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Large Cell Carcinoma of the Lung

— An analysis of clinical features and survival —

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This is a retrospective review of 33 patients with large cell lung carcinoma treated at Yonsei University Cancer Center between Jan. 1985 and Dec. 1989. Of the thirty-three patients, twenty eight were men and five women. Median age was 59 years. Large cell undifferentiated carcinoma was the most common pathologic type, 78.8%. Twenty one of thirty three patients had far advanced diseases, stage IIIB-IV at the time of initial diagnosis. Pleural effusion was initially presented in 12 patients, and SVC syndrome appeared in 5 patients. As to location of the primary tumor, 19(57.6%) appeared in the right lung and 14 (42.4%) in the left. Patients with a centrally located primary tumor mass were nearly the same as those peripherally located (17 vs. 16). Fifteen of thirty three patients developed metastasis involving not only bone, brain, the opposite lung, adrenal gland but also soft tissue, skin, pancreas and appendix.

Treatment was individualized with 19 treated radically and 14 palliatively. After treatment, only two patients showed a complete response.

Long term survival was observed in 4 patients: 1 (24 mo.), 2 (41 mo.) and 1 (54 mo.). The overall 2 year survival rate was 14.3% while the median survival time was 6.0 months. Through the analysis of the various factors affecting survival, we observed that pleural effusion-absent group and complete response group had a statistical significant better survival rate ($p<0.01$).

Key Words: Large cell carcinoma

INTRODUCTION

Large cell carcinoma of the lung constitutes about 10 to 20% of all lung carcinoma. Generally, large cell carcinomas present as large peripheral subpleural lesions with necrotic or cavitary surfaces. These tumors usually are unrelated to bronchi except by contiguous growth, and they have a tendency to invade pulmonary parenchyma and the overlying pleura. Because of these clinical features, many patients with large cell carcinoma of the lung are diagnosed initially as advanced disease and have a poor survival rate[1].

Until now, large cell carcinoma of lung was thought to resemble other non small cell lung carcinoma and was treated with the same method as other non small cell lung carcinoma. But several studies have reported some differences in clinical and pathological features of large cell lung carcinoma, especially in the giant cell lung carcinoma, from other types of non-small cell lung carcinom[2~5]. In this country, we lack reports on large cell lung carcinoma. So, we analysed 33 patients with large cell carcinoma of the lung, its clinical features and their survival rate.

MATERIALS AND METHODS

During the five year period from January 1985 through December 1989, thirty-three patients with large cell carcinoma of the lung were treated at the Department of Radiation Oncology, Yonsei University College of Medicine and Yonsei Cancer Center.

A regular 3 month follow up was done with the last follow up obtained by sending questionaires to the home address of patients or by calling.

Treatment was done by individualized modality. Surgery with postoperative radiotherapy and adjuvant chemotherapy was used for 3 patients. Chemotherapy combined with radiotherapy was used for 15 patients. Surgery with postoperative radiotherapy was used for 3 patients. Radiation therapy alone was used for 10 and chemotherapy alone for 2 patients. A total of six patients were operated on by pneumonectomy and lobectomy, three patients each. Several combinations of

chemotherapy agents was used. Nine patients were treated with VP 16 plus cisplatin, 4 with CAP (cyclophosphamide+doxorubicin+cisplatin), 2 with VP 16 plus cisplatin plus 5-FU, 2 with cisplatin plus doxorubicin plus cytoxan, 2 with cisplatin plus doxorubicin plus cytoxan, 2 with retrospectively VP 16 plus cisplatin plus doxorubicin or vincristin and the remains 1 with bleomycin plus cisplatin. Thus, a total of 20 patients were treated with combination chemotherapy. Because many patients initially had metastatic diseases or very advanced diseases, during the radiation therapy only 19 patients were treated by radical aim; the rest were treated with palliative radiation therapy. The range of total radiation tumor dose was also wide (400-6,300 cGy).

The response criteria were defined in the following manner. A complete response was defined as the disappearance of all clinical evidence of disease. A partial response was defined as a greater than 50% decrease of disease. No response was scored when there were no objective signs of response.

