Hyperfractionated Radiotherapy Following Induction Chemotherapy for Stage III Non-Small Cell Lung Cancer

-Randomized for Adjuvant Chemotherapy vs. Observation-

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Since Jan. 1991 a prospective randomized study for Stage III unresectable non small cell lung cancer (NSCLC) has been conducted to evaluate the response rate and tolerance of induction chemotherapy with MVP followed by hyperfractionated radiotherapy and evaluate the efficacy of maintenance chemotherapy in Asan Medical Center.

All patients in this study were treated with hyperfractionated radiotherapy (120 cGy/fx BID, 6480 cGy/54 fx) following 3 cycles of induction chemotherapy, MVP (Mitomycin C 6 mg/m^2, Vinblastin 6 mg/m^2, Cisplatin 60 mg/m^2) and then the partial and complete responders from induction chemotherapy were randomized to 3 cycles of adjuvant MVP chemotherapy group and observation group. 48 patients were registered to this study until December 1992; among 48 patients 3 refused further treatment after induction chemotherapy and 6 received incomplete radiation therapy because of patient's refusal, 39 completed planned therapy.

Twenty-three (58%) patients including 2 complete responders showed response from induction chemotherapy. Among the 21 patients who achieved a partial response after induction chemotherapy, 1 patient rendered complete clearance of disease and 10 patients showed further regression of tumor following hyperfractionated radiotherapy. Remaining 10 patients showed stable disease or progression after radiotherapy. Of the sixteen patients judged to have stable disease or progression after induction chemotherapy, seven showed more than partial remission after radiotherapy but nine showed no response in spite of radiotherapy. Of the 39 patients who completed induction chemotherapy and radiotherapy, 25 patients (64%) including 3 complete responders showed more than partial remission. Nineteen patients were randomized after radiotherapy. Nine patients were allocated to adjuvant chemotherapy group and 4/9 showed further regression of tumor after adjuvant chemotherapy. For the time being, there is no suggestion of a difference between the adjuvant chemotherapy group and observation group in distant metastasis rate and survival. Median survival time was 13 months. Actuarial survival rates at 6, 12 and 18 months of 39 patients who completed this study were 84.6%, 53.7% and 40.3%, respectively. The partial and complete responders from induction chemotherapy showed significantly better survival than non-responders ($p=0.028$). Incidence of radiation pneumonitis in this study group was less than that in historical control group inspite of induction chemotherapy.

All patients tolerated hyperfractionated radiotherapy without definite increase of acute complications compared with conventional radiotherapy group. The longer follow up is needed to evaluate the efficacies of induction and maintenance chemotherapy and survival advantage by hyperfractionated radiotherapy but authors are encouraged with an excellent tolerance, higher response rate and improvement of one year survival rate in patients of this study.

Key Words: NSCLC, Hyperfractionated radiotherapy, MVP chemotherapy

INTRODUCTION

Fewer than 25% of non-small cell lung cancer (NSCLC) patients have resectable lesions at the time of diagnosis. However the majority of patients are diagnosed as advanced stage III and IV disease with localized intrathoracic disease or distant metastasis. Renewed efforts to expand the use of surgical resection may prove to be useful for some advanced cases, but standard therapy for inoperable patients with stage IIIa and IIIb disease has remained thoracic radiotherapy at a dose of 6000 cGy, administered in conventional daily fractions for 6 weeks[1]. Unfortunately median survival time with this approach is 8~12 months in most series with 2 year survival rates of 10~20%[2,3].

Although significant proportion of unresectable non-small cell lung cancer patients develop distant metastases during their course of disease, intrathoracic failure remains as an important cause of death for these advanced stage patients[4]. Radiation Therapy Oncology Group (RTOG) study showed improved local control rate with increased radiation dose[1]. Treatment with multiple daily fractions (MDF), using smaller than conventional doses per fraction, was a theoretically appealing approach that offered the promise of an increased total dose to the tumor, recoverable mild to moderately increased acute normal tissue effects, and no increase in late normal tissue effects. Phase I/II trial of hyperfractionation in advanced NSCLC aimed at finding the highest total dose with acceptable acute and late morbidity and examining the effect of increasing total dose on local tumor control were performed. RTOG study[5] demonstrated acceptable acute and late toxicity at all total doses tested, up to 79.2 Gy, and a survival advantage for favorable patients with stage III disease who received 69.6 Gy in 1.2 Gy twice daily fractions. This group had a 13 months median survival and a 29% 2-year survival.

