

## The Treatment Results of Radiotherapy for Nonsmall Cell Lung Cancer

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From Nov. 1983 through Jan. 1986, 43 patients with nonsmall cell lung cancer were treated by radiation therapy at InJe Medical College Paik Hospital. 38 patients were available for the analysis of this study. 33 patients received definite irradiation with curative intent, while 5 patients received postoperative irradiation. Chemotherapy was added in 12 patients before, during and after radio-therapy. 28 patients were squamous cell carcinoma and 10 patients were adenocarcinoma. There were 29 men and 9 women (median age, 58 years; range 34 to 74 years). Stage 1 was 1 patient, Stage 11, 7 patient, and Stage 111, 30 patients.

Among 33 patients who received radiotherapy with curative intent, follow up radiological study revealed complete response in 12 patients (36%), partial response, in 9 patients (27%), and minimal response, in 5 patients (15%), while 7 patients (21%) were nonresponders. Median survival for all patients was 6.9 months; squamous cell carcinoma, 7.3 months, adenocarcinoma, 5.9 months. Responders survived median 7 months, while nonresponders survived median 1.9 months.

Improved complete response rate and survival were shown in high radiation dose group. As prognostic factors, age, initial performance status, sex, histology and tumor location were evaluated.

Key words: Nonsmall cell lung cancer, Radiotherapy, Response, Survival, Prognostic factors.

### INTRODUCTION

Lung cancer is a disease that draws interest because of steadily increasing incidence with no significant improvement in survival in the past few decades.

Lung cancer is the third most common malignant disease with men in Korea but it constitutes only 2.5% of cancer with female in Korea.

Despite the continued efforts for the treatment including chemotherapy, radiotherapy and surgery, the results continue to be poor.

Early stage of lung cancer can be treated by surgical resection.

However, only one third of all patients with lung cancer are eligible for the surgery.

Rests of the patients belong to advanced stage and these patients reveal a very poor prognosis, with only 8% to 10% of patients alive at 30 months<sup>3)</sup>

Radiotherapy serves a great role in palliation of distressing symptoms caused by the intrathoracic tumor or its distant manifestations.

When the tumor is obviously confined to the thorax, radiotherapy is aimed to eradicate the tumor, to form a local and regional treatment capable of sterilizing both the primary tumor and metastasis in the regional lymph nodes.

Radiotherapy is also carried out as an adjuvant to surgery in a subset of patients with resectable

carcinoma of the lung.

This study analyzed the results of radiation treatment of nonsmall cell lung cancer on 43 patients who were treated between Nov. 1983 and Jan. 1986 at Inje Medical College Paik Hospital.

## METHODS AND MATERIALS

Between Nov. 1983 and Jan. 1986, 43 patients with nonsmall cell lung cancer were seen at radiation therapy department of Inje Medical College Paik Hospital. Among these 43 patients, 3 patients were excluded from the study because of lack of histology and the other 2 patients were excluded because of incomplete treatment. For the present study, 38 patients who have histologic confirmation and complete staging work up were analyzed.

Staging work-up included history, physical examination, routine serum chemistries, bone scan, brain scan, CT scan, fiberoptic bronchoscopy with biopsy and cytology, and sputum cytology. Exploration thoracotomy were performed in 2 patients. AJC (American Joint Committee on Cancer Staging and End Results Reporting) staging were utilized in this study.

30 patients were Stage 111, 7 patients were Stage 11 and 1 patient was Stage 1. There were 29 men and 9 women; median age, 58 years (range from 34 to 74 years). There was 28 squamous cell carcinoma and 10 adenocarcinoma. The analysis of anatomic location of the lung cancer revealed RUL, 11 patients(29%), RML, 3(8%), RLL, 9(24%), LUL, 9(24%) and LLL, 6(15%).

Table 1 shows the characteristics of all patients. 33 patients were treated with curative aim, and 5 patients received irradiation as postoperative measure.

Patients treated with curative intent received radiation dose ranging from 5,000 cGy to 6,580 cGy in 5 to 7 weeks(average 6,000 cGy). Radiation field for curative aim encompasses the primary tumor with 2-3 cm margin, mediastinum, bilateral hilum and bilateral supraclavicular area if the tumor located in the upper lobe or the supraclavicular lymph node is obviously involved clinically and histologically.

If the tumor is located in the upper and mid lung, lower border of irradiation field extends down to about 5-6 cm below the carina, and if the tumor is present in the lower lobe, entire phrenic lymph nodes are included as a irradiation volume. Radiation machine was a 4 Mev Linear Accelerator for all

the patients treated. Radiation was delivered through either AP, 3 field or 4 field.

