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Twice Daily Radiation Therapy Plus Concurrent Chemotherapy for Limited-Stage Small Cell Lung Cancer

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Purpose: A retrospective study was performed to evaluate the efficiency and feasibility of twice daily radiation therapy plus concurrent chemotherapy for limited-stage small cell lung cancer in terms of treatment response, survival, patterns of failure, and acute toxicities.

Materials and Methods: Between February 1993 and October 2002, 76 patients of histologically proven limited-stage small cell lung cancer (LS-SCLC) were treated with twice daily radiation therapy and concurrent chemotherapy. Male was in 84% (64/76), and median age was 57 years (range, 32~75 years). Thoracic radiation therapy consisted of 120 or 150 cGy per fraction, twice a day at least 6 hours apart, 5 days a week. Median total dose was 50.4 Gy (range, 45~51 Gy). Concurrent chemotherapy consisted of CAV (cytoxan 1000 mg/m^2, adriamycin 40 mg/m^2, vincristine 1 mg/m^2) alternating with PE (cisplatin 60 mg/m^2, etoposide 100 mg/m^2) or PE alone, every 3 weeks. The median cycle of chemotherapy was six (range, 1~9 cycle). Prophylactic cranial irradiation (PCI) was recommended to the patients who achieved a complete response (CR). PCI scheme was 25 Gy/ 10 fractions. Median follow up was 18 months (range, 1~136 months).

Results: Overall response rate was 86%; complete response in 39 (52%) and partial response in 26 (34%) patients. The median overall survival was 23 months. One, two, and three year overall survival rate was 72%, 50% and 30%, respectively. In univariate analysis, the treatment response was revealed as a significant favorable prognostic factor for survival ($p<0.001$). Grade 3 or worse acute toxicities were leukopenia in 46 (61%), anemia in 5 (6%), thrombocytopenia in 10 (13%), esophagitis in 5 (6%), and pulmonary toxicity in 2 (2%) patients. Of 73 evaluable patients, 40 (55%) patients subsequently had disease progression. The most frequent first site of distant metastasis was brain.

Conclusion: Twice daily radiation therapy plus concurrent chemotherapy produced favorable response and survival for LS-SCLC patients with tolerable toxicities. To improve the treatment response, which proved as a significant prognostic factor for survival, there should be further investigations about fractionation scheme, chemotherapy regimens and compatible chemoradiotherapy schedule.

Key Words: Twice daily radiation therapy, Concurrent chemoradiation, Limited stage, Small cell lung cancer

Introduction

In cancer incidence rates of Korea, lung cancer ranks the second (17%) in male and the fifth (8%) in female.[1] And, in cause of cancer deaths, it ranks the first (24%) in male and the second (15%) in female.[2] Small cell lung cancer (SCLC) comprises approximately 11% of lung cancer[1] and about 45% of them present with limited stage disease.[3] SCLC is characterized by high aggressiveness and potential to metastasize early. Although it has been shown to be responsive to initial therapies including both chemotherapy and radiation therapy, most patients relapse and die of their disease.

Limited-stage small cell lung cancer (LS-SCLC) is defined as a disease clinically confined to one side of the chest and treatable by radiotherapy field size tolerated by normal tissues.[4] The recent recommendation for LS-SCLC is combined

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chemotherapy and modest dose (45～50 Gy) of thoracic radiation therapy (TRT) since two meta-analyses showed it improves local control and survival compared with chemotherapy alone.[5,6] However, local relapse rate with conventionally fractionated TRT was high, for example, intrathoracic relapse rate was 75% in modern randomized trial.[3] In pursuit of optimal methods of delivering radiation therapy for LS-SCLC, fractionation of customary once daily radiotherapy dose into twice daily treatments (BID RT) was developed from the findings that SCLC cell lines *in vitro* have a high sensitivity to small dose of radiation. In addition, lower fraction dose has advantages of reducing damage to normal tissues and risks of late radiation toxicity.[4,7]

In a randomized trial conducted by Turrisi et al., 45 Gy of BID RT beginning with the first cycle of concurrent four cycles PE (cisplatin and etoposide) chemotherapy resulted in a survival advantage compared with the same dose given in once daily fractions.[4]

The purposes of this retrospective study were first, to evaluate the response rate and survival, and second to assess the feasibility and toxicity of BID RT given concurrently with chemotherapy.