Attempts to improve outcome have included altered RT fractionation schedules and the introduction of a chemotherapy on a neoadjuvant or concurrent basis. Although generally ineffective in stage IV or recurrent disease, studies using various combinations of drugs in stage III disease have generated response rates, as high as 73%, when used prior to definitive local treatment[6]. Induction chemotherapy combined with radiation therapy has been reported to have increased survival in phase III trial of the Cancer and Leukemia Group B (CALGB 84~33)[7]. In this study, rates of survival in combined treatment group were 55 percent after one year, 26 percent after two years, and 23 percent after three years, as compared with 40, 13, and 11 percent, respectively in radiotherapy group.

Based on these studies, authors have conducted a prospective randomized study to evaluate the efficacies and survival advantages of MVP chemotherapy and hyperfractionated radiotherapy.

MATERIALS AND METHODS

All eligible patients with stage IIIa or IIIb unresectable NSCLC were treated with hyperfractionated radiotherapy following 3 cycles of induction chemotherapy with MVP and then the partial and complete responders from induction chemotherapy were randomized to 3 cycles of maintenance MVP chemotherapy and observation groups (Fig. 1). The eligibility of the patients was determined by a medical and radiation oncologist before treatment assignment. All patients had pathologically documented non-small cell lung cancers, including squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Radiologic evaluation consisted of chest X-ray,

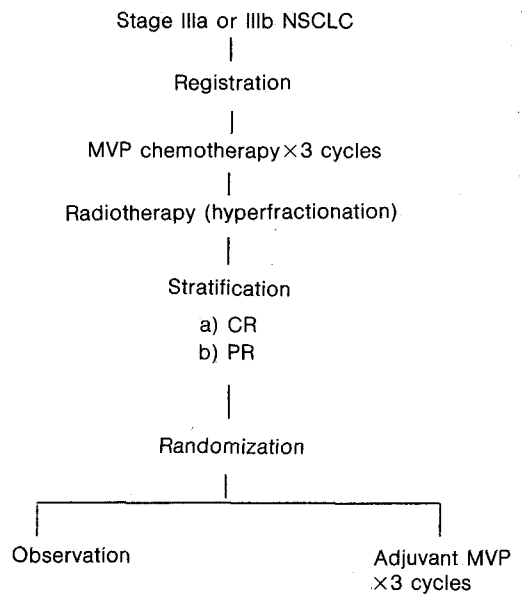

Fig. 1. Study design for locally advanced non-small cell lung cancer.

bone scan and computerized axial tomograpy of the chest and upper abdomen, including the adrenals. A performance status of 0 to 2 was required. Laboratory studies required at entry included a leukocyte count higher than 4000 per mm^3, platelet count higher than 10^5 per mm^3 and blood urea nitrogen, creatinine and bilirubin levels less than 1.5 times than upper range of normal value. Patients with involvement of ipsilateral or contralateral supraclavicular lymph nodes and pleural effusions were included.

Chemotherapy consists of mitomycin C (6 mg/m^2 given IV on day 2), vinblastine (6 mg/m^2 given IV on day 2) and cisplatin (60 mg/m^2 IV over 3 hours with hydration on day 1). The doses were modified on the basis of blood counts and tests of renal and hepatic function on the day of therapy.