For the most of patients, computerized treatment plan was carried out and treatment was delivered accordingly. Radiation field was shaped during the course of treatment after repeated serial chest X-ray to minimize the dose to normal lung parenchyme.

The total dose to the spinal cord never exceeded 4500 cGy. The daily dose was usually 180 cGy. The average radiation dose for postoperative irradiation was 5,000 cGy equivalent dose at conventional fractionation. Laryngeal block was utilized in most of patients except the case of Pancoast tumor. 12 patients received chemotherapy before, during or after irradiation. Chemotherapy regimen consisted of BCNU, DDP, and Holoxan(BDH) in 10 patients and Mitomycin, BCNU, DDP, and 5-FU(MBDF) or vincristine, BCNU, DDP and adriamycin(VBDA) in 2 patients. Tumor response was evaluated by serial radiographs and CT scan of chest. In a few patients, response to radiation therapy was checked by fiberoptic bronchoscopy with biopsy.

Follow up period was from 5 to 26 months.

A complete response(CR) was defined as total disappearance of the tumor on follow up X-ray or CT scan. A partial response(PR) indicated a reduction in size of at least 50% of the surface area and minimal response (MR) indicated a reduction in size of at least 25% of lesion. All other patients were categorized as nonresponders.

Survival according to age, sex, histology, tumor

Table 1. Patients Characteristics (N=38)

Characteristics	No. of patients (%)
sex	
Male	30
Female	8
Median age (yr)	58(34-74)
Histology	
Squamous cell ca.	28(73.7%)
Adenocarcinoma	10(26.3%)
Stage	
1	1
11	7
111	30
Tumor location	
RUL	11(29%)
RML	3( 8%)
RLL	9(23.6%)
LUL	9(23.6%)
LLL	6(15.8%)

location, Stage, treatment modalities and performance status was analyzed.

The occurrence of radiation pneumonitis was analyzed according to each contributing factors.

## RESULTS

Among 33 patients who received radiation with curative aim, 12 patients(36%) was complete response, partial response in 9 patients(27%) and

minimal response in 5 patients(15%).

No response was seen in 7 patients(21 %).

Table 2 shows the tumor response according to radiation dose.

There appear to be higher response rates in high radiation dose group, while three fourths of patients receiving less than 4,000 cGy were nonresponders.

Tumor response by treatment according to histology was shown in Table 3.

As shown in Table 3, high CR rate was shown in

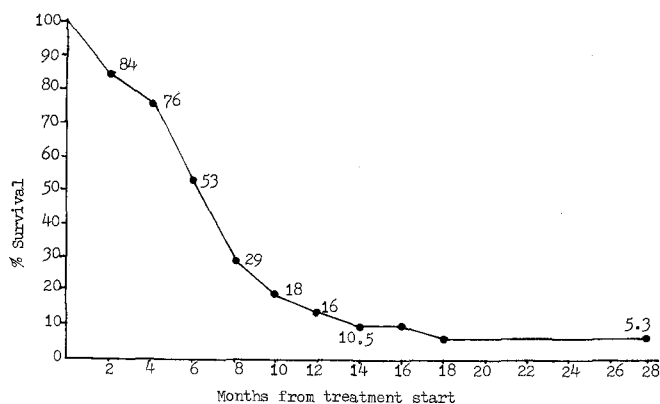


Fig. 1. Total survival

Table 2. Tumor Response according to Radiation Dose

Response	Dose (cGy)			
	3,000-4,000	4,000-5,000	5,000-6,000	6,000
CR	1 (12.5%)		9 (56%)	2 (25 %)
PR			6 (38%)	3 (37.5%)
MR	1 (12.5%)	1 (100%)		3 (37.5%)
NR	6 (75 %)		1 (6%)	
Total	8	1	16	8

Table 3. Tumor Response by Treatment according to Histology

Response	Squamous cell ca.	adenocarcinoma
	No. (%)	No. (%)
CR	11(42.3)	1(14.3)
PR	7(27)	2(28.6)
MR	3(11.5)	2(28.6)
NR	5(19.2)	2(28.6)
Total	26(100)	7(100)

Table 4. Response and Survival according to Stage and Age

Stage & Age	Total pts	Response(%)	Survival(M)	
			Median	(range)
Stage I	1	100	8	(8)
Stage II	7	100	11.4	(2-17)
Stage III	30	75	5.8	(1-26)
50	9	85.5	10.8	(2.5-26)
50-70	23	80	5.9	(1-17)
70-	6	67	5.1	(1-8)

squamous cell carcinoma than in adenocarcinoma.

The median survival of all patients was 6.9 months from the start of treatment(Fig. 1).

