Concurrent Chemoradiation Therapy in Stage III Non-small Cell Lung Cancer

In Ah Kim M.D.*, Ihl Bhong Choi M.D.*, Ki Mun Kang, M.D.*
Jie Young Jang M.D.*, Jung Sub Song, M.D.†, Sun Hee Lee, M.D.†
Mun Sub Kuak, M.D.†, and Kyung Sub Shinn, M.D.*

*Departments of Radiation Oncology, †Internal Medicine, & ‡Thoracic Surgery
St. Marys Hospital, Catholic University, Medical College Catholic Cancer Center

=Abstract=

Purpose : This study was tried to evaluate the potential benefits of concurrent chemoradiation therapy (low dose daily cisplatin combined with split course radiation therapy) compared with conventional radiation therapy alone in stage III non-small cell lung cancer. The end points of analyses were response rate, overall survival, survival without locoregional failure, survival without distant metastasis, prognostic factors affecting survival and treatment related toxicities.

Materials and Methods : Between April 1992 and March 1994, 32 patients who had stage III non-small cell lung cancer were treated with concurrent chemoradiation therapy. Radiation therapy for 2 weeks (300 cGy given 10 times up to 3000 cGy) followed by a 3 weeks rest period and then radiation therapy for 2 more weeks (250 cGy given 10 times up to 2500 cGy) was combined with 6mg/M^2 of cisplatin. Follow-up period ranged from 13 months to 48 months with median of 24 months. Historical control group consisted of 32 patients who had stage III non-small cell lung cancer were received conventionally fractionated (daily 170-200 cGy) radiation therapy alone. Total radiation dose ranged from 5580 cGy to 7000 cGy with median of 5940 cGy. Follow-up period ranged from 36 months to 105 months with median of 62 months.

Results : Complete reponse rate was higher in chemoradiation therapy (CRT) group than radiation therapy (RT) group (18.8% vs. 6.3%). CRT group showed lower in-field failure rate compared with RT group(25% vs. 47%). The overall survival rate had no significant differences in between CRT group and RT group (17.5% vs. 9.4% at 2 years). The survival without locoregional failure (16.5% vs. 5.3% at 2 years) and survival without distant metastasis (17% vs. 4.6% at 2 years) also had no significant differences. In subgroup analyses for patients with good performance status (Karnofsky performance scale 80), CRT group showed significantly higher overall survival rate compared with RT group (62.5% vs. 15.6% at 2 years). The

이 논문은 1996년 12월 6일 접수하여 1997년 3월 3일 채택되었음.
통신저자 : 김인아 서울시 서초구 반포동 505 강남성모병원 방사선종양학과

prognostic factors affecting survival rate were performance status and pathologic subtype (squamous cell cancer vs. nonsquamous cell cancer) in CRT group. In RT alone group, performance status and stage (IIIa vs IIIb) were identified as a prognostic factors. RTOG/EORTC grade 2-3 nausea and vomiting(22% vs 6%) and bone marrow toxicities (25% vs. 15.6%) were significantly higher in CRT group compared with RT alone group. The incidence of RTOG/EORTC grade 3-4 pulmonary toxicity had no significant differences in between CRT group and RT group (16% vs. 6%). The incidence of WHO grade 3-4 pulmonary fibrosis also had no significant differences in both group (38% vs. 25%). In analyses for relationship of field size and pulmonary toxicity, the patients who treated with field size beyond 200cm^2 had significantly higher rates of pulmonary toxicities.

Conclusion : The CRT group showed significantly higher local control rate than RT group. There were no significant differences of survival rate in between two groups. The subgroup of patients who had good performance status showed higher overall survival rate in CRT group than RT group. In spite of higher incidence of acute toxicities with concurrent chemoradiation therapy, the survival gain in subgroup of patients with good performance status were encouraging. CRT group showed higher rate of early death within 1 year, higher 2 year survival rate compared with RT group. Therefore, to evaluate the accurate effect on survival of concurrent chemoradiation therapy, systematic follow-up for long term survivors are needed.

Key Words : Cisplatin, Radiation Therapy, Non-small Cell Lung Cancer

INTRODUCTION

The prognosis of patients presenting with locally advanced stage III non-small cell lung carcinoma (NSCLC) remains poor. Two main factors for this failure are the abscence of effective chemotherapeutic regimens to treat the subclinical distant metastases and high local failure rate even after high dose radiation therapy.