Materials and Methods

1. Patients

Patients with histologically confirmed LS-SCLC, treated between February 1993 and October 2002, were enrolled in this study. Pretreatment staging was done with physical examination, chest X-ray, fiberoptic bronchoscopy, pulmonary function test, computed tomography (CT) scans of chest including liver and adrenals, CT or magnetic resonance imaging (MRI) of brain, radionuclide bone scan, complete blood cell count with differential, and serum chemistry profile. Limited-stage was defined as disease confined to one hemithorax including bilateral mediastinal, ipsilateral hilar and supraclavicular lymph nodes with no pleural effusion. Patients with history of prior cancer, or prior treatments with either chemotherapy or radiation therapy were excluded in this study.

2. Radiation therapy

Radiation therapy used 6 or 10 MV photons. Fraction dose of 120 or 150 cGy, twice daily with at least 6 hours interfraction interval, was given 5 days a week. Total thoracic radiation dose ranged from 45 to 51 Gy with median 50.4 Gy. The target volume, as defined by chest CT scan, included the gross tumor with minimum margin of 2 cm, bilateral mediastinal and ipsilateral hilar lymph nodes. If a significant reduction of tumor volume occurred after preceding chemotherapy, radiation field was chosen in consideration of the reduced tumor volume. Uninvolved supraclavicular lymph node was not irradiated.

In 33 (43%) patients, initial opposed anteroposterior and posteroanterior (AP/PA) fields were used until 45 Gy, then field reduction was done. AP/PA fields were changed to oblique fields after 30 Gy (fraction dose 150 cGy) or 36 Gy (fraction dose 120 cGy) in 12 (16%) and 20 (26%) patients, respectively. Most recent method, performed in 11 (15%) patients, was to use AP/PA and oblique fields in the first and second fraction of a day, respectively, from the start of BID RT. All oblique fields were devised with two dimensional plan technique considering normal tissue tolerance i.e., spinal cord, lung, and esophagus.

Prophylactic cranial irradiation (PCI), 25 Gy/10 fractions administered 5 days a week for 2 consecutive weeks, was recommended for patients who achieved a complete response (CR).

3. Chemotherapy

Chemotherapy consisted of CAV (cytoxan 1000 mg/m^2, adriamycin 40 mg/m^2, vincristine 1 mg/m^2) alternating with PE (cisplatin 60 mg/m^2, etoposide 100 mg/m^2) every 3 weeks in 62 (82%) patients, and 14 (18%) patients received PE alone every 3 weeks. Median cycle of chemotherapy was six (range, 1～9). When to add TRT during chemotherapy was largely decided by attending medical oncologist, and it was added more early in the later period.

4. Evaluation of response

One to two months after completion of chemoradiothearpy, response was evaluated with clinical examination, chest X-ray, fiberoptic bronchoscopy and chest CT. A complete response (CR) was defined as the disappearance of all clinical evidence of tumor. A partial response (PR) was defined as a decrease of 50% or more in the product of the length and width of any measurable tumor. A stable disease (SD) was defined as a less than 50% decrease or a less than 25% increase. A progressive disease (PD) was defined as an increase of more than 25% or the appearance of any new tumor.

Local progression was considered as redevelopment of tumor within thorax. Distant metastasis was defined to have tumor developed outside thorax.

5. Toxicity and statistics

The acute complications including pulmonary, esophageal and hematologic toxicities were evaluated according to the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring scheme.[8]

Survival period was calculated from the first day of treatment to death or last follow up. Survival curves were constructed using Kaplan-Meier method, and Log-rank test was used to evaluate prognostic variables.