The patients who responded to therapy had a median survival of 7 months, while nonresponders had a median survival of 1.9 months. As shown in Fig. 2, there was significant difference between responders and nonresponders.

Survival according to histologic subtype is illustrated in Fig. 3. The median survival was 7.3 months for patients with squamous cell carcinoma, 5.9 months for patients with adenocarcinoma. These difference are not statistically significant.

There were superior results in Stage 11 patients than Stage 111 patients; median survival for Stage 11 patients is 11.4 months, while Stage 111 patients, 5.8 months(Table 4).

It should be noted that higher survival rates was seen in high radiation dose group (Table 5).

Radiotherapy combined with chemotherapy achieved relatively superior results than radiotherapy

alone. Patients treated with radiotherapy alone showed 4.1 months median survival, while patients treated with combined modalities showed 9.2 months median survival.

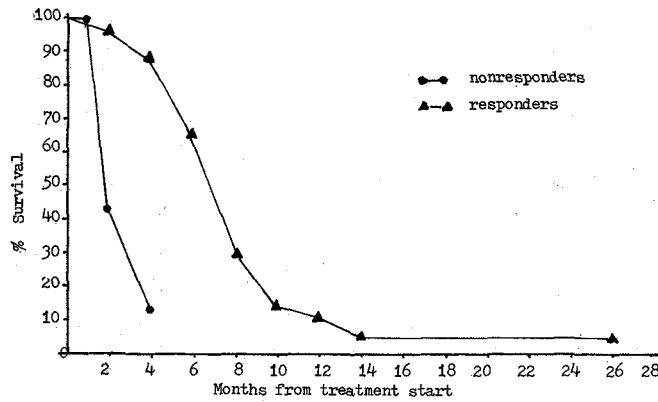
Analysis of patients receiving postoperative radiation was shown in Table 6.

Response and survival showed no significant difference by sex. Median survival of men was 6.3 months, while that of women was 7.5 months.

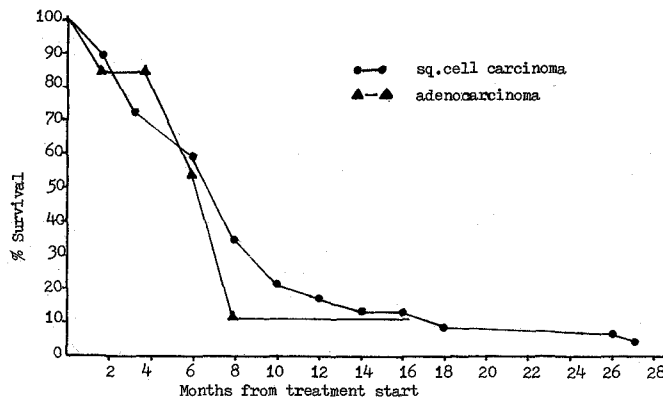
Survival according to tumor location showed no significant difference but there was a trend toward slight increased survival in patients with

**Table 5.** Actuarial Survival according to Radiation Dose

RT dose(cGy)	No. of pts	Survival(M)
< 4,000	8	2.8
4,000-5,000	2	1.5
5,000-5,500	6	10.3
5,500-6,000	14	9.1
>6,000	8	5.5



**Fig. 2.** Survival curves for responders versus nonresponders.



**Fig. 3.** Survival curves according to histology

upper lung lesion. Median survival of patients with upper lung lesion was 8.4 months, while that of patients with lower lung lesion was 5.2 months.

23 patients showed initial performance status 1 on the ECOG scale, 2 in 14 patients and only one patient was 3 on the ECOG scale. As shown in Fig. 4, patients with good performance status showed better survival than patients with poor performance status. Patients with poor performance status received lower radiation dose (mean 4,270 cGy) than patients with good performance status (mean 5,700 cGy).

The pattern of relapse was not different between squamous cell carcinoma and adeno-carcinoma. Sites of relapse are shown in Table 7. In only one patient, tumor recurred in multiple sites; bone and

brain. Solitary relapse occurred in lung, bone, brain, supraclavicular lymph nodes, abdomen and contralateral lung.

