

Short-Term Results of Non-Small Cell Lung Cancer with Curative Radiotherapy

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A retrospective analysis was performed on 102 patients with non-small cell lung cancer who received the curative radiotherapy from August 1985 to October 1988 at the Department of Therapeutic Radiology of Chonnam University Hospital. The follow-up period was ranged from 1 to 37 months and the median follow-up time was 15 months. The actuarial 1 and 2 year survival rate of all the patients was 28% and 5%, respectively. The median survival was 10 months for stage II, 6 months for stage IIIA, and 9 for IIIB and the actuarial 2 year survival rate was 12.5%, 12.1%, and 0% respectively. The treatment failure was identified in 32 patients and the locoregional failure was seen in 9 patients (28%) and the distant failure in 23 patients (72%). The initial performance status was related to the survival with statistical significance ($p < 0.01$), but the survival difference by the radiation dose was not statistically significant ($p > 0.05$).

Key Words: Non-small cell lung cancer, Radiotherapy, Survival

INTRODUCTION

Lung cancer is a disease of steadily increasing incidence with no significant improvement in survival during the past few decades. Due to the difficulty in making an early diagnosis and the high propensity of the tumor to metastasize easily through the lymphatic and hematogenous pathways, most patients are treated when the disease is at a relatively advanced biologic state regardless of the clinical stage. This can be said to be one of the factors contributing to the poor results of lung cancer¹.

In the treatment of small cell lung cancer regarded as initially systemic disease at diagnosis, the approach of combined modality therapy produced improved results in recent years. In the non-small cell lung cancer only 20 to 30% of total patients are candidates for surgical resection known as the most probable way of obtaining cure. However, after completion of surgical staging fewer than 20% of patients fall into this category¹⁻⁵.

At the present time, radiation therapy is widely used for the treatment of patients with unresectable carcinoma of the lung or for the medically inoperable patients. This study analysed the outcomes of 102 non-small cell lung cancer patients who had the curative radiotherapy from 1985 to 1988 at the Department of Therapeutic Radiology of Chonnam University Hospital.

MATERIALS AND METHODS

From 1985 to 1988, 102 patients with non-small cell lung cancer were treated with curative aim by radiotherapy at the Department of Therapeutic Radiology of Chonnam University Hospital (Table 1).

Histologic subtype was classified according to the results of sputum cytology, bronchoscopic biopsy and supraclavicular lymph node biopsy. All the patients were evaluated by the detailed history and a thorough physical examination, routine serum chemistry, complete blood counts, simple chest x-ray and chest CT scan. Some patients had the brain CT scan and the radionuclides scan of the bone and or liver, if necessary.

83 patients could be restaged by the TNM staging system of the American Joint Committee revised on 1988⁶. We divided symptom status into 3 groups based on the scale introduced by

Table 1. Chonnam University Hospital Tumor Registry of Non-small Cell Lung Cancer with Curative Radiotherapy (1985. 8—1988. 10)

| | No. of Patients | Follow-up time (months) | |
|----------|-----------------|-------------------------|--------|
| | | range | median |
| Total | 102 | 1 — 37 | 6 |
| Followed | 72 | 2 — 37 | 9 |
| Lost | 30 | 1 — 16 | 3 |

Zubrod⁷⁾, e.g., I(EOG 0 and 1), II(EOG 2), III(EOG 3 and 4).

All the patients were treated with 6 MV linear accelerator. The planned total tumor dose was 6000_cGy to 6500_cGy in 6 or 7 weeks with conventional fractionations. The initial field included the primary tumor, both hilum, mediastinum, and supraclavicular lymph nodes. After 3600 or 4000_cGy was delivered, chest plan CT was done and used to simulate the multiple complex fields minimizing the dose to the adjacent critical organs, such as, the spinal cord, heart, and normal lung. All patients had individually tailored cerrobend blocks so that all normal lung tissue beyond 2 cm clear margin around the primary tumor was excluded.

The Nominal Standard Dose (NSD) of Ellis⁸⁾ was calculated using the formula, TD (total dose) = NSD (