Radiation therapy was started in 1 month after the completion of the 3rd chemotherapy. Treatment volumes consisted of original and boost volumes irradiated sequentially. The original treatment volume was based on X-ray films and CT scan taken before cytotoxic therapy. The original volume included the primary lesion with a 2 cm margin, the ipsilateral pulmonary hilum and an inferior margin that extended either 5 cm below the carina or 2 cm below the inferior border of visible tumor. The ipsilateral supraclavicular fossa was included. The boost volume included the primary lesion before therapy with a 2 cm margin. The dose to the original volume was 4320 cGy in 36 fractions of 120 cGy BID. Minimum 6 hour interval was given between two daily treatments. The dose to the boost volume was 2160 cGy in 18 fractions of 120 cGy BID. The total tumor dose was 6480 cGy and the maximum dose to any point along the spinal cord was 45 Gy. One month after radiotherapy the partial and complete responders from induction chemotherapy were randomized to 3 cycles of adjuvant MVP chemotherapy and observation groups.

Response was assessed one month after the completion of chemotherapy and in one month after the completion of radiotherapy by computerized tomography. A complete remission was defined as the disappearance of the tumor by CT scan. A partial remission was defined as a reduction of more than 50 percent of measurable disease and stable disease as a reduction of less than 50 percent. Survival time was calculated from the first day of the induction chemotherapy using the Kaplan-Meier method.

RESULTS

Forty eight patients were registered to this study until December 1992; among these patients three refused further treatment after induction chemotherapy and six received incomplete radiation therapy because of patient's refusal. So thirty nine patients (81%) completed planned therapy. The characteristics of the 39 patients are shown in Table 1 and 2. The median age of patients was 57 years with range of 44 to 72 years. Ten (26%) had advanced stage IIIa disease, and twenty nine (74%) had IIIb disease. Minimum follow up was 10 months.

After induction chemotherapy twenty three patients (58%) had responses, including two (5%) with complete and twenty one (53%) with partial remissions (Table 3). Among the twenty one patients who achieved a partial response after induction chemotherapy, one showed complete clearance of disease and ten patients showed fur-

Table 1. Patient Characteristics (1991. 1~1992. 12)

Characteristics	No. of Patients (%)
Age (years)	
Range	44~72
Median	57
Sex	
Male	34 (87)
Female	5 (13)
Stage	
IIIa	10 (26)
IIIb	29 (74)
Pathology	
Adenoca	11 (28)
Squamous	24 (62)
Undetermined	4 (10)
F/U period (months)	10~29

Table 2. TNM Stage of the Patients

	T_1	T_2	T_3	T_4*	Total
N_0				3	3
N_1			1	0	1
N_2		7	2	11	20
N_3+	1	5	2	7	15
Total	1	12	5	21	39

+4 Patients had supraclavicular mets.
*5 Patients had pleural effusion.

ther regression of tumor following hyperfractionated radiotherapy. Remaining ten patients showed stable disease or progression after radiotherapy. Of the sixteen patients judged to have stable disease or progression after induction chemotherapy, seven showed more than partial remission after radiotherapy but nine showed no response despite of radiotherapy. So, of the thirty nine patients who completed induction chemotherapy and radiotherapy, twenty five patients (64%) including three complete responders showed more than partial remission.

Nineteen patients were randomized after radiotherapy. Nine patients were allocated to adjuvant chemotherapy group and four of these (44%) showed further regression of tumor after adjuvant chemotherapy. For the time being, there is no difference between the adjuvant chemotherapy and observation groups in distant metastasis rates and survival (Table 4).

Median survival time was 13 months. Actuarial survival rates at 6, 12 and 18 months of thirty nine patients who completed this study were 84.6% and 53.7% and 40.3% respectively (Fig. 2). The difference in survival by stage (Fig. 3) or by randomization (Fig. 4) was not significant. But the partial and complete responders from induction chemotherapy showed significantly ($p=0.0287$) better survival than non-responders (Fig. 5). Distant metastases have occurred in 15 (38%) at the following sites: brain-6, bone-3, pericardium-2, neck (contralateral)-2, lung (contralateral)-1, soft tissue-1.

Radiation pneumonitis was noted in 3 patients between 2 and 4 months after the completion of the radiotherapy. But none of these patients had continuous symptom after steroid treatment.

