Extrapulmonary Small Cell Carcinoma：A Review

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Abstract

Extrapulmonary small cell carcinoma (EPSCC) is a relatively rare malignancy accounting for only 2.5~4% of all small cell carcinomas. The head and neck, gastrointestinal tract, genitourinary and gynecologic organs are most common tumor sites. EPSCC behaves aggressively like the small cell lung cancer (SCLC) and its prognosis is dismal. Its tumorigenesis and molecular alternations remain poorly understood. The clinical diagnosis, staging and treatment of EPSCC are challenging. The extent of disease is important for prognosis whereas the tumor location affects the choice of treatment modality. Currently there is no standard guideline as yet. Combined modality (surgery, radiation or chemotherapy) treatment has often been applied to limited-stage EPSCCs in which long-term survivors have ever been reported. However, the sequence of these combinations is not well-defined. Palliative chemotherapy is used for extensive and recurrent/ metastatic EPSCCs with high response rate but short progression-free interval. More research is warranted for improving the survival. (J Intern Med Taiwan 2009; 20:294-300)

Key Words：Extrapulmonary small cell carcinoma (EPSCC), Small cell lung cancer (SCLC)

Introduction

Small cell lung cancer (SCLC) accounts for approximately 15-20% of bronchogenic cancers in the United States[1]. In Taiwan, there are annually 750-800 new cases, which represent about 10% of all lung cancers[2]. This type of cancer is characterized by an increased propensity for early distant metastases and poor prognosis[3]. Small cell carcinomas (SCCs) may also originate in non-pulmonary organs. Duguid and Kennedy first reported in 1930 two cases of mediastinal oat cell tumor where autopsy failed to reveal pulmonary involvement[4]. Since then, numerous sites of small cell carcinoma have been documented, most commonly seen in the head and neck[5], gastro-intestine[6],and genitourinary system[7]. Small cell cancers were occasionally reported in breast, thyroid, skin, and thymus[8]. Rarely, the primary site is undetermined, making such tumors known as small cell carcinoma of unknown primary[9,10]. In general, they are classified as "extrapulmonary

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small cell carcinoma" (EPSCC), encompassing 2.5-4% of all SCCs[11,12].

EPSCC is defined as biopsy-proven small cell carcinoma from non-pulmonary primary site. By definition, a plain chest radiography or computed tomography scan should reveal no evidence of tumor in lung. The sputum cytology and/or bronchoscopy are negative for malignant cells[8]. Irrespective of the origin, EPSCCs resemble their pulmonary counterpart with regard to morphology, immunohistochemistry and electron microscopic features. Moreover, the cytogenetic and molecular abnormalities detected in EPSCCs are similar to the primary SCLC and other carcinomas typically encountered in the organ involved. The differentiation between primary and metastatic EPSCCs as well as other types of neuroendocrine tumors is thus a clinical challenge. Because EPSCCs are rare cancers, there are no well-established clinical trials to establish treatment guideline as yet. Herein, we review the literature in EPSCC in respects to its histology, site of occurrence, cytogenetic and molecular alterations, staging, treatment and prognosis.

Histology

Small cell carcinomas, regardless of the site of origin, share the similarity in their histology. They are characterized as round to spindle-shaped small cells with dense nuclei, inconspicuous nucleoli, and sparse cytoplasm under light microscopy. SCCs have a high mitotic index, grow in sheets and trabecular patterns, and may contain areas of necrosis[8]. SCCs are classified as part of the neuroendocrine family of tumors containing neurosecretory granules in which only electron microscopy can identify[9].

The immunophenotypes of EPSCCs suggest both epithelial and primitive neuroendocrine differentiation. It is not surprising that EPSCC cells possess positive stains for the common neuroendocrine markers like neuron-specific enolase (NSE), neurofilament, synaptophysin and the specific marker of neuroendocrine differentiation, chromogranin-A. Besides, ESPCC cells may also be stained diffusely for general epithelial markers such as keratin. Thyroid transcription factor-1 (TTF-1) has been used widely to differentiate primary and metastatic pulmonary adenocarcinoma[13,14], however, it could not differentiate pulmonary from extrapulmonary small cell carcinomas[15]. TTF-1 is useful for differentiating small cell carcinomas from other types of neuroendocrine tumors[14,16,17] because EPSCC cells generally stain positive for TTF-1 while other extrapulmonary neuroendocrine tumors do not.

