The Result of Combined Modality Treatment for Limited Stage Small Cell Lung Cancer

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From July 1984 to September 1988, 27 patients with limited stage small cell lung cancer were treated with combined modality (combination chemotherapy plus radiotherapy) at the Department of Therapeutic Radiology in Kyungpook National Unviersity Hospital.

Of the 27 patients, 19 (70%) achieved a complete response, 6 (22%) a partial response, and 2 (8%) no response. Female, performance status H0, serum enolase level below 30 ng/ml, radiation dose over 4500 cGy, and 4 or more cycles of chemotherapy had a favorable effect on the rates of complete response, although there were no statistical differences according to the variables.

Median survival time was 10 months and overall 1- and 2-year survival rates were 40.7% and 12.2%, respectively. Complete response ($p<0.05$), performance status HO ($p<0.05$), 4 or more cycles of chemotherapy ($p<0.05$), and radiation dose over 4500 cGy had a significantly favorable effect on 2-year survival rate. Prophylactic cranial irradiation or sex had no effect on survival. The results of this study suggest that radiation treatment should be combined with combination chemotherapy in the therapeutic strategy of SCLC of limited stage.

Key Words: Lung cancer, Small cell Carcinoma, Limited stage, Combined modality therapy

INTRODUCTION

Small cell carcinoma of the lung (SCLC) represents 15% to 25% of all cases of bronchogenic carcinoma[1]. Combination chemotherapy, alone or with radiation therapy is the mainstay of treatment for SCLC[2]. However, the outlook for SCLC is grave with 2-year survival 25% or less even in limited disease and 5-year survivors infrequent[1,7,16].

A retrospective analysis of patients with SCLC treated with combined modality (combination chemotherapy puls radiotherapy) was carried out.

The purpose of this study is to evaluate the efficacy of combined modality treatment for SCLC in terms of response rate and survival.

MATERIALS AND METHODS

From July 1984 to September 1988, 27 patients with limited stage SCLC were treated with radiation with or without chemotherapy at the Department of Therapeutic Radiology in Kyungpook National University Hospital.

Table 1 lists the characteristics of the 27 patients: 23 were men and 4 were women. Median age was 56 years with a range of 47 to 72. According to ECOG scale[3], 7 were classified as H0, 16 as H1 and 4 as H2. All pateints had histologic or cytologic confirmation of their diagnosis and were clinically evaluated by complete history, physical examination, full blood count, blood chemistry, chest X-ray, bronchoscopy, chest CT scan, and liver and bone scan.

All patients had the disease confined to the chest and ipsilateral supraclavicular lymph nodes. Patients with ipsilateral pleural effusion were included as long as all evident disease could be encompassed within a single radiation port. Of the 27 patients, 7 had ipsilateral pleural effusion, 8 had disease on ipsilateral supraclavicular lymph nodes, 8 had SVC syndrome, and 2 had SIADH. 25 were treated with combined modality and 2 were treated with radiation alone. Several combinations of chemotherapy were applied and the range of cycles of chemotherapy was 1~18 (median 3). Thirteen patients received 1~18 cycles of CAE (cyclophosphamide, adriamycin, etoposide), 10 received alternating CAV-PE (cyclophosphamide, adriamycin, vincristine followed by cisplatin, etoposide) for a total of 2~7 cycles, 1 received 2 cycles of CAV, and 1 received 6 cycles of PE. Radiation was delivered after 1~9 cycles of chemotherapy with 6 MV X-ray encompassing primary tumor, mediastinum and/or bilateral supraclavicular lymph nodes. Median total tumor dose was 5000 cGy with a range of 4000~6000

cGy and median fraction size was 180 cGy with a range of 180~250 cGy. Seven patients received prophylactic cranial irradiation of total 3000 cGy in 10 fractions.

All roentgenograms and clinical charts were evaluated retrospectively to obtain as uniform and accurate determination of response as possible. 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 respone.

Survival was calculated from the start of initial treatment. The survival curves were plotted using Kaplan-Meier method and were analyzed by the log-rank test[4]. Differences between response rates were evaluated using the Fisher's exact test[5].