As the radiotherapy dose applied is determined by normal tissue tolerance, there is a need for selective potentiators of radiation damage in the tumor cells. In vitro data have shown a variable degree of tumor cell radiosensitization by cisplatin including some supra-additive response[1]. This has been confirmed in some animal studies[1, 2]. These observations led four groups of investigators to conduct randomized studies in which radiation and concurrent cisplatin were compared to radiation alone in locally advanced NSCLC[3-6]. The highest therapeutic gain has been observed when cisplatin is given daily during fractionated irradiation[2, 7]. Radiotherpy and Lung Cancer Cooperative Groups of European Organization for Research and Treatment of Cancer (EORTC) study suggested the therapeutic gain existed in this approach[3]. Our study was tried to evaluate the potential benefits of concurrent chemoradiation therapy using low dose daily cisplatin combined with split course radiation therapy compared with conventional radiation therapy alone in stage III non-small cell lung cancer.

MATERIALS AND METHODS

Between April 1992 and March 1994, 32 patients who had stage III non-small cell lung cancer were treated with concurrent chemoradiation ther-

apy. Eligible patients had to fulfill the following criteria : histopathological confirmation of non-small cell lung cancer with stage III disease, performance status according to Karnofsky scale 60, Zubrod-ECOG scale 2, age less than 80 years and no evidence of renal problem. Radiation therapy was administered for 2 weeks in a dose of 300 cGy given 10 times up to 3000 cGy followed by a rest period of 3 weeks. The dose was delivered with two opposing anterior-posterior fields. Radiation therapy was again administered for 2 more weeks in a dose of 250 cGy given 10 times up to 2500 cGy with two oblique fields to spare spinal cord. Initial fields included the primary tumor and regional lymphatics. For the second part of treatment, original primary lesion and involved nodal region were encompassed. Radiation therapy was preceded daily by chemotherapy with intravenous cisplatin in a dose of 6mg/M^2. Follow-up period ranged from 13 months to 48 months with median of 24 months.

Historical control group consisted of 32 patients who had stage III non-small cell lung cancer received conventionally fractionated radiation therapy alone. Fraction size ranged from 170 to 200 cGy with median of 180 cGy. Total radiation dose ranged from 5580 cGy to 7000 cGy with median of 5940 cGy. Follow-up period ranged from 36 months to 105 months with median of 62 months. Table 1 showed patients characteristics by treatment arm. Comparisons of patient characteristics from each arm suggest that patients groups are relatively similar.

The end points of analyses were response rate, overall survival, survival without locoregional failure, survival without distant metastasis, prognostic factors affecting survival and treatment related acute toxicity and pulmonary toxicity.

Table 1. Patients Characteristics

Characteristics		Chemoradiation group	RT alone group
Number of patients		32	32
Age	Range	41-77	46-79
	Median	61	32
Sex (M / F)		24 / 8	30 / 2
Pathology			
Sqamous cell		22	23
Adenocarcinoma		5	6
Large cell		2	1
Adeno-sqamous		-	1
Poorly differentiated		3	1
Stage (IIIa / IIIb)		12 / 20	3 / 19
Performance status			
KPS	60	10	7
	70	14	17
	80	6	8
	90	2	-
ECOG	0	2	-
	1	6	6
	2	24	25
	3	-	1
Weight loss (+ / −)		32 / 9	26 / 6

Table 2. Response Rate

Response Rate (%)	Chemoradiation group	RT alone group
*Complete response	6(18.8%)	2(6.3%)
Partial response	15(46.9%)	17(53.1%)
Stable disease	11(34.4%)	11(34.3%)
Disease progression	0(0%)	2(7.3%)
Total	32(100%)	32(100%)

*Chi-squre test : p = 0.03

Table 3. Pattern of Locoregional Failure

Pattern of failure	Chemoradiation group	RT alone group	p-value
*In field failure	8(25.0%)	15(47.0%)	
†In & out field failure	2(6.3%)	5(15.6%)	
†Out field failure	7(21.9%)	3(9.4%)	
*& †	10(31.3%)	20(62.6%)	0.04
Total	17(53.4%)	23(72.0%)	>0.05

*& † : actual locoregional failure rate including in field failure component
†Out field failure : lung to lung metastasis or malignant pleural effusion

Table 4. Pattern of Distant Metastasis

Site of metastasis	Chemoradiation group	RT alone group
Bone	9	7
Brain	4	4
Retroperitoneal LN	-	3
Liver	1	1
Soft tissue	1	-
Adrenal	-	1
more than 2 sites	4	3
Total	12 / 32 (37.5%)	13 / 32 (40.6%)

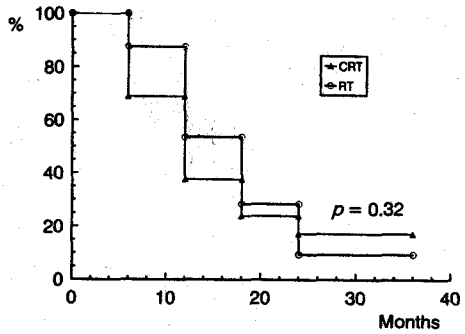

Fig 1. Overall survival rate.