## DISCUSSION

Radiation therapy has remained the treatment of choice for locally advanced nonsmall cell lung cancer. But the results of radiation treatment was poor except it was combined with other modalities of treatment. It is generally conceded that a radiation dose of less than 4,000 cGy represents palliation rather than an attempt at cure. However, there is no clear evidence to suggest that a dose in excess of 4,000 cGy resulted in improved survival. For un-

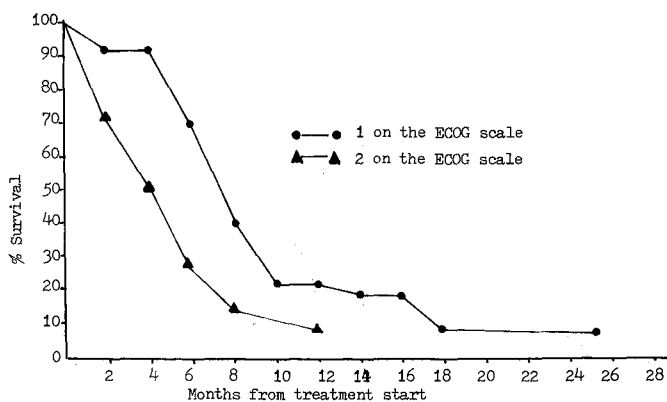


Fig. 4. Survival curves according to performance status.

Table 6. Analysis of Results of Postoperative Irradiation

Cases	Age/Sex	Stage	Tumor location	Histology	Surgery	RT dose (cGy)	Survival
1	34/M	11	RUL	Sq. cell	Pneumonectomy	5,140	25 M Living
2	60/F	11	RML	Sq. cell cancer	Lobectomy	5,940	17 M Living
3	48/F	11	LUL	Adenoca.	Lobectomy	5,220	17 M Living
4	57/M	111	RUL	Adenoca.	Lobectomy	4,250*	1 M Dead
5	53/F	111	LUL	Adenoca.	Pneumonectomy	5,220	5 M Living

\*: Palliative RT to rib.

Table 7. Sites of Relapse after Irradiation

	Locoregional	Bone	Brain	Pleura	Lymph node	Abdomen	Contralateral lung
Sq. cell ca	9	8	2	1	2	1	1
Adenocarcinoma	4	1			1	1	

resectable, nondisseminated, nonsmall cell lung cancer, a randomized trial clearly demonstrated that 5,000-6,000 cGy was superior to 4,000 cGy in terms of induction of tumor regression: 4,000 cGy, 55%, 5,000 cGy, 72%, and 6,000 cGy, 76%. Although increased doses of radiation had beneficial effects on response and local control, no survival advantage was demonstrated.<sup>7)</sup> In a recent report, Choi and Doucette found that five year survival following irradiation for localized, unresectable nonsmall cell lung cancer did vary with the radiation dose and target volume. Actuarial 5 year survival was 7.5% with the dose greater or equal to 5,000 cGy, whereas there was no 5 year survival from patients receiving less than this dose.<sup>8)</sup>

Coy and Kennelly reported a 49% response rate and 12% 5 year survival with squamous cell carcinoma treated with minimum 5,000 cGy.<sup>5)</sup>

In a series by Cox and associates, 92 patients with unresectable lung cancer and a high performance status (80-100%) received curative radiation therapy; the locoregional control rate was 59% with a 5-year survival of 11%.

In our study, among 33 patients who received definite irradiation, complete response rate was 36%, partial response rate, 27%, and minimal response rate, 15%. Patients who failed to have local control of tumor lived only several months. Our study demonstrated that improved response rate was shown in high radiation dose group (56% versus 12.5%). Median survival was also increased with high radiation dose group (8.3 months versus 2.5 months); while other reports showed unaffected survival.

Patients receiving only curative radiotherapy for unresectable lung cancer are at risk for distant metastasis despite achieving local control. Combination chemotherapy has been shown to be of benefit in control of small cell lung cancer. It has been hoped that for nonsmall cell lung cancer, effective chemotherapy could be found which would eradicate subclinical deposits of tumor when combined with curative surgery or radiation. To date most studies of combined modality therapy for nonsmall cell lung cancer have been disappointing. Single agent chemotherapy combined with radiation gives inferior results to radiation alone. Combination chemotherapy in disseminated lung cancer shows only a modest improvement in response rates when compared to a single agent.<sup>11, 12)</sup> A few recent studies have been reported using combination chemotherapy with radiation. In a study of the European Organization for Research on Treatment of Cancer (EORTC), 4,500 to 5,000 cGy followed by a

three drug regimen (CCNU, Adriamycin, and Vinblastine) resulted in a better locoregional control in positive node patients than did radiotherapy alone. No survival advantage was demonstrated.<sup>14)</sup> Whether or not the addition of combination chemotherapy confers any benefit-by preventing the occurrence of distant metastasis or by permitting a lower dose of radiation to be employed- cannot be ascertained. Our study demonstrated that 12 patients treated with combined modality showed better median survival than patients treated with radiation alone.

There are differences in prognosis after complete surgical resection related to histologic type; squamous cell carcinoma is more favorable than adenocarcinoma and large cell carcinoma.