EPSCCs were once thought to come from the amine-precursor uptake and decarboxylase (APUD) cells but this theory was questioned by the concomitance of heterogeneous tumor cells composing of both small cells and epithelial cells. It is more accepted that EPSCCs could originate from multipotential stem cell cells with the capability of divergent differentiation[18-20].

Site of Occurrence

EPSCC can occur in almost every organ. Most reports were retrospective showing the most common locations were the head and neck, gastrointestinal tract, genitourinary and gynecologic system[8,12,21-24]. Galanis *et al*. reported a series of 81 EPSCC patients treated in Mayo clinic and 36% of the primary disease originate from gastrointestinal tract, 17% from head and neck, 15 % from genitourinary and 12% from gynecologic system[8]. In a large series of 101 EPSCC patients in Canada, Haider *et al*. reported that 20% of cases were from gastrointestinal origin, 10% from head and neck, 18% from genitourinary tract, 11% from gynecologic organs, and 31% from the unknown primary site[21]. Lee *et al*. reported in a series of 61 patients with EPSCC in South Korea that the most

common primary sites were the gastrointestinal tract (56%) and uterine cervix (18%)[22]. Lin *et al*. also reported a series of 90 EPSCC patients in Taiwan[23]. They found gastrointestinal origin (30%), genitourinary (11%), gynecologic system (30%) and head and neck (19%). Among 544 cases of gastrointestinal SCC, Brenner *et al*. found approximate 70% arise in the upper gastrointestinal tract where esophagus is the most common location (56%), especially in its lower two thirds[6].

Cytogenetic and Molecular Alterations

Despite small cell carcinomas share similar morphology, they differ cytogenetically. For example, loss of chromosome 3p is common in SCLC but rare in EPSCC[25]. Cytogenetic abnormalities, such as microsatellite instability, loss of heterozygosity and chromosome deletion or loss have been reported in EPSCCs from gastrointestinal tract, gallbladder, cervix, urinary bladder and breast[20]. Additionally, some molecular alterations were shared by SCLC and EPSCC such as p53 over-expression, Rb inactivation, increased bcl-2 expression, c-myc amplification, telomerase activation and k-ras mutation[6,20].

Clinical Presentation and Diagnosis

EPSCC was usually found in patients at 60-70 years of age[23], with a slight preponderance in males[8,21]. A significant male predominance (male: female, 6-7:1) occurs in gastrointestinal SCC[6], while a reverse incidence (male: female, 1:3.4) was found in renal SCC[26]. Smoking and alcohol had been presumed as risk factors for EPSCC but were not verified.

The clinical presentation of EPSCC is associated with the location. SCC shows the tendency of rapid growth, local invasion and early metastases. Paraneoplastic syndromes, akin to SCLC, may accompany with EPSCC[29,30].

The final diagnosis of EPSCC is made only by biopsy. A careful assessment should include brain CT/MRI and bone scan for exclusion of central nervous system and bone metastases. A bone marrow exam is suggested especially for those patients with cytopenia[31]. The differential diagnosis of EPSCC should include metastatic SCLC, other types of neuroendocrine or carcinoid tumors, Merkel cell tumors, metastatic melanoma, lymphoma and poorly differentiated carcinoma. Carcinoid can be easily distinguished from EPSCC by distinct morphological features[20]. Merkel cell carcinoma is morphologically similar to SCC but lacks TTF-1 expression and also displays a characteristic perinuclear CK-20 immunostaining[15,32]. Melanoma and lymphoma could be easily identified by their specific markers such as S-100, HMB-45 and CD45. Other small round blue cell tumors, including rhambdomyosarcoma, Ewing's sarcoma, mesenchymal chondrosarcoma, olfractory neuroblastoma, small cell osteosarcoma should be differentiated by immunophenotypes and ultrastructures[33].

Staging

There is no established system for EPSCC staging. Most clinicians adopt the two-stage classification used for SCLC. The limited-stage represents SCC confined to the primary site and surrounding organs which can be encompassed within a tolerable radiation therapy port. The extensive-stage applies to SCC that is beyond the extent of limited-stage[34]. The survival rate is impacted by the extent of disease. Unfortunately, over 50% of EPSCC cases present as extensive-stage at diagnosis[6,8,21-23].