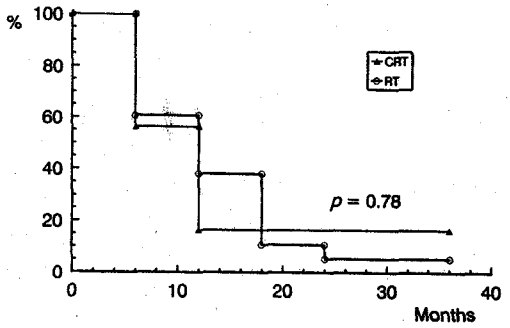

Fig 2. Survival without locoregional failure.

Statistica methods

The chi-square tests were used to analyze thedifferences of response rate, locoregional failure rate, distant metastsis rate and toxicity rate in between CRT group and RT group. Survival was calculated according to method of Kaplan and Meier. To identify the prognostic factors, univariate analyses using log rank test and multivariate analyses using Cox's regression model for concomitant variables were performed.

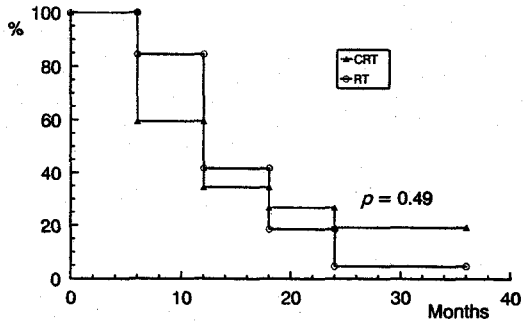

Fig 3. Survival without distant metastasis.

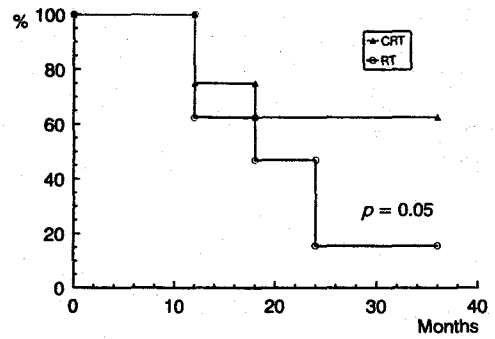

Fig 4. Survival rate in patient with KPS≥80.

RESULTS

The major response rate including complete and partial response rate were similar in between CRT group and RT group (65.7% vs. 59.4%). But complete response rate was significantly higher in CRT group than RT group (18.8% vs. 6.3%) (Table 2). The actual locoregional failure rates including in-field failure component were siginficantly higher in RT group than CRT group (p=0.04) (Table 3). There was no significant differences in the rate of distant metastasis between two groups (37.5% vs. 40.6%). Bone and brain were common sites of metastasis(Table 4).

Fig. 1, 2 and 3 shows overall survival rate, survival without locoregional failure and survival

Table 5. Prognostic Factors in Chemoradiation Therapy Group

Prognostic factors	Univariate analysis*	Multivariate analysis†
Performance status KPS (60-70 vs 80-90)	0.0014	0.025
ECOG (0 vs 1 vs 2)	0.001	0.015
Patholoic subtype (Sqamous vs non-sqamous)	0.0013	0.0079
Stage (IIIa vs IIIb)	> 0.05	> 0.05
Weight loss (positive vs negative)	0.005	> 0.05

*: Log rank test †: Cox regression model

Table 6. Prognostic Factors in Radiation Therapy Alone Group

Prognostic factors	Univariate analysis*	Multivariate analysis†
Performance status		
KPS (60-70 vs 80-90)	0.001	0.0028
ECOG (1 vs 2 vs 3)	0.046	> 0.05
Stage (IIIa vs IIIb)	0.003	0.0086
Pathologic subtype		
(Squamous vs non-sqamous)	0.035	> 0.05
Weight loss		
(positive vs negative)	> 0.05	> 0.05