Results

1. Patients and treatments

The characteristics of 76 patients with LS-SCLC who were included in the study are shown in Table 1, with treatment schemes including radiation therapy and chemotherapy. Median age was 57 years (range, 32~75) and 64 (84%) patients were male. Eastern Cooperative Oncology Group (ECOG) performance scale was 1 or less in 66 (87%) patients.

Forty two (55%) patients received thoracic radiation dose of 5,040 cGy with fraction dose of 120 cGy BID. Twenty two (29%) patients were given 4,560 cGy/120 cGy BID and in 12 (16%) patients, 4,500 cGy/150 cGy BID was performed. The timing of adding TRT during chemotherapy was varied among patients. In 47 (62%) patients, TRT started on the first to third chemotherapy, and in 29 (38%) patients, TRT started on the fourth or later chemotherapy. Prophylactic cranial irradiation (PCI) was administered to 77% of patients with CR (30/39) and all of them received scheduled cranial dose.

Table 1. Patients Characteristics and Treatments Scheme

		No (%)
Characteristics		
Gender	Male	64 (84)
	Female	12 (16)
Age	≤60	47 (62)
	>60	29 (38)
	Median	57 years
Performance scale	0	5 (7)
(ECOG)	1	61 (80)
	2	10 (13)
Treatment scheme		
TRT* (total dose/	5040 cGy/120 cGy BID	42 (55)
fraction dose)	4560 cGy/120 cGy BID†	22 (29)
	4500 cGy/150 cGy BID	12 (16)
Chemotherapy	Alternating CAV/PE	62 (82)
	PE alone	14 (18)
Timing of TRT	Early TRT‡	47 (62)
	Late TRT§	29 (38)
PCI	2500 cGy/250 cGy	30/39‖ (77)

*thoracic radiation therapy, †three patients received additional boost 540 cGy/180 cGy once daily, ‡TRT started on 1st~3rd chemotherapy, §TRT started on 4th chemotherapy or later, ‖PCI (Prophylctic cranial irradiation) was administered to 30 patients among 39 CR (complete response) patients

2. Efficacy of treatments

Overall response rate was 86% (Table 2); complete response in 39 (52%), partial response in 26 (34%), stable disease in 4 (5%) and progressive disease in 4 (5%) patients. Three patients were not evaluated for treatment response. Two patients did not take follow-up examinations and one patient died before evaluation of response.

Table 2. Treatment Response

Type of response	No (%)
Complete response	39 (52)
Partial response	26 (34)
Stable disease	4 (5)
Progressive disease	4 (5)
Not evaluable	3 (4)
Total	76 (100)

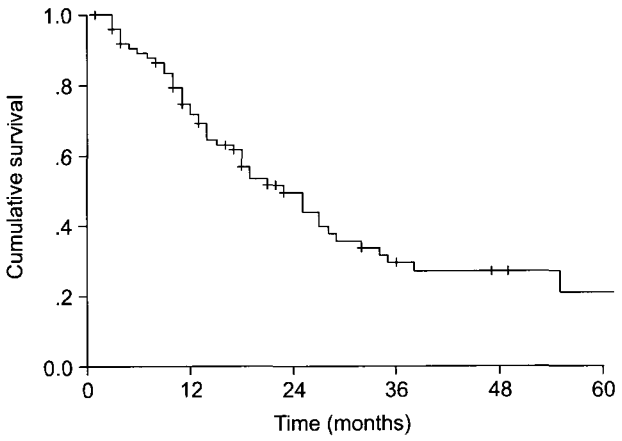

Fig. 1. Overall survival curve. Median survival was 23 months. One, two and three year overall survival rates was 72%, 50% and 30%, respectively.

Table 3. Type of Disease Progression

Progression	No (%)*
Local progression	5 (7)
Distant metastasis	26 (36)
Both	9 (12)
Total	40 (55)

*among 73 evaluable patients

Table 4. Acute Toxicities Scored by RTOG Criteria

Type of toxicity	Grade	No (%)
Leukopenia	0	8 (11)
	1~2	22 (29)
	3~4	46 (60)
Anemia	0	24 (32)
	1~2	47 (62)
	3~4	5 (6)
Thrombocytopenia	0	50 (66)
	1~2	16 (21)
	3~4	10 (13)
Lung	0	44 (58)
	1~2	30 (40)
	3	2 (2)
Esophagus	0	14 (19)
	1~2	57 (75)
	3	5 (6)

Median follow up was 18 months (range, 1~136 months). Median overall survival was 23 months. One, two, and three year overall survival rate was 72%, 50%, and 30%, respectively (Fig. 1).