Survival was calculated from the beginning of the initial treatment. The survival curves were plotted using the Kaplan-Meier method and statistical differences between survivals were evaluated using the z-test.

RESULTS

1. Clinical Features

Table 1 lists the characteristics of the 33 patients: 28 were men and only 5 were women. Median age was 59 years with a range of 30 to 73. According to ECOG scale for performance status, 18 were classified as H1, 10 as H2 and 5 as H3.

Table 1. Patient Characteristics (Total 33 from 1985 to 1989)

Age	59 yrs (30 – 73)
Sex	M : F = 28 : 5
Performance (ECOG)	
0 – 1	18 (54.5%)
2 – 4	15 (45.5%)
Weight loss	(+) : (–) = 20 : 13
Histology (AFIP)	
large cell undiff.	26 (78.8%)
giant cell	6 (18.2%)
clear cell	1 (3.0%)
Stage (AJC)	
I – IIIA	12 (36.3%)
IIIB – IV	21 (63.7%)
Pleural effusion	(+) : (–) = 12 : 21
SVC syndrome	(+) : (–) = 5 : 28

The number of patients who experienced weight loss greater than 5 kg during the last 3 months was 20. Many histologic classifications of lung tumors have been suggested but we used a simple and practical classification proposed by the Armed Forces Institute of Pathology (AFIP). By the AFIP classification, 26 were classified as large cell undifferenciated, 6 as giant cell and 1 as clear cell type. Stage (AJC) I to IIIA included 12 patients and IIIB to IV 21 patients. Of the 33 patients, 12 had pleural effusion and 5 had superior vena cava syndrome. As to location of the primary tumor mass, 13 (39.4%) patients in right upper lobe, 7 (21.2%) in left lower lobe, 5 (15%) each in right lower lobe and left upper lobe, 2(6%) in left main stem bronchus and 1(3%) in right main stem bronchus. Seventeen patients had centrally presented tumor masses, but the rest showed peripheral presentation of the tumor masses. Figure 1 shows the location of the primary tumor masses. Central presentation of tumor masses was nearly as frequent as peripheral presentation.

In lymph node metastasis, 2(6.1%) patients had a NO lesion, 3 (9.1%) a N1 lesion, 21(63.3%) a N2 lesion and 7 (21.2%) a N3 lesion.

Of the 33 patients, distant metastasis was observed in 15 patients. Eleven of the fifteen patients with distant metastasis had a synchronous metastasis and the rest had a metachronous metastasis. Distant metastatic sites were variable and are shown in Table 2. The most common distant metastatic site was bone and was observed in 9 patients. Next was the brain in 3 patients. Soft tissue in 2 patients and skin, appendix, adrenal gland, pancreas head,

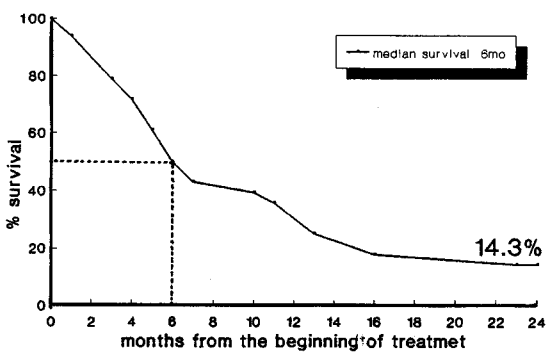

Fig. 1. Location of tumor mass.

Table 2. Distant Metastatic Sites in Large Cell Lung Carcinoma

Site	Bone	Brain	Soft tissue	Adrenal or GI	Opp. lung	Skin	Total
Bone	6	1	1	1*			9
Brain		2		1**			3
Soft tissue			1				1
Opp. lung					1		1
Skin						1	1
Total	6	3	2	2	1	1	15