*: Log rank test
†: Cox regression model

without distant metastasis, respectively. The global comparison of overall survival rate had no significant differences in between CRT group and RT group. Whereas CRT group showed higher rate of early death within 1 year, but showed higher long-term survival rate more than 2 years compared with RT group. The 1 year survival rate of CRT group and RT group was 37.5% and 53.3%, respectively. The 2 year survival rate was 17% and 9.4%, respectively. The median survival of CRT group and RT group was 12 months and 13 months respectively. The survival without locoregional failure(16.5% vs. 5.3% at 2 years) and survival without distant metastasis (19.1% vs. 4.6% at 2 years) also had no significant differences between two groups. In subgroup analyses for patients with good performance status (Karnofsky performance scale[80], CRT group showed significantly higher overall survival rate compared with RT group (62.5% vs. 15.6% at 2 years)(Fig. 4).

The prognostic factors affecting survival rate were performance status and pathologic subtype in CRT group(Table 5). In RT group, performance status and stage (IIIa vs. IIIb) were identified as a prognostic factors by multivariate analyses(Table 6).

Table 7. Acute Toxicities according to RTOG/ EORTC Grading Scale 2-3

Acute toxicitie	Chemoradiation Group	RT alone Group
*Nausea & Vomiting	7 / 32(22.0%)	2 / 32(6.3%)
Esophagitis	17 / 32(53.0%)	12 / 32(40.6%)
†BM toxicities	8 / 32(15.6%)	4 / 32(9.4%)

Chi-squre test : *: p = 0.04, †: p = 0.02

Acute toxicities were analyzed according to RTOG/EORTC grading scale[8](Table 7). Grade 2-3 nausea and vomiting requiring ondansetrone and fluid therapy were noted in 22% of CRT group and 6% of RT group(p=0.042). Grade 2-3 radiation esophagitis were noted in 53% of CRT group and 41% of RT group(p>0.05). Grade 2-3 bone marrow toxicities were noted in 25% of CRT group and 15.6% of RT group(p=0.02). Pulmonary toxicities were analyzed according to RTOG/ EORTC grading scale[8](Table 8) and WHO grading scale[3] (Table 9), respectively. The incidence of RTOG/ EORTC grade 3-4 pulmonary toxicity had no significant differences in between CRT group and RT group(16% vs. 6%). The incidence of WHO grade 3-4 pulmonary fibrosis also had no significant differences in both group (38% vs... 25%). In analyses for relationship of field size and pulmonary toxicity, the patients who were treated with field size beyond 200cm^2 had significantly higher rates of pulmonary toxicities(Table 10).

DISCUSSIONS

Approximately 80% of all lung cancers are clas-

sified as non-small cell lung cancer. While pulmonary resection provides cure for many patients with early stage disease, only about 25% of patients are surgical candidates. Approximately 35-40% of NSCLC patients have no obvious evidence of distant metastases, but have locally advanced disease (Stage III) which is either unresectable or marginally resectable. Thoracic radiation provides palliation for many of these patients but the median survival for patients treated with radiation alone is 9-12 months, and 2 year survival rate is approximately 15-20%[9]. These disappointing survival results for thoracic radiation alone has led to testing the neoadjuvant concept in locally advanced NSCLC patients. At least five randomized trials have tested chemotherapy followed by thoracic radiation versus thoracic radiation alone[10-14]. In two of these trials patients treated with combined modality treatment survived significantly longer[10, 11] and in one study there was a significant reduction in the rate of distant failure[11]. In the two positive neoadjuvant trials the survival gains have been modest with 2 year survival rates being 7 and 13% higher for patients receiving combined modality therapy[10, 11]. Therefore, alternative approachs are needed. At least four groups of investigators have conduct randomized studies in which curative thoracic radiation given simultaneously with cisplatin was compared to radiation alone[3-6]. In the EORTC trial patients who received daily cisplatin survived significantly longer than patients who received radiation therapy alone or radiation and weekly cisplatin. The 2 year survival

Table 8. Pulmonary Toxicities according to RTOG/EORTC Grading Scale

Grade	Chemoradiation Group	RT alone Group
1	12	13
2	5	4
3	4	2
4	1	0
2-4*	10 / 32(31%)	6 / 32(19%)
3-4†	5 / 32(16%)	2 / 32(6%)
Total	22 / 23(69%)	19 / 32(59%)

*& †Chi-squre test : P > 0.05
#RTOG/EORTC Grading Scale
Grade 1 : asymptomatic or mild symptoms (dry cough)/ slight radiographic appearances
Grade 2 : moderate symptomatic fibrosis or peumonitis (severe cough), low grade fever/patch radiographic appearances
Grade 3 : severe symtomatic fibrosis or pnumonitis/ dense radiographic changes
Grade 4 : severe respiratory insufficiency/ continuous O_2 assisted ventilation
Grade 5 : death directly related to radiation effect