Treatment and Prognosis

Currently there is no standard guideline for EPSCC treatment because of its rarity and limited experience in the management. Most concepts of treatment follow the SCLC. For example, chemotherapy is the mainstay of treatment for

extensive-stage. For limited-stage, the sequence of surgery, radiotherapy and chemotherapy, as well as the role of single or combined modality, is still less-defined. In contrast to SCLC, which upfront surgery is uncommon even for limited-stage, the EPSCC has often undergone a curative-intent resection first. The median survival for those whom received surgical resection followed by adjuvant treatment was longer than those without resection[6,8,12,22,28,35-37]. Nevertheless, it is still controversial for the role of combined modality with radiotherapy and chemotherapy. One large study revealed no difference in overall survival for limited-stage EPSCC treated with combined modality versus single treatment[21].

Chemotherapy is the treatment of choice for patients with relapse or metastasis and who has the extensive-stage EPSCC. Platinum- or adriamycin-based regimens are the most common protocols with a response rate of 30% to 90%. But the progression-free interval is usually short. Lin *et al*. reported that there was no significant difference in patient outcome among different chemotherapy regimens[23].

Interestingly, brain metastasis is less common in EPSCC compared to SCLC[28]. Although prophylactic cranial irradiation has been suggested for the complete responder of SCLC[38], however, there are insufficient data to suggest prophylactic cranial irradiation for EPSCC[8,28].

EPSCC is considered a fatal disease with 3-year survival rate around 30% and 5-year survival rate 11-13%[8,12,22,39]. Patients with untreated EPSCC have a dismal outcome and the survival ranges from weeks to 3 months[21-23]. With treatment, patients with EPSCC have the median survival of 8-16 months[12,21,22,25,39]. The extent of disease is an important prognostic factor in which the limited-stage has better survival. Most patients with limited disease survived over 2 years, compared to 2~9 months in patients with extensive disease[6,8,21-24,39]. EPSCC originated from gynecologic organs, especially the uterine cervix, and the head-and-neck have more favorable outcome[12,21-24]. This can be partly attributed by the early detection and intensive treatment in these two areas[22-24]. ESPCCs from gastrointestinal tract are usually more extensive at diagnosis and have worse survivals[8,22,23]. EPSCC of unknown origin also has a shorter survival[10,21]. Combined modality treatment has been found an independent predictor of survival in one study[23] but unfortunately it shows no better survival benefit over single treatment in the other study[21]. The disease characteristics, treatment and survival are summarized in Table 1.

Conclusion

The diagnosis and treatment of EPSCCs remain challenging. Combined modality preferred in the treatment of limited-stage disease but the sequence remains unclear. Concurrent chemoradiation needs to be further explored in this setting. Palliative chemotherapy is the mainstay for extensive-stage and relapse but new agents and targeted therapy should be tested. Prospective trials are warranted to help the establishment of treatment guidelines in the future.

References

1. American Cancer Society: Cancer Facts and Figures 2005. Atlanta, GA, American Cancer Society, 2005.
2. Cancer Registry Annual Report, Republic of China. Bureau of Health Promotion, Department of Health, executive yuan, Republic of China 2005.
3. Stupp R, Monnerat C, Turrisi AT III, et al. Small cell lung cancer: State of the art and future perspectives. Lung Cancer 2004; 45: 105-17.
4. Duguid J, Kennedy A. Oat cell tumors of mediastinal glands. J Pathol Bacteriol 1930; 33: 93-9.
5. Gelot R, Rhee TR, Lapidot A. Primary oat-cell carcinoma of head and neck. Ann Otol Rhinol Laryngol 1975; 84: 238-44.
6. Brenner B, Tang LH, Klimstra DS, et al. Small-cell carcinomas of gastrointestinal tract: a review. J Clin Oncol 2004; 22: 2730-9.
7. Eichhorn JH, Young RH. Neuroendocrine tumors of the genital tract. Am J Clin Pathol 2001; 115: S94-112(suppl).
8. Galanis E, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. Cancer 1997; 79: 1729-36.
9. Hainsworth JD, Johnson DH, Greco FA. Poorly differentiated