Table 1. Patient Characteristics

Characteristics	No. of patients (%)
Age	
Range	47–72 years
Median	56 years
Sex	
Male	23 (85)
Female	4 (15)
Performance status (ECOG)	
H0	7 (26)
H1	16 (59)
H2	4 (15)

RESULTS

Of the 27 patients, 19 (70%) achieved a complete response, 6 (22%) a partial response,

Table 2. Response Rate

Response	No. of patients (%)
CR	19 (70)
PR	6 (22)
NR	2 (8)

CR : Complete response
PR : Partial response
NR : No response

Table 3. Response Rate According to Variables

	No. of patients (%)			
	CR	PR	NR	Total
Sex				
Male	15 (65)	6 (26)	2 (9)	23
Female	4 (100)			4
Performance status				
H0	6 (86)	1 (14)		7
⩾ H1	13 (65)	5 (25)	2 (10)	20
Radiation dose (cGy)				
< 4500	1 (25)	2 (50)	1 (25)	4
⩾ 4500	18 (78)	4 (17)	1 (4)	23
No. of chemotherapy cycles				
1–3	7 (54)	4 (31)	2 (15)	13
⩾ 4	11 (92)	1 (8)		12
None				2
Serum enolase (ng/ml)				
< 30	8 (89)	1 (11)		9
⩾ 30	6 (67)	2 (22)	1 (11)	9
Unchecked				9

CR : Complete response, PR : Partial response, NR : No response,

and 2 (8%) no response, as shown in Table 2. Table 3 shows the response rates according to the variables. Women had higher rates of complete response than man (100% vs. 65%). Performance status H0 had a favorable effect on the rates of complete response than over H1 (86% vs. 65%).

Table 4. CR Rate by Radiation Dose & Chemotherapy (N=19)

No. of chemotherapy cycles	Radiation dose (cGy)	
	< 4500	⩾ 4500
None	–	1/19
1–3	–	7/19
⩾ 4	1/19	10/19

CR : Complete response

Serum enolase level below 30 ng/ml had a favorable effect on the rates of complete response compared with that above 30 ng/ml (89% vs. 67%). Radiation dose over 4500 cGy had a positive effect on the rates of complete response compared with that below 4500 cGy (92% vs. 25%). Four or more cycles of chemotherapy had a favorable effect on the rates of complete response compared with those less than 4 cycles (92% vs. 54%). Considering radiation dose and number of cycles of chemotherapy together, there was also a positive relationship with the rates of complete response (Table 4). There were no statistical significances according to the variables.

Survival was complete for 22 patients with 5 patients alive at the conclusion of the study. Overall actuarial survival is illustrated in Fig. 1. One-year survival was calculated to be 40.7% and 2-year

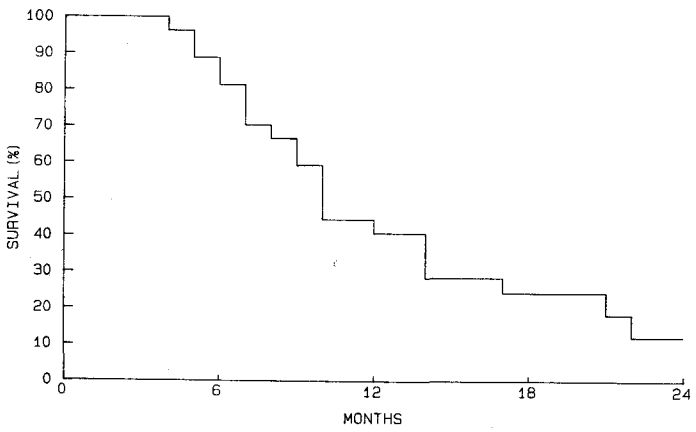

Fig. 1. Overall survival.

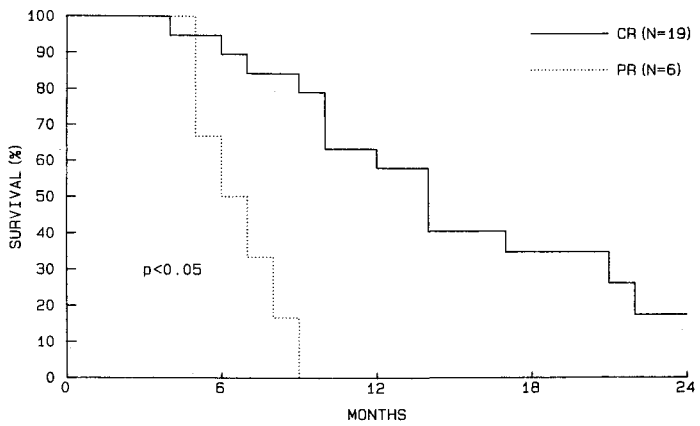

Fig. 2. Survival by response.

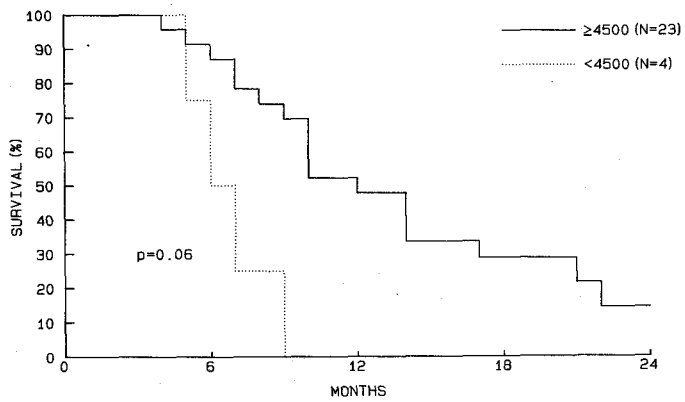

Fig. 3. Survival by radiation dose.