Table 9. Pulmonary Toxicities accoding to WHO Grading Scale

Grade	Chemoradiation Group	RT alone Group
1	3	5
2	7	6
3	4	5
4	8	3
3-4*	12 / 32(38%)	8 / 32(25%)
Total	22 / 23(69%)	19 / 32(59%)

*Chi-squre test : P > 0.05
#WHO Grading Scale
Grade 1 : faint shadowing without distortion of anatomy
Grade 2 : moderate shadowing without distortion of anatomy
Grade 3 : faint shadowing with distortion of anatomy
Grade 4 : moderate to dense shadowing with distortion of anatomy

Table 10. Pulmonary Toxicities according to Treatment Volume

RT volume(cm2)	Grade≥ 2 Chemoradiation		WHO Grade≥3	
	RTOG/ECOG	RT alone	Chemoradiation	RT alone
≥ 200	5 / 13(38.5%)	5 / 20(25%)	7 / 13(53.8%)	5 / 20(25%)
< 200	5 / 19(26.3%)	1 / 12(8.3%)	5 / 19(26.3%)	3 / 12(25%)
Total	10 / 32	6 / 32	12 / 32	8 / 32

*Chi-squre test : P=0.046

for patients receiving daily cisplatin was 26% compared to 13% for patients receiving radiation therapy alone. There was no difference in distant failure rate for any of three arms in EORTC study. However, the rate of local failure was significantly lower in patients who received daily cisplatin compared to patients who received radiation alone or weekly cisplatin combined with radiation. Therefore, EORTC investigators concluded that the survival advantage was secondary to more effective treatment of locoregional disease[3]. In contrast, Trovo et al observed no significant difference in median survival or 2 year survival rate with patients treated with radiation therapy alone versus those treated with daily cisplatin[6]. Bonomi explained the contradictory results observed in these two trial : The dose of radiation therapy in Italian trial was only 45Gy in 15 fractions compared to 54Gy in 20 fractions and the total dose of cisplatin was 30% higher in EORTC trial[9]. Komaki pointed out the patient population of Italian trial was unfavorable. Half of patients had KPS score less than 80 and up to 10% weight lloss was permitted. These may obscured possible differences between arms in this trial[15]. In our study, locoregional failure rate including in-field failure compnent was significantly lower in CRT group than RT group. There was no significant survivial advantage in CRT group compared to RT group. But significant survival gain was achieved with combination of cisplatin in subgroup of patients with good performance status(2KPS 80). Whereas CRT group showed higher rate of early death within 1year, but showed higher long-term survival rate more than 2 years compared with RT group in our data. These results might be related to toxicities from concurrent chemoradiation therapy especially in patients with poor performance status. It was uncertain that the cause of early death in CRT group was directly related to toxicities of treatment rather than locoregional failure or distant metastasis. There were two major differences in between EORTC trial and our study: First, our study was consist of patients with stage III disease only. But EORTC study was consist of the patients with all stage of nonmetastatic inoperable NSCLC including stage I and II diseases. The poorer outcome in our data might result from poorer prognostic population of patients compared with EORTC trial. Second, historical control group of our study received continuous radiation therapy with conventional fraction size in contrast to split course radiation therapy with large fraction size in EORTC study. Bonomi pointed out that surprising result in which radiation was given on split course schedule of EORTC trial produced a survival advantage. Because general trials of radiation therapy have shown that continuous radiation therapy is superior to split course radiation therapy in NSCLC[9]. In our data, negative survival advantage might be explained by the potential that suboptimal radiation schedule of CRT group nullified possible survival gain from concurrent cisplatin compared with RT group. The Southwest Oncology Group (SWOG) reported an similar pilot study of concurrent daily low dose cisplatin (5mg/m^2) plus continuous course RT to 61Gy in 6.5 weeks in 58 assessable stage IIIa and IIIb patients. This study differed from the EORTC study in that the chest RT was administered continuously instead of split course, and the cisplatin dose was 5mg/m^2/day instead of 6mg/m^2/day. However, if one adds up the total cisplatin dose administered during the course of chest RT in both studies, a higher total dose was delivered in the SWOG trial(165mg vs. 120mg). This outpatient regimen was well tolerated (no severe hematologic toxicities) and produced an excellent median survival > 13 months[16].