* Bone + Appendix ** Brain + Adrenal + Pancreas

Table 3. Analysis of Prognostic Factors

Factors		n	Median survival (Mo)	2YSR (%)
Sex	male	(28)	6	11.6
	female	(5)	3	50
Age	< 60	(17)	7	33.7
	> 60	(16)	6	14.8
Performance	0 – 1	(18)	10	23.6
	2 – 4	(15)	4.5	9
Weight loss	(+)	(20)	5	12.5
	(–)	(13)	10	19.3
Pathology	undiff.	(26)	6	27.8
	giant	(6)	8.5	16.7
	clear	(1)	1	0
Location	central	(17)	5	18.9
	peripheral	(16)	7	7.9
Pleural effusion	(+)	(12)	3.5	9.6
	(–)	(21)	11.5	50.2**
SVC synd.	(+)	(5)	13	20
	(–)	(28)	6	12.8
Stage	I–IIIV	(12)	9.5	20.5
	IIIB–IV	(21)	5	10.7
Treatment	radical	(19)	10	19
	palliative	(14)	4	7.9
Response	CR	(2)	47.5	100
	PR ↓	(31)	6	7.6**

** $p < 0.01$ by Z-test

opposite lung also found in 1 patients respectively. Four of fifteen patients had multiple distant metastatic sites. One of four had a distant metastasis in

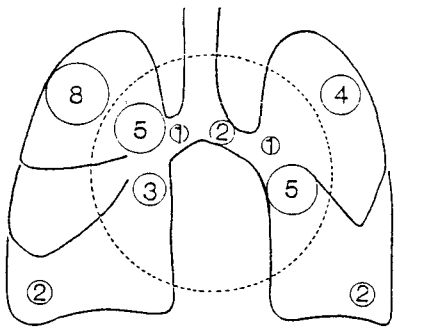

Fig. 2. Overall survival rate of LCLC.

bone and appendix and one in brain, adrenal gland and pancreas head. Uncommon distant metastatic sites in other types of lung carcinomas such as soft tissue, skin, appendix and pancreas head were observed.

2. Survival

Of the 33 patients, only 2 (6.1%) achieved a complete response, 26 (78.8%) a partial response, 3 (9.1%) a minimal response and 2 (6.1%) no response.

Long term survival was observed in 4 patients: 1(24 months), 2 (41 months respectively) and 1(54 months).

Overall survival is illustrated in Figure 2. Overall 2 year survival rate was 14.3% and overall median survival time was 6.0 months.

Two year survival rate and median survival time according to various factors affecting survival are shown in Table 3. Performance status HO-1 had a longer median survival time and higher two year survival rate than H2-4, but there was no statistical significance. Also other differences between survivals occurred according to sex, age, weight loss, pathology, location of tumor mass, SVC syndrome, stage and treatment aim had no statistical

significances. But the pleural effusion-absent group had a longer median survival and a higher two year survival rate than pleural effusion-present group (11.5 vs. 3.5 months and 50.2 vs. 9.6% respectively). The CR group in initial treatment response also had a longer median survival time and higher two year survival rate than the non-CR group with a statistical significance ($p<0.01$).

DISCUSSION

Large cell lung carcinoma was categorized with non-small cell lung carcinoma and was treated like non-small cell lung carcinoma.

The incidence of large cell lung carcinoma is relatively low, and it constitutes only about 10 to 20% of all autopsied lung carcinoma[1]. Because of this low incidence, there are few reports on clinical features and survival of large cell lung carcinoma.

Until now, the typical clinical characteristics of large cell lung carcinoma was presented as peripheral presentation of a large tumor mass[1]. Byrd et al[6] reported that a peripheral mass on the chest radiograph was found to occur most in association with adenocarcinoma, being present in 72% of the cases. Of patients with large-cell tumors, 63% had peripheral masses. In contrast, peripheral masses were seen much less frequently in cases of squamous-cell and small-cell carcinoma, occuring in 31% and 32% respectively. Unlike that report, in our study, central presentation of the primary tumor masses was nearly equal to peripheral presentation. Although our case size was smaller than Byrd et al, our experience of relative larger percentages of central presentation seems to have a significance, a point of view which will be further evaluated. Metastatic sites of lung cancer are found in nearly every organ system. Again, there are differences in the frequency of metastases to different sites for each of the histologic types and also for each of the literatures[1].

