KS-CGMH	Samsung	Mayo clinic
HEENT	5 (25)	2 (8)	18 (22)	43	13.7	14.5
Thymus	1 (5)	1 (4)	3 (4)	12	2.4	14.5
GI	3 (15)	7 (29)	29 (36)	13.6	8.5	5
GU	4 (20)	7 (29)	12 (15)	5	22.7	18
GYN	7 (35)	7 (29)	10 (12)	14.8	32.4	20

Abbreviations: HEENT: head and neck ; GI: gastrointestinal system; GU: genitourinary system; GYN: internal genitalia.

the head and neck region in our study was longer than that of the other two centers. The reason was that all patients with EPSCC of the head and neck region in our study had LD and the multimodality treatment was used. The treatment of one patient in the Samsung center was concurrent chemoradiotherapy (CCRT) and operation alone for the other one. The majority of patients at the Mayo Clinic were treated by operation alone. In conclusion, EPSCC is a clinicopathological entity distinct from SCC of the lung. Because the major disease extent of EPSCC is LD, and that of SCC of lung is ED, integrated chemoradiotherapy with surgery for patients with LD generates a realistic survival result. EP-based chemotherapy should be the mainstay of treatment for patients with ED. Patients with EPSCC sites other than the head and neck region usually had poor overall outcomes.

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肺外小細胞癌——一所醫學中心的經驗

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背 景： 本篇研究的目的，就是在探討本院肺外小細胞癌的分佈，臨床表現及治療成效。

方 法： 利用本院電腦，收集於高雄長庚醫院，從 1986 年 7 月至 2005 年 4 月，診斷爲肺外小細胞癌的病人；符合診斷的病人，需是病理組織爲肺外小細胞癌，同時胸部 X 光，電腦斷層及痰液細胞學，或是支氣管鏡檢查均爲正常者。

結 果： 共收集了 20 例，其中 12 人(60%) 爲局部疾病，8 人爲廣泛疾病。局部疾病的病人接受化學治療，其反應性爲 73% (36.5% 完全反應；36.5% 部分反應)，但絕大部分病人，都很快復發，平均無疾病存活約爲 8 個月。廣泛疾病的病人，絕大多數病人接受 Etoposide-Cisplatin (EP) 化療，其反應性爲 50%。平均整體存活，在局部疾病的病人及廣泛疾病的病人，分別爲 22 個月及 3 個月。頭頸部的病人有較好臨床過程，平均整體存活約爲 43 個月。其他非頭頸部的病人，有較惡化的臨床過程，平均整體存活約爲15.5 個月。

結 論： 開刀合併同步化學及放射線治療，對於局部疾病的病人，有較好的存活。針對廣泛疾病的病人，目前化學治療的最佳選擇藥物是 Etoposide-Cisplatin。非頭頸部的病人，大多是整體結果較差的疾病。

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關鍵字：肺外小細胞癌，局部疾病，廣泛疾病。

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