The RTOG has randomized 452 patients with good performance status and less than 5% weight loss in stage III NSCLC, a three arm randomized phase III study. Combined treatment given by vinblastin and cisplatin repeated for two cycles followed by radiation therapy, 63Gy in 6.5 weeks with concurrent cisplatin. The median survival was 13.8 months and 2 year survival was 32%. The other two arms were radiation therapy alone giving 60Gy in 6 weeks versus 69.6Gy hyperfractionated radiation therapy with fraction size of 1.2Gy. The survival difference between standard RT and

hyperfractionated RT was not significant. Combined treatment compared with radiotherapy alone showed a significantly better 2 year survival rate[17].

There has been increased acute toxicity by combined treatment in regard to hematologic toxicities and esophagitis especially if the chemotherapy and radiotherapy are given concurrently. The result of RTOG 91-06 study showed that one third of patients developed grade 3-4 esophagitis compared with 8% of patients who developed grade 3-4 esophagitis by radiotherapy alone[18]. In our study, nausea, vomiting and hematologic toxicities were definitely increased in CRT group compared with RT alone group. But there was no significant differences in regard to esophagitis. This might be explained by that CRT group received split course schedule in contrast to continuous schdule in RT alone group.

The term radiation pneumonitis is used to refer to the symptomatic syndrome as opposed to the radiographic diagnosis. In order to weigh the risks and benefits of combined modality therapy, it is useful to quantitate the severity of radiation peumonitis. The failure of most published series to use uniform criteria for defining radiation peumonitis precludes precise estimation of the incidence and severity of radiation peumonitis[19]. Using well defined criteria using RTOG/EORTC grading scale and data gathered from prospective randomized trials using conventional fractionation in a total of 6000cGy for the treatment of inoperable lung cancer, the incidence of grade 3-4 radiation peumonitis is approximately 10%. Grade 4-5 peumonitis is much less common, occuring in approximately 1% of patients[18, 20]. In our series, the incidence of grade 3-4 pneumonitis according to RTOG/EORTC grading scale were comparable to this data in both group. Whether or not peumonitis occurs, some degree of fibrosis usually does. The incidence of grade 3-4 pulmonary fibrosis according to WHO grading scale were comparable to EORTC data[3]. Whether the late end point is peumonitis or fibrosis, many reports have suggested that small differences in the dose per fraction can dramatically alter lung tolerance[21-23]. Because larger dose per fraction was used in CRT group, we had a clinical impression that the higher incidence of pulmonary toxicities were existed in CRT group compared with RT group that was treated with conventional fraction size. In actual analysis, these differences between two groups did not reach to statistical significances.

In spite of higher incidence of acute toxicities with concurrent chemoradiation therapy, the survival gain in subgroup of patients with good performance status were encouraging. CRT group showed higher rate of early death within 1 year, higher 2 year survival rate compared with RT group. Therefore, to evaluate the accurate effect on survival of concurrent chemoradiation therapy, systematic follow-up for long term survivors are needed. At present, the results of clinical trials support two cycles of induction chemotherapy consisting of cisplatin and vinca alkaloid followed by thoracic irradiation showing a modest survival advantage over radiation therapy alone. The weekly concurrent cisplatin and thoracic irradiation has not improved survival rates, although there was a significant improvement in local control and survival giving daily cisplatin concurrent with radiotherapy. Instead of split course radiotherapy with large fraction size, continuous radiotherapy or hyperfractionated radiotherapy combined with cisplatin has to be tested to achieve better local control and survival.

REFERENCES

1. **Dewit L.** Combined treatement of radiation and cis-diammine dichloreplatinum (II): a review of experimental and clinical data. Int J Radiat Oncol Biol Phys 1987; 13:403-426
2. **Steel G.** The search for therapeutic gain in combination of radiotherapy and chemotherapy. Radiat Oncol 1988; 11:31-54
3. **Schaake-Koning C, Van den Bogaert W, Dalesio O, et al.** Effect of concomitant cisplatin and radiotherapy on inoperable non-small cell lung cancer. N Engl J Med 1992; 326:524-530
4. **Ansari K, Tokara R, Fisher W, et al.** A phase III study of theracic irradiation with and without con-

comitant cisplatin in locally advanced unresectable non-small cell lung cancer: a Hoosier Oncology Group Study. Proc Am Soc Clin Oncol 1986; 13(suppl. 3):88-91