Of 73 evaluable patients, 40 (55%) patients subsequently had disease progression (Table 3). The mean time to progression was 22 months and median progression-free survival was 14 months. Local progression occurred in 5 (7%), distant metastasis in 26 (36%) and both of them in 9 (12%) patients. The most frequent first site of distant metastasis was brain (17 patients, 22%) and for patients who received PCI, brain metastasis rate was 17% (5/30).

In univariate analysis, treatment response was revealed as a significant prognostic factor for survival ($p<0.001$). Other factors including gender, ECOG performance, fraction dose, timing of TRT and chemotherapy regimen did not show statistically significant difference in survival. Subgroup analysis was also performed, and in patients with PE alone chemotherapy (n=14), early TRT group showed, not significant but, increased survival compared to late TRT group (32 vs. 19 months, p=0.278)(Table 5).

Table 5. Prognostic Factors for Overall Survival by Univariate Analysis

Variables	p value
Gender (M vs. F)	0.767
Age (≤60 vs. >60)	0.323
Performance (ECOG) (≤1 vs. 2)	0.389
Treatment response*	<0.001
Fraction dose (120 vs. 150 cGy)	0.133
Early vs. late TRT	0.854
CAV/PE group (n=62)	
Early vs. late TRT	0.466
PE alone group (n=14)	
Early vs. late TRT	0.278
CAV/PE vs. PE alone	0.517
Early TRT group (n=47)	
CAV/PE vs. PE alone	0.595
Late TRT group (n=29)	
CAV/PE vs. PE alone	0.234

*complete response vs. partial response vs. no response (stable disease or progressive disease)

3. Acute toxicity

Grade 3 pulmonary and esophageal toxicity occurred in 2 (3%) and 4 (5%) patients, respectively (Table 4).

In hematologic toxicities, grade 3 and 4 leukopenia occurred in 28 (37%) and 18 (24%) patients, respectively. Grade 3 anemia occurred in 5 (7%) patients. Grade 3 and 4 thrombocytopenia occurred in 7 (9%) and 3 patients (4%), respectively (Table 4). There were no severe acute toxicities related to PCI.

Discussion

Among all lung cancer subtypes, small cell lung cancer is the most aggressive disease with very rapid tumor doubling time and early tendency to metastasize, and when left untreated, median survival is only 2 to 4 months.[9]

Since 1990s, PE (cisplatin and etoposide) chemotherapy has been considered a standard treatment for LS-SCLC[10,11] and its response rate was 80 to 90%[9], but the locoregional control rate was only 40 to 50%.[6,7] After two meta-analyses, in which the addition of TRT to chemotherapy increased local control rate to about 70%, the combination of chemotherapy and TRT

became the first line management for LS-SCLC.[6,7] However, local relapse rate was high and toxicities were increased.

To reduce toxicities and improve local control, hyperfractionated radiotherapy was developed based upon its several biologic advantages. SCLC *in vitro* is highly sensitive to even small dose of radiation because the dose-response curve of SCLC lacks a shoulder, and reduced dose per fraction can lower radiation toxicity in normal tissues that have a shoulder.[12] In addition, accelerated treatment can counter the theoretical problem of fast repopulation of small cells, and small fraction dose may lower the risk of late radiation toxicities.