neuroendocrine carcinoma of unknown primary site. A newly recognized clinicopathologic entity. Ann Intern Med 1988; 109: 364-71.
10.Lobins R, Floyd J. Small cell carcinoma of unknown primary. Semi Oncol 2007; 34: 39-42.
11.Van der Henricus H, Heijdra YF. Extrapulmonary small cell carcinoma. South Med J 2005; 98: 345-9.
12.Kim JH, Lee S, Park J, et al. Extrapulmonary small-cell carcinoma: A single-institute experience. Jpn J Clin Oncol 2004; 34: 250-4.
13.Reis-Filho JS, Carrilho C, Valenti C, et al. Is TTF-1 a good immunohistochemical marker to distinguish primary from metastatic lung adenocarcinoma. Pathol Res Pract 2000; 196: 835-40.
14.Chang Y, Lee Y, Liao W, et al. The ulility and limitation of thyroid transcription factor-1 protein in primary and metastatic pulmonary neoplasms. Lung Cancer 2004; 44: 149-57.
15.Cheuk W, Kwan MY, Suster S, et al. Immunostaining of thyroid transcription factor-1 and cytokeratin 20 aids the distinction of small cell carcinoma from Merckel cell carcinoma, but not pulmonary from extrapulmonary small cell carcinomas. Arch Pathol Lab Med 2001; 125: 228-31.
16.Kauffmann O, Dietal M. Expression of thyroid transcription factor-1 in pulmonary and extrapulmonary small cell carcinoma and other neuroendocrine carcinomas of various primary site. Histopathology 2000; 36: 415-20.
17.Agoff SN, Lamos LW, Folpe AL, et al. Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. Mod Pathol 2000; 13: 238-42.
18.Richardson RL, Weiland LH. Undifferentiated small cell carcinomas in extrapulmonary site. Semin Oncol 1982; 9: 484-92.
19.Hoang MP, Maitra A, Gazdar AF, et al. Primary mammary small-cell carcinoma: A molecular analysis of 2 cases. Hum Pathol 2001; 32: 753-7.
20.Frazier SR, Kaplan PA, Loy TS. The pathology of extrapulmoanry small cell carcinoma. Semin Oncol 2007; 34: 30-8.
21.Haider K, Shahid RK, Finch D, et al. Extrapulmonary small cell carcinoma: A Canadian province's experience. Cancer 2006; 107: 2262-9.
22.Lee SS, Lee JL, Ryu MH, et al. Extrapulmonary small cell carcinoma: single center experience. Acta Oncol 2007; 46: 845-51.
23.Lin YL, Chung CY, Chang CS, et al. Prognostic factors in extrapulmonary small cell carcinoma: a large retrospective study. Oncology 2007; 72: 181-7.
24.Huang TL, Huang CH, Yeh T, et al. Extrapulmonary small cell carcinoma -A medical center's experience. Chang Gung Med J 2006; 29: 590-5.
25.Welborn J, Jenks H, Taplett H, et al. High-grade neuroendocrine carcinomas display unique cytogentic aberrations. Cancer Genet Cytogenet 2004; 155: 33-41.
26.Majhall NS, Elson P, Bukowski RM. Therapy and outcome of small cell carcinoma of the kidney: report of two cases and a systemic review of the literature. Cancer 2003; 97: 1436-41.
27.Remick SC, Ruckdesche JC. Extrapulmonary and pulmonary small cell carcinoma: Tumor biology, therapy, and outcome. Med Pediatr Oncol 1992; 20: 89-99.
28.Cicin I, Karagol H,Uzunoglu S, et al. Extrapulmonary small cell carcinoma compared with small-cell carcinoma: a retrospective single-center study. Cancer 2007; 110: 1068-75.
29.Ferlito A, Barnes L, Rinaldo A, et al. A review of neuroendocrine neoplasms of the larynx: update on diagnosis and treatment. J Laryngol Otol 1998; 112: 827-34.
30.Shahab N. Extrapulmonary small cell carcinoma of the bladder. Semin Oncol 2007; 34: 15-21.
31.Benett D, Doll D, Yarbro W. Bone marrow involvement in small cell lung cancer. Cancer 1988; 63: 763-6.
32.Leech SN, Kolar AJ, Barett PD, et al. Merkel cell carcinoma can be distinguished from metastatic small cell carcinoma using antibodies to cytokeratin 20 and thyroid transcription factor-1. J Clin Pathol 2001; 54: 727-9.
33.Devoe K, Weidner N. Immunohistochemistry of small round-cell tumors. Semin Diagn Pathol 2000; 17: 216-24.
34.Mountain CF. Revision in the international system for staging lung cancer. Chest 1997; 111: 1710-7.
35.Van Der Gaast A, Verway J, Prins E, et al. Chemothearpy as treatment choice in extrapulmonary undifferentiated small cell carcinoma. Cancer 1990; 1: 422-4.
36.Lo Re G, Canzonieri V, Veroneri A, et al. Extrapulmonary small cell carcinoma: a single institute experience and review of the literature. Ann Oncol 1994; 5: 909-13.
37.Sved P, Gomez P, Manohargan M, et al. Small cell carcinoma of the bladder. BJU Int 2004; 94: 12-7.
38.Slotman B, Fairre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small cell lung cancer. N Engl J Med 2007; 357: 664-72.
39.Sengoz M, Abacioglu U, Salepci T, et al. Extrapulmonary small cell carcinoma: multimodality treatment results. Tumori 2003; 89: 274-7.