5. **Soresi E, Clerici M, Grilli R, et al.** A randomized clinical trial comparing radiation therapy versus radiation therapy plus cis-diaminedichloro platinum in the treatment of locally advanced non-small cell lung cancer. Sem. Oncol. 1988; 15(Suppl.7):20-25
6. **Trovo MG, Minotel E, Fravelun G, et al.** Radiotherapy versus radiotherapy enhanced by cisplatin in stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1992; 24:11-16
7. **Douple EB, Richmond RC.** Enhancement of potentiation of radiotherpy by platinum drug in a mouse tumor. Int J Radiat Oncol Biol Phys 1982; 8:501-503
8. **John MJ.** Grading of chemoradiation toxicity. In: John MJ, Flamm MS, Legha SS, Phillip TL, eds. Chemoradiation: An integrated approach to cancer treatment. 1st ed. Philadelphia, PA: Lea & Fibiger Co. 1993; 601-606
9. **Bonomi P.** Radiation and simultaneous cisplatin in non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1993; 27:739-746
10. **Dillman RO, Seagren SL, Propert KJ, et al.** A randomized trial of induction chemotherapy plus high dose radiation versus radiation alone in stage III non-small cell lung cancer. N Engl J Med 1990; 323:940-945
11. **LeChevalier T, Arriagade R, Quaix E, et al.** Radiotherapy alone versus combined chemotherapy and radiotherapy in non-resectable non-small cell lung cancer: first analysis of randomized trial in 353 patients. J Natl Cancer Inst 1991; 83:417-422
12. **Mattsen K, Holsti LP, Jacobsson M, et al.** Inoperable non-small cell lung cancer; radiation with or without chemotherapy. Eur J Cancer Clin Oncol 1988; 24:477-482
13. **Mira JG, Miller TP, Crowley JJ.** Chest irradiation versus chest irradiation + chemotherapy &/or prrophylactic brain radiation in localized non-small cell lung cancer: a Southwest Oncology Group randomized study. Int J Radiat Oncol Biol Phys 1990; 18(Suppl. 1):145
14. **Morton R, Jett JR, McGinnis WL, et al.** Thoracic radiation therapy alone compared with chemoradiation therapy for locally unresectable non-small cell lung cancer. Ann Intern med 1991; 115:681-686
15. **Komaki R.** Is concomitant cisplatin and radiotherpy more efficacious treatment than radiotherapy alone in stage III non-small cell lung cancer? Int J Radiat Oncol Biol Phys 1992; 24:185-186
16. **Hazuka M, Crowley J, Bunn P, et al.** Concurrent daily low-dose cisplatin combined with chest irradiation in locally advanced non-small cell lung cancer: Preliminary results of a Southwest Oncology Group study. Proc Am Soc Clin Oncol 1992; 11:295(Abstr)
17. **Sause WT, Scott C, Taylor S, et al.** Radiation Therapy Oncology Group 88-08 and Eastern Cooperative Oncology Group 4588: Preliminary result of a phase III trial in regionally advanced, unresectable non-small cell lung cancer. J Natl Cancer Inst 1995; 87:198-205
18. **Lee JS, Scott C, Komaki R et al.** Concurrent chemoradiation therapy with oral VP-16 and cisplatin for locally advanced inoperable nonsmall cell lung cancer: RTOG protocol 91-06. Proc Am Soc Clin Oncol 1994; 13:363-372
19. **Roach M III, Phillips TL.** Pulmonary toxicity. In: John MJ, Flamm MS, Legha SS, Phillip TL, eds. Chemoradiation: An integrated approach to cancer treatment. 1st ed. Philadelphia, PA: Lea & Fibiger Co. 1993; 444-454
20. **Perez CA, Stanly K, Rubin P, et al.** A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat cell carcinoma of lung. Cancer 1980; 45:2744-2753
21. **Mah K, van Vyk J, Keane T, Poon PY.** Acute radiation induced pulmonary damage: A clinical study on the response to fractionated radiation therapy. Int J Radiat Oncol Biol Phys 1987; 13:179-184
22. **Wara WM, Phillips TL, Margolis LW, Smith W.** A new approach to the derivation of time-dose factors. Cancer 1973; 32:547-551
23. **van Dyk J, Keane TJ, Kan S, et al.** Radiation peumonitis following large single dose irradiation: A reevaluation based on absolute dose to lung. Int J Radiat Oncol Biol Phys 1981; 7:461-469

= 국문 초록 =

III 기 비소세포성 폐암에서 Cisplatin-방사선동시병합요법의 효과

가톨릭의대 성모병원 방사선 종양학과*, 내과†, 흉부외과‡

김인아* · 최일봉* · 강기문* · 장지영* · 송정섭† · 이선희‡ · 곽문섭‡ · 신경섭*

목 적 : 국소진행된 III기 비소세포성 폐암에서 방사선감작제로서의 저용량 Cisplatin과 방사선 동시병합요법의 효과를 알아보고자하여, 관해율, 전체생존율, 무병생존율 및 치료에 따른 부작용을 방사선 단독치료군과 후향적으로 비교분석하였다.