Turrisi et al. randomized LS-SCLC patients either to receive 45 Gy TRT in twice daily fractions beginning with the first cycle of concurrent four cycles PE chemotherapy, or to receive the same dose in once daily fractions. After 8 years median follow up, survival was significantly improved for the twice daily group, median survival as 19 vs. 23 months, 5YSR as 16 vs. 26% (p=0.04).[4]

Our institution published the results of a retrospective study, in 1998, comparing once versus twice daily TRT given with sequential or concurrent alternating CAV and PE chemotherapy in LS-SCLC. Timing of chemotherapy was sequential in 88% of once daily TRT, and concurrent in 93% of BID RT patients. Treatment response was better in BID RT patients but not significant, and there was no survival difference. Severe esophagitis and leukopenia occurred more in BID RT patients.[13]

In the present study, timing of TRT was varied among patients and the regimen of concurrent chemotherapy was median six cycles of alternating CAV/PE or PE alone. After median follow up of 18 months, median overall survival was 23 months, and one, two, three year overall survival rate was 72%, 50%, 30%, respectively. Better response to chemoradiotherapy was realized in improved survival ($p<0.001$)(Fig. 2).

When we divided the patients according to timing of TRT, 47 (62%) patients received TRT started on the first to third chemotherapy (early TRT) and 29 (38%) patients on the fourth or later chemotherapy (late TRT). A significant difference in survival between these two groups was not found (p=0.854). In subgroup analysis, statistically not significant but, increased survival was detected with early TRT in PE only group (32 vs. 19 months, p=0.278)(Table 5). A recent meta-analysis of seven randomized trials showed a significantly increased 2YSR for early versus late TRT and a suggestion of similar trend at 3,

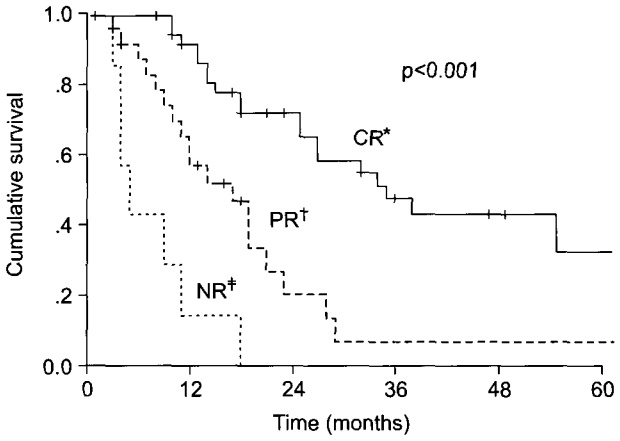

Fig. 2. Overall survival by treatment response. *Complete response, †partial response, ‡no response (stable disease or progressive disease)

5 years. This effect was greater in studies that used hyperfractionated RT and platinum-based chemotherapy regimens.[14]

The SCLC, while highly chemosensitive, also has a tendency to develop resistance to standard chemotherapy, and one of the ways developed to overcome this problem was alternating non-cross-resistant regimens. It is based on the findings of clonal heterogeneity within tumor and the inability to use more than four drugs simultaneously due to overlapping toxicities.[15,16] In our study, no significant survival difference was seen between alternating CAV/PE and PE alone group (p=0.517)(Table 5). A randomized study by Fukuoka et al. found alternating CAV/PE to improve survival for patients with LS-SCLC, compared with CAV (p=0.058) or PE alone (p=0.032).[10] But it used only chemotherapy not chemoradiation. In concurrent chemoradiotherapy for LS-SCLC, PE alone has become recent standard regimen.[17]

In the setting of concurrent chemoradiotherapy, delivering multiple fractions of radiation in a day increased incidence of esophagitis. In Turrisi et al. trial, toxicities were not significantly different between two groups except grade 3 esophagitis which was greater in twice daily TRT group (27 vs. 11%, $p<0.001$).[4] In our study, major toxicity was leukopenia as grade 3 or worse in 61%. Grade 3 pulmonary (2%) and esophageal (6%) toxicity rate was relatively low and could be managed properly with conservative managements.

Recurrence in the brain remains the primary site of treatment failure in SCLC.[18] A PCI overview including seven randomized trials and 987 patients was reported, and showed a significant

mortality reduction of 14%, with an absolute benefit on overall survival of 5.4% at 3 years.[19] Also in a French randomized trial, PCI decreased the risk of brain metastases two-fold, but survival advantage was not seen.[20] We reports brain metastasis rate of 17% for patients with PCI in this study, and future study is needed to evaluate survival benefit and late neurotoxicity.