Table 3. Locoregional Response after Chemotherapy and after Radiotherapy

After ChemoTx	After RadioTx
CR (2/39)	CR (1)
	PD (1)
PR (21/39)	CR (1)
	PR (10)
	NR (6)
	PD (4)
NR (8/39)	CR (1)
	PR (3)
	NR (4)
PD (8/39)	PR (3)
	NR (2)
	PD (3)

DISCUSSION

Our study is based on CALGB study 8433[7] and RTOG 8311 data[5]. Since there is no significant data about adjuvant chemotherapy, we also study the

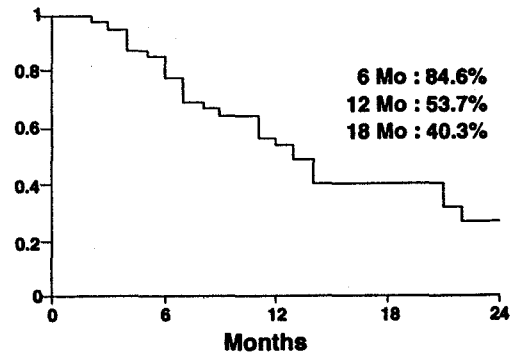

Fig. 2. Overall survival.

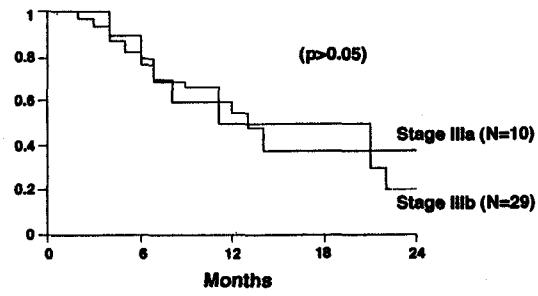

Fig. 3. Overall survival by stage.

Table 4. The Differences Between Adjuvant Group and Observation Group

	F/U (months)	DM (%)
Adjuvant Group (9)	Expired: 12, 13, 14, 25, 26 Alive: 15, 19, 21, 28	3 (33)
Observation Group (10)	Expired: 7, 11, 11, 13, 21, 22 Alive: 11, 18, 22, 28	3 (30)

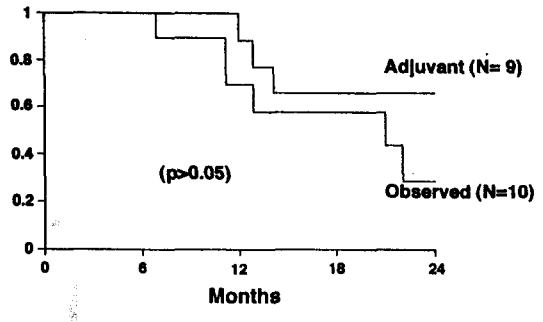

Fig. 4. Overall survival by randomization.

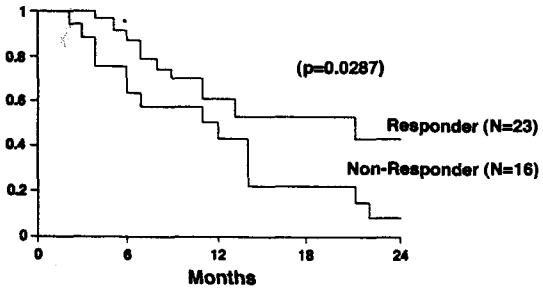

Fig. 5. Survival by response after induction chemotherapy.

effect of adjuvant chemotherapy by randomization.

There are multiple combination chemotherapy programs currently in use. Particularly cisplatin based programs seem to produce superior response rates. Mitomycin C, vinblastin, and cisplatin combination chemotherapy has produced response rates of 30% to 70%[8,9]. In our study, the response rates of MVP induction chemotherapy were 58%; complete remission, 5% and partial remission, 53%. There are multiple possible ways to combine chemotherapy and radiotherapy, including concomitant administration, sequential administration. For concomitant administration the major advantage is the delivery without undue delay of both modalities. The advantage of sequential administration is the reduction of acute cumulative side effects by the two modalities. But the disadvantage is the long protraction of the treatment time. In our study, induction chemotherapy was used with the intent of increasing the potential for local control by radiotherapy and delivering the earliest possible treatment to micrometastatic disease without increase of acute complications[10].