Table 1

Study Year (country)	Van Der Gaast[35] 1990 (Netherland)	Lo Re G[36] 1994 (Italy)	Galanis[8] 1997 (US)	Sengoz[39] 2003 (Turkey)	Haider [21] 2006 (Canada)
Patient number	11	24	81	16	101
Median age	55	60.5	63	62	72
Primary site					
HEENT	1	5	14	1	12
GI	5	1	29	5	20
GU	0	11	12	3	18
GYN	2	2	10	3	11
MUO	3	5	8	4	31
Others			8 (resp. tract & thymus)		9 (breast)
LD/ ED	5 / 6	>50%	54 / 17	9 / 7	51 / 50
Treatment#					
Single	7	9	48*	0	48
Multimodality	4	6	6	16	26
No treatment	0	NS	NS	0	24
MS					
All	12	NS	NS	14	9.83
LD			3 year OS: 38%	25	34
ED			5 year OS: 13%	12	2

Study Year (country)	Cicin[28] 2007 (Turkey)	Kim[12] 2004 (Korea)	Lee[22] 2007 (Korea)	Huang[24] 2006 (Taiwan)	Lin[23] 2007 (Taiwan)
Patient number	11	24	61	20	90
Median age	56	53	67	56	62
Primary site					
HEENT	0	3	5	5	17
GI	5	7	34	3	27
GU	3	7	6	4	10
GYN	1	7	12	7	27
MUO	2	0	4		9
Others				1(thymus)	
LD/ ED	3 / 8	16 / 8	37 / 24	12/ 8	49 / 41
Treatment#					
Single	9	12	22	2	35
Multimodality	2	11	25	18	45
No treatment	0	1	--		10
MS					
All	32	15.3	16	NS	NS
LD		NS	23	22	No treat (1.1)
ED		9.6	6	3	Single (13.8, 6.7)** Multimodality(24.9)

HEENT = Head, eyes, ears, nose, throat; GI = gastrointestinal; GU = genitourinary; GYN = gynecological; MUO = unknown origin cancer
LD = limited disease; ED = extensive disease; MS= median survival, NS= not shown
#Single treatment means surgery, radiotherapy or chemotherapy alone as primary treatment.
Multimodality treatment means combination of more than one single treatment.
*Only limited stage disease patients
**Radiation or chemotherapy alone respectively

肺外小細胞癌

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摘 要

肺外小細胞癌是種少見的惡性腫瘤，占所有小細胞癌的2.5-4%。常見好發部位爲頭頸部，腸胃道，泌尿生殖器官與女性生殖系統。臨床表現與肺小細胞癌類似，相當惡性且預後不佳。肺外小細胞癌的致癌機轉與其生物分子變化不明。臨床上對於其診斷，分期與治療是一難題。疾病的分期是最重要的存活因子。治療計畫也需考慮腫瘤原發部位。因其少見與治療經驗不足，目前尚未發展治療準則。對於局部腫瘤通常採合併治療，偶見長期存活的患者。但如何併用與治療順序尚待研究。對於廣泛性與復發轉移的患者則使用化學治療。雖其反應率高，但效果持續短暫。更多的基礎與臨床研究將有助於改善其治療結果。