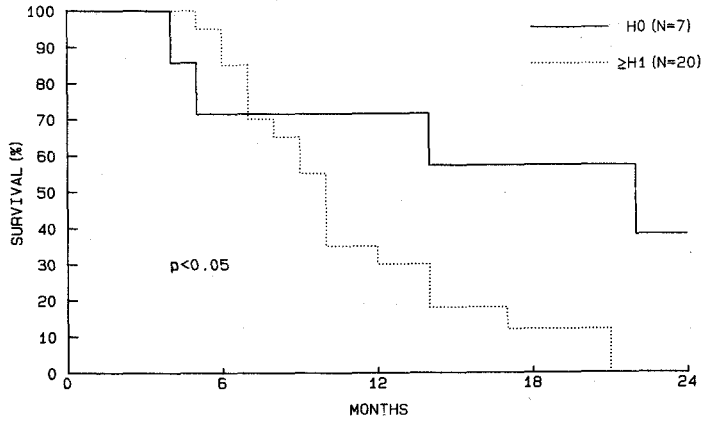

Fig. 4. Survival by performance status.

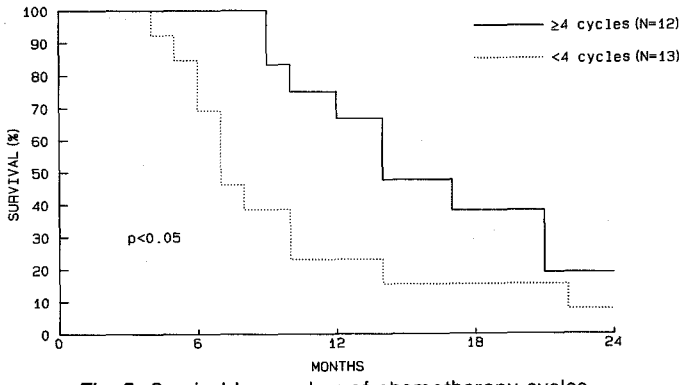

Fig. 5. Survival by number of chemotherapy cycles.

survival 12.2%. The median survival time was 10 months. The patients with complete response had a significantly greater survival as compared with those with partial response ($p<0.05$, Fig. 2). The 2-year survival rate of patients with performance status H0 was significantly better than those with over H1 ($p<0.05$, Fig. 4.). The 2-year survival rate after irradiation above 4500 cGy was better than

below 4500 cGy ($p=0.06$, Fig. 3). The 2-year survival rate of patients received 4 or more cycles of chemotherapy was better than less than 4 cycles ($p<0.05$, Fig. 5). Prophylactic cranial irradiation or sex had no impact on survival.

DISCUSSION

SCLC is responsive to both radiation and a variety of chemotherapeutic agents[6,20~22]. Chemotherapy is required as the core of therapy for SCLC because virtually all patients have widespread metastases at presentation[7,20,23]. Despite the high response rate to chemotherapy, however, most patients with SCLC suffer relapse with tumor that proves drug resistant[7,17]. Chemotherapy alone is insufficient to obtain the high rate of prolonged local control[8]. After chemotherapy-induced complete remission, the thorax remains a significant site of failure in patients with limited disease and the initial sites of relapse are lung and mediastinum in the majority of SCLC patients treated with chemotherapy alone[7~9,20,23]. Prospective randomized trials-[6,9,21,22,24] have found less intrathoracic recurrences, more complete responses, and longer duration of disease-free as well as overall survival with combined modality therapy. When significantly increased complete response rates and failure-free survival rates are considered along with improved local control in the chest, the role of chest irradiation as a part of the definitive theapy for limited SCLC is clear[9].

In several large series using chemotherapy with or without radiotherapy, the patients with limited disease had a complete response rate more than 60%, an overall objective tumor regression rate of 80%, and median survival of 60 weeks[7]. Our complete response rate of 70% and objective tumor regression rate of 92% are comparable to those reported by other investigators.

The treatment goal in SCLC is to achieve a complete response. Only complete responders are the candidates for a prolonged survival [8,25,28]. Patients who are complete responders survive longer than those who have a partial response or stable disease[6,26]. Any response less than complete response is of only modest clinical benefit because survival prolongation results entirely from a prolongation of the duration of complete response[10]. Our result was consistent with these findings, i.e., the complete responders had a significantly longer survival than the partial responders.