대상 및 방법 : 1992년 4월부터 1994년 3월까지 32명의 III기 비소세포성 폐암환자(IIIa 12명, IIIb 20명)가 항암제 및 방사선동시병합요법을 받았다. 방사선치료는 3000cGy/10회를 2주간에 걸쳐 시행한 뒤 3주후에 2500cGy/10회를 추가하였으며, 방사선감작제로 cisplatin 6mg/m^{2}를 매일 방사선치료 전에 정맥주사하였다. 추적관찰기간은 13개월에서 48개월로 중간값은 24개월이었다. 방사선단독치료군 32명(IIIa 13명, IIIb 19명)은 매일 170-200cGy씩 총 5580-7000cGy (중간값 5960cGy) 치료받았으며, 추적관찰기간은 36개월에서 105개월로 중간값은 62개월이었다.

결 과 : cisplatin-방사선동시요법군이 방사선 단독치료군에 비해 유의하게 높은완전반응률(18.8% vs. 5.6%)및 낮은 조사야내 재발율(25% vs. 47%)을 나타내었다. 2년 전체생존율은 Cisplatin-방사선동시요법군이 17%, 방사선단독치료군이 9.4%로 유의한 차이는 보이지 않았다. 국소재발 없는 2년 무병생존율(16.5% vs. 5.3%) 및 원격전이 없는 2년 무병생존율(17% vs. 4.6%)도 두군간에 유의한 차이를 보이지 않았다. 그러나 Karnofsky performance scale 80 이상인 환자군만을 대상으로 분석한 결과, cisplatin-방사선동시요법군이 방사선단독치료군에 비해 유의하게 높은 2년 전체생존율을 보였다(62.5% vs. 15.6%). 전체생존율에 영향을 미치는 예후인자로 cisplatin-방사선동시요법군에 있어서는 performance status 및 조직학적 진단유형(상피세포암 vs. 비상피세포암)으로 나타났고, 방사선단독치료군에 있어서는 performance status 및 병기(IIIa vs. IIIb)로 나타났다. 치료에 따른 급성부작용으로 RTOG/ECOG grade 2 이상의 오심, 구토는 cisplatin-방사선동시요법군이 방사선단독치료군 (22% vs. 6%)에 비해 유의하게 높은 빈도를 나타내었다. Grade 2 이상의 혈액학적 독성은 Cisplatin-방사선동시요법군에서 방사선단독치료군에 비해 높은 빈도를 나타내었다(25% vs. 15.6%). 방사선단독치료군에 비해 cisplatin-방사선동시요법군에서, RTOG/ECOG Grade 2 이상의 폐독성의 빈도(31% vs. 19%)나 WHO Grade 3 이상의 폐섬유화의 빈도(38% vs. 25%)의 유의한 증가는 관찰되지않았다. 방사선치료부위의 면적이 200cm^2 이상이었던 경우, 두군 모두에서 폐독성 빈도의 유의한 증가를 보였다.

결 론 : cisplatin-방사선동시병합요법이 방사선단독치료군에 비해 높은 국소제어율을 나타내었으나, 전체생존율이나 무병생존율의 유의한 증가는 보이지 않았다. KPS 80이상인 환자군에 있어서는 cisplatin-방사선동시요법군이 방사선단독군에 비해 높은 전체생존율을 보였다. cisplatin-방사선동시병합요법군에서 급성부작용이 증가되는 경향을 보였으나, 방사선에 의한 폐독성의 유의한 증가는 관찰되지 않았다. cisplatin-방사선동시병합요법군이 방사선단독치료군에 비해 1년 이내에 조기사망율이 높은 반면, 2년이상 장기생존율이 높은 경향을 보여, 이러한 환자군에 대한 장기적인 추적조사를 통해 생존율에 대한 본 치료의 영향을 좀더 명확하게 평가할 수 있을것으로 기대되며, 향후 치료효과를 증가시키기위해 large fraction size의 split course RT 대신 continuous course의 conventional RT 혹은 hyperfractionated RT와 Cisplatin의 동시병합요법 등이 고려되어야할 것으로 사료된다.