Despite the fact that squamous cell carcinoma remains confined to the thorax more frequently, and adenocarcinoma and large cell carcinoma have a great propensity to spread, the longer survival seems to be better with the adenocarcinoma and large cell carcinoma.<sup>1)</sup>

The Stage of the tumor is one of the most important prognostic factors in cancer of the lung.<sup>15, 20, 21)</sup> There have been several studies that have demonstrated a clear correlation between survival rate and rate of control of the local tumor.<sup>8, 18)</sup> Histologic type alone do not have any significant impact on 5 year cure rates.<sup>17)</sup> There is no difference in the local tumor control rate among different types of cancer of the lung at 18 months or more after definite radiation therapy. Also, age and sex probably does not have any significant bearing on prognosis.

Sealy et al.<sup>19)</sup> reported that older patients (60 year) tend to fail as a result of local progression of the tumor or death without progression whereas younger patients tend to die from metastatic cause after curative radiation therapy. Adenocarcinoma is the most common histologic type among female patients. Thus female patients tend to have better survival than male patients. In our report, no significant difference according to histology was seen; median survival for squamous cell carcinoma was 7.3 months, adenocarcinoma, 5.9 months.

Performance status is closely related to the patients tolerance to surgery, radiation therapy, and chemotherapy and is close relation to overall survival. As shown in Fig. 4, there was a correlation between initial performance status and overall survival.

In a recent study of Veterans Administration Lung Group (VALG), locoregional failure was analyzed in patients with inoperable cancer of the lung who re-

ceived definite radiation therapy. A large proportion of patients with squamous cell carcinoma had local recurrence or persistence of the tumor in the chest. By contrast, local recurrence was a relatively less important mode of failure in patients with adenocarcinoma and large cell carcinoma and distant metastasis were more important. In our study, patients with squamous cell carcinoma showed a high incidence of distant metastasis. Most frequent metastatic site was bone.

Despite of good local tumor control rate by high dose radiation therapy, the majority of these patients with advanced disease still die with distant metastasis that were present before the start of radiation therapy.<sup>15, 18)</sup> For the improvements in the results of current radiation treatment in advanced Stage of lung cancer, new treatment approaches are needed to improve the local and regional control of tumors and to deal with distant metastasis.

## SUMMARY

Evaluable 38 patients of nonsmall cell lung cancer treated with radiation alone or radiotherapy combined with chemotherapy or surgery were analyzed and the following results were obtained.

1. Among 33 patients who received radiation with curative intent, complete response (CR) was seen in 12 patients(36%), partial response(PR) in 9 patients(27%), and minimal response in 5 patients(15%). No responders was 7 patients (21%).
2. The median survival of all patients was 6.9 months from the start of treatment.
3. Responders have a better median survival(7M) than nonresponders(1.9M).
4. High response rate and survival were achieved in high radiation dose group.
5. Patients with early Stage and age below 50 showed better median survival than patients with advanced Stage and age above 50.
6. There was no significant difference in survival according to histology and sex.
7. Combined modality of chemotherapy and radiotherapy showed slightly improved results than radiotherapy alone.

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=국문초록=

### 비 소세포성 폐암의 방사선 치료 결과

인제대의부속 백병원 치료방사선과  
윤 종 철 · 손 승 창 · 서 현 숙

진 단 방 사 선 과  
전 우 기  
내 과  
김 동 순  
흉 부 외 과  
손 광 현

1983년 11월부터 1986년 1월까지 인제대의 부속 백병원 치료방사선과에서 43명의 비 소세포성 폐암 환자를 치료하였다. 그중에서 분석 가능한 38명에 대한 치료결과를 보고하는 바이다.

33명이 근치적 목적으로 방사선 치료를 받았고 나머지 5명은 수술후 방사선 치료를 받았다. 12명의 환자는 방사선 치료하기전 혹은 방사선치료와 더불어, 그리고 방사선 치료후에 약물치료를 병행하였다.

38명의 환자중 28명이 편평상피종이었고 10명은 선종이었다. 남자 환자가 29명, 여자 환자가 9명이었고 평균 나이는 58세로 34세로부터 74세까지의 분포를 보였다. 병기별로 보면 1기가 1명, 2기가 7명, 그리고 3기가 30명이었다.

근치적 목적으로 치료한 환자중 치료후 흉부 X선사진과 컴퓨터 단층촬영상에서 완전히 종양이 소실된 경우가 36%, 50%이상의 종양크기 감소를 보인 경우가 27%, 25%이상의 종양크기 감소를 보인 경우가 15%였고 반응을 보이지 않은 경우가 21%였다.