Distant metastases in large cell carcinoma of the lung have been reported to be statistically greater than with other cell types of bronchogenic carcinoma as evidenced by the number organs affected, with the brain most commonly involved[2,5,7]. Liver, adrenal gland, bones and kidney are also commonly involved[1,8]. Also in our study, many variable sites of distant metastasis such as bone, brain, opposite lung, adrenal gland, pancreas head, soft tissue, skin and appendix were observed. The most commonly involved site was bone. It was interesting that uncommon distant metastatic sites in the other cell types of the lung carcinoma such as soft tissue, skin, pancreas and appendix were also observed.

There are many prognostic factors affecting survival, as we know. In 1980 Stanley[9] evaluated 77 prognostic factors in approximately 5000 patients with inoperable carcinoma of the lung from Veterans Administration lung group protocols. He proposed that the three most important prognostic factors affecting survival were performance status, extent of disease, and weight loss. Tumor size and histologic type also appeared to be important prognostic factors. Some differences in long-term survival rates according to the histologic type of lung cancer were analyzed in previous reports. At present, patients with epidermoid cancers have the best survival (25% 5year survival rate), followed by those with adenocarcinomas and large cell carcinomas (12% and 13% 5 year survival rate, respectively).

Until recently, it was rare for a patient with small cell carcinoma to survive for 5 years. But Kirsh at al[10] reported a poorer 5 year survival rate of large cell carcinomas than oat cell carcinomas in the past. In recent Korean reports, it was difficult to determine the difference in the survival between large cell and small cell carcinomas because there were only a few reports. A reported median survival time of large cell carcinomas was 6 to 9.7 months in Korean reports. The same 6-month median survival time was also observed in our study. Ban et al[11] reported 12 month and 18 month survival rates of large cell carcinomas as 23 and 11%. And Sung et al[12] reported a 5 year survival rate of 16%. In our study a rate of 14.3% for 2 year survival was observed. Of the variable factors affecting survival, only the pleural effusion-absent group and CR group in initial treatment response showed better survival with a statistical significance ($p<0.01$), probably a reflection of the small number of our patients.

Further studies are required to analyze the difference between the survivals of those with large cell and other non-small cell carcinomas and those with small cell carcinomas.

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= 국문초록 =

대세포 폐암의 임상적 양상과 생존률에 대한 분석

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1985년 1월부터 1989년 12월까지 연세대학교 의과대학 치료방사선과 및 연세암센터에서 치료받은 33명의 대세포 폐암 환자에 대한 후향적 분석을 시행하였다. 이중 28명이 남자로 대부분을 차지했으며 평균 연령은 59세였다. 대세포 미분화 폐암이 가장 많았으며 종양의 위치는 우측 폐에 19명, 좌측 폐에 14명에서 발견되었다. 일반적으로 대세포 폐암은 상당수가 폐의 주변부에 종양이 위치해 있는 것으로 알려져 있지만 본 조사에서는 중심부에 위치해 있는 경우가 주변부 만큼 많이 관찰되었다 (51.5%와 48.5%). 33명의 환자중 21명이 IIIB기 이상의 상당히 진행된 병변을 갖고 진단되어 졌다. 총 15명의 환자에서 원격전이가 관찰되었는데 이중 11명이 진단당시부터 원격전이를 갖고 있었고 나머지 4명은 치료 도중이나 치료 후 발견된 경우였다. 원격전이 부위는 다양하였는데, 연부조직, 피부, 췌장 및 충수돌기등 다른 폐암에서는 흔치 않는 부위에서의 원격전이가 관찰되었다. 치료는 개인별로 차이가 많았는데, 초기에 진행된 병변을 가진 환자가 많았으므로 19명 만이 근치적 목적의 치료를 받았으며 나머지 14명은 고식적인 방법으로 치료를 받았는데 치료후 2명의 환자에서 완전 관해를 얻었다. 4명의 환자가 24개월에서 54개월까지 장기 생존하였으며 2년 생존율은 14.3%였고 중앙생존 기간은 6개월 이었다. 생존율에 영향을 주는 인자들을 분석해 본 결과 늑막 유출액이 없었던 환자군과 치료후 완전 관해를 보였던 환자군에서 통계학적으로 유의하게 생존율이 좋았다 ($p<0.01$).