To gain a probability of 50% or more permanent control of non-small cell lung cancers requires higher doses than are presently given by external irradiation and these doses would exceed the accepted tolerance levels of intrathoracic normal tissues. By administering fractions twice daily at 6 hour intervals (hyperfractionation), normal cells will repair sublethal damage, while tumor cells will be less likely to, since they are less capable of sublethal damage repair[11~13]. Based on these radiobiology data we delivered hyperfractionated radiotherapy of 64.8 Gy in 1.2 Gy twice daily fractions. A phase I/II trial of hyperfractionated radiotherapy for non small cell lung cancer was conducted by Radiation Therapy Oncology Group[5]. In this study patients were randomized to receive minimum total doses of 60.0, 64.8, and 69.6 Gy. Survival with 69.6 Gy (median, 13 months; 2 years, 29%) was significantly (p=.02) better than the lower total dose. We selected a total dose of 64.8 Gy because we delivered chemotherapy before radiotherapy. Incidence of radiation pneumonitis in this study group was less than that in historical control group in spite of chemotherapy.

We also studied the effect of adjuvant chemotherapy by randomization after the completion of the radiotherapy. Although the longer follow up is needed, for the time being, there is no suggestion of a difference between the adjuvant chemotherapy group and the observation group in distant metastasis rates and survival.

The median survival time was 13 months. Actuarial survival rates at 6, 12 and 18 months of this study were 84.6% and 53.7%, and 40.3% respectively. Although we included the more advanced patients with involvement of ipsilateral or contralateral supraclavicular lymph nodes and pleural effusion in this study, this aggressive regimen produced a high rate of locoregional response and the 1 year survival was comparable to the most active multimodality regimens reported in locally advanced NSCLC[14,15]. Especially the responders from induction chemotherapy showed significantly better survival than non-responders. So, it is worthwhile to continue combination treatment of radiotherapy and chemotherapy. Although the longer follow up is needed, authors are encouraged with higher response rate, longer survival, and acceptable toxicity of this treatment. For next study we consider further increase of total radiation dose or concurrent hyperfractionated radiation with MVP chemotherapy to shorten the treatment time.

REFERENCES

1. **Perez CA, Stanley K, Grundy G, et al:** Impact of irradiation technique and tumor extent in tumor control and survival of patients with unresectable non-oat cell carcinoma of the lung. Report by the Radiation Therapy Oncology Group. Cancer 50: 1091-1099, 1982
2. **Komaki R, Cox JD, Hartz AJ, et al:** Characteristics of long term survivors after treatment for inoperable carcinoma of the lung. Am J Clin Oncol 8(5): 362-370, 1985
3. **Petrovich Z, Stanley K, Cox JD, et al:** Radiotherapy in the management of locally advanced lung cancer of all cell types. Cancer 48:1335-1340, 1981
4. **Stanley K, Cox JD, Petrovich Z, et al:** Patterns of failure in patients with inoperable carcinoma of the lung. Cancer 47:2725-2729, 1981
5. **Cox JD, Azarnia N, Byhardt RW, et al:** A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: Possible survival benefit with=69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III NSCLC: Report of RTOG 83-11. J Clin Oncol 8(9):1543-1555, 1990
6. **Martini N, Kris MG, Gralla RJ, et al:** The effects of preoperative chemotherapy on the resectability of non-small cell lung cancer with mediastinal lymph node metastases. Am Thorac Surg 45:370-379, 1988
7. **Dillman RO, Seagren SL, Propert K, et al:** A randomized trial of induction chemotherapy plus high dose radiation versus radiation alone in stage III non-small cell lung cancer. NEJM 323(14):940 -945, 1990
8. **Gralla RJ, Kris MG:** Chemotherapy in non-small cell lung cancer: Results of recent trials. Semin Oncol 15:Suppl 4:2-2, 1988
9. **Bonomi P:** Brief overview of combination chemotherapy in non-small cell lung cancer. Semin Oncol 13:89-91, 1986
10. **Frei F:** What's in a Name-neoadjuvant. JCNI 80: 1088-1089, 1988
11. **Fowler JF:** New horizons in radiation oncology. Br J Radiol 52:523-535, 1979
12. **Parsons JT, Mendenhall WM, Cassisil VJ, et al:** Hyperfractionation for head and neck cancer. Int J Radiat Oncol Biol Phys 14:649-658, 1988
13. **Thames HD, Withers HR, Peter LJ, et al:** Changes in early and late radiation responses with altered dose fractionation: Implications for dose survival relationship. Int J Radiat Oncol Biol Phys 8:219 -226, 1982
14. **Albain K, Rusch V, Crowley J, et al:** Concurrent cisplatin, VP-16, and chest irradiation followed by surgery for stage IIIa and IIIb non-small cell lung carcinoma: A South-western Oncology Group study. Proc Am Soc Clin Oncol 10A:836, 1991
15. **Recine D, Rowland K, Reddy S, et al:** Combined modality therapy for locally advanced non-small cell lung carcinoma. Cancer 66:2270-2278, 1990