Among novel advances in radiation therapy, three dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT) have a potential to concentrate radiation dose within tumor volume and reduce dose to surrounding normal tissues, so improved local control and decreased radiation toxicities are anticipated. And, in a recent trial of escalating radiation dose, it is reported that 70 Gy once daily TRT was delivered safely with encouraging efficacy.[21]

However, the optimal methods regarding TRT and chemotherapy for LS-SCLC still remain controversial, and further studies are needed to find better ways that can improve treatment response and increase survival.

Conclusion

Twice daily radiation therapy plus concurrent chemotherapy yielded favorable response and survival with tolerable toxicities for LS-SCLC patients. To improve the treatment response, which revealed as a significant prognostic factor for survival, there should be further investigations about fractionation scheme, chemotherapy regimens, and compatible chemoradiotherapy schedule.

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국문초록

국한성병기 소세포폐암에서 하루 두 번 분할조사와 동시 화학방사선치료

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목 적: 국한성병기 소세포폐암 환자에서 하루 두 번 분할조사에 의한 동시 화학방사선치료의 효율성을 치료반응률, 생존율, 실패양상, 치료부작용 등의 관점에서 평가하기 위해 후향적 연구를 수행하였다.

대상 및 방법: 1993년 2월부터 2002년 10월까지 총 76명의 환자가 조직학적으로 증명된 국한성병기 소세포폐암으로 하루 두 번 분할조사에 의한 동시 화학방사선치료를 시행 받았다. 대상환자 중 남성은 84% (64/76)이었고, 중앙연령은 57세였다(32~75세). 흉부방사선치료는 120 또는 150 cGy/fraction로 최소 6시간의 간격을 두고 하루 두 번, 한 주에 5일 시행하였다. 총 흉부조사선량의 중앙값은 50.4 Gy였다(45~51 Gy). 동시 화학치료은 3주 간격으로 교대 CAV (cytoxan 1,000 mg/m^2, adriamycin 40 mg/m^2, vincristine 1 mg/m^2)/PE (cisplatin 60 mg/m^2, etoposide 100 mg/m^2)이거나, 혹은 단독 PE 요법이 사용되었다. 화학치료 횟수의 중앙값은 6회였다(1~9회). 예방적 전뇌조사는 완전관해를 보인 환자에게 25 Gy/10 fractions로 시행되었다. 중앙추적관찰기간은 18개월이었다(1~136개월).

결 과: 치료의 반응률은 86%이었다; 완전관해가 39명(52%), 부분관해가 26명(34%)이었다. 중앙생존기간은 23개월이었다. 1년, 2년, 3년 생존율은 각각 72%, 50%, 30%이었다. 단변량분석에서 치료 반응률이 생존율의 유의한 예후인자로 밝혀졌다($p<0.001$). 등급 3 이상의 급성부작용은 백혈구감소 46명(61%), 적혈구 감소 5명(6%), 혈소판 감소 10명(13%), 식도염 5명(6%), 그리고 폐독성이 2명(2%)에서 있었다. 추적관찰이 가능했던 73명의 환자 중 총 38명(52%)에서 병의 진행이 관찰되었다. 첫 번째 원격전이 장소의 빈도는 뇌가 가장 높았다.

결 론: 하루 두 번 분할조사에 의한 동시 화학방사선치료는 국한성병기 소세포폐암 환자에서 나쁘지 않은 부작용과 함께 양호한 치료반응 및 생존율의 결과를 보였다. 생존율의 유의한 예후인자로 밝혀진 치료 반응률을 향상시키기 위해 방사선치료 분할방식, 화학요법제제, 화학방사선치료의 결합방식에 대한 추가적인 연구가 필요할 것으로 생각된다.

핵심용어: 다분할 방사선치료, 동시 화학방사선요법, 국한성 병기, 소세포 폐암