Radiation dose is a critical factor in improving overall survival[11]. Radiation doses vary considerably but are usually about 4000~4500 cGy over 15~20 days. McMahon et al[12] suggested that a total dose of 4000~4500 cGy delayed local recurrence in comparison with 3000 cGy, and Chalk et al[13] reported that 5000 cGy over 5 weeks reduced the incidence of local failures in patients who responded completely to radiotherapy. The Southwest Oncology Group[14] noted a complete response rate of 32% in patients received 3000 cGy of chest irradiation versus 57% complete respone rate with 4500 cGy. Eaton et al[15] reported in-field recurrences of 80% at 3500 cGy fell to 0% at 4500 cGy. Our result showed 92% complete response rate with more than 4500 cGy compared to 25% with less than 4500 cGy. It suggests, therefore, that at least 4500 cGy should be administered to achieve a good result when combined modality therapy is selected.

Although long-term disease-free survival in patients with limited diseas is achievable without prolonged cyclic maintenance chemotherapy, more than 4 cycles of chemotherapy would be probably required to eradicate drug-sensitive tumor populations[16]. Our result also revealed that 4 or more cycles of chemotherapy had a positive relationship with the rates of complete response and survival which was in agree with that at least 4 courses of chemotherapy were necessary for a favorable outcome. Considering radiation dose and number of cycles of chemotherapy together, at least 4500 cGy of radiation and 4 courses of chemotherapy appeared to be necessary for a complete remission and eventually a long-term survival with combined modality treatment.

Many authors reported that performance status was an important prognostic factor both for response to therapy and for survival[1,10,17,18]. This was consistent with our result that the complete respone rate of the patients with performance status H0 was higher than those with over H1 (86% vs. 65%) and a significant survival advantage was noted in the patients with H0.

It has been reported that the pretreatment serum enolase levels reflected overall tumor burden because raised serum enolase levels in patients with SCLC were due to production by the tumor itself[17,27]. Normalization of previously elevated serum enolase levels portends a better survival, but response rates and overall survival rate are not influenced by the pretreatment levels[18].

These facts were somewhat different from our result that pretreatment serum enolase level over 30 ng/ml had a lower complete response rate (67%) than that below 30 ng/ml (89%) through without any statistical significance.

Our result of 2-year survival rate, 12.2% was lower than the previously reported series of which the highest rate was approximately 27%[7,9]. We included, in this study, 7 patients with pleural effusion and this could be an explanaton for our result. Although whether pleural effusion is associated with poor prognosis is not well established, many regard it as a poor prognostic factor and exclude it from the category of limited disease[2,17].

The trial at the Finsen Institute[19], which also employed concurrent chemotherapy and radiotherapy, reported 4 deaths in complete responders due to pulmonary toxicity or pericardial effusion. In addition to symptomatic pulmonary infiltrates, several trials reported high rates of esophagitis and more severe bone marrow suppression among patients with combined modality therapy[9,19,21]. Arriagada et al[8] reported the most frequent toxicity was severe bone marrow hypoplasia during the courses of radiotherapy and required close follow-up. Southwest Oncology Group[20] reported that combined modality therapy didn't cause obvious greater chronic toxicity compared with chemotherapy alone. In our study, only 2 patients didn't received full courses of therapy due to severe bone marrow suppression. There were no treatment-related deaths.

The results of this study suggest that radiation treatment should be combined with combination chemotherapy in the therapeutic strategy of SCLC of limited stage.

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═국문초록═

국소성 소세포 폐암에 대한 복합화학요법 및 방사선 병용치료의 효과

경북대학교 의과대학 치료방사선과학교실

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1984년 7월부터 1988년 9월까지 경북대학교병원 치료방사선과에서 소세포 폐암으로 진단되어 복합화학요법 및 방사선 병용치료를 받은 27명을 대상으로 치료성적을 분석하였다.

완전관해율은 70%, 부분관해율은 22%, 무반응은 8%였다. 여자, 수행상태 H0, 방사선량 4500 cGy 이상, 화학요법 4회 이상, 그리고 혈청 enolase 수치 30 ng/ml 이하 등에서 완전관해율이 높게 나타났으나 통계적 의의는 없었다.

중앙생존기간은 10개월이었고 1년생존율과 2년생존율은 각각 40.7% 및 12.2%였다. 생존율을 높이는 인자로는 수행상태 H0 ($p<0.05$), 완전관해 ($p<0.05$), 화학요법 4회 이상 ($p<0.05$), 방사선량 4500 cGy 이상 등으로 나타났으며, 성별과 예방적 전뇌조사는 영향을 미치지 않았다.