= 국문초록 =

절제 불가능한 제 3 기 비소세포 폐암의 MVP 복합 항암요법과 다분할 방사선 치료

— 추가 항암요법에 대한 임의 선택 —

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최은경 · 장혜숙 · 안승도 · 양광모 · 서철원* · 이규형* · 이정신*
김상희* · 고윤석* · 김우성* · 김원동* · 송군식** · 손광현 #

절제 불가능한 제 3 기 비소세포 폐암에서의 MVP (Mitomycin C 6 mg/m², Vinblastine 6 mg/m², Cisplatin 60 mg/m²) 복합 항암요법과 다분할 방사선 치료의 효과를 판정하기 위하여 1991년 1월부터 전향성 임의 선택연구 (prospective randomized study)를 시작하였다.

본 연구는 제 III기의 비소세포 폐암중 절제가 불가능한 환자를 대상으로 하여 MVP 항암요법을 3회 시행한 후 다분할 방사선 치료 (120 cGy/fx, BID)를 6480 cGy까지 시행하였다. 방사선 치료가 끝난 1개월 후 유도 항암요법에 부분 관해 이상의 반응을 보였던 환자를 대상으로 추가 항암요법을 시행하는 군과 계속 관찰하는 군으로 임의 분류하였다.

1992년 12월까지 48명의 환자가 등록되었으며, 이중 3명은 항암요법후 치료를 중단하였으며, 6명은 방사선 치료중 치료를 중단하거나, 개인적 사정으로 다분할 방사선 치료를 시행받지 못하여 39명의 환자에 대한 분석을 시행하였다. 유도 항암요법을 마친 환자중 2명은 완전 관해를 보였으며, 21명은 부분 관해를 보여 MVP 유도항암요법에 대한 관해율은 58% (23/39)이었다. 항암요법에 부분관해를 보인 21명중 1명은 방사선 치료후 완전관해를 보였으며, 10명은 부분관해를 보였으나, 나머지 10명은 방사선 치료에 반응을 보이지 않았다. 항암요법에 반응을 보이지 않았던 16명의 환자중 9명은 방사선 치료에도 전혀 반응을 보이지 않았다. 유도항암 요법과 다분할 방사선 치료후의 관해율은 64%이었다. 방사선 치료후 19명의 환자에 대하여 추가 항암요법에 대한 임의 선택을 시행하여 이중 9명은 추가 항암요법 군으로 분류되어, 3회의 추가 항암요법을 시행하였다. 아직까지는 추가 항암요법군과 관찰군 사이에 원격전이나 생존율의 차이가 관찰되지 않았다. 전체 환자의 중앙 생존은 13개월이었고, 6개월과 12개월의 생존율은 각각 84.6%와 53.7%, 40.3%이었다. 특히 유도항암요법에 부분관해 이상의 반응을 보였던 환자들은 무반응환자에 비하여 통계적으로 유의하게 증가된 생존율을 보였다 ($p=0.0287$).

아직까지 추적 관찰기간이 짧으나, 64%의 높은 치료 관해율과 증가된 생존율, 그리고 합병증의 증가가 관찰되지 않는 점으로 보아 본 연구를 계속 진행함으로써 더 좋은 결과를 얻을 수 있을 것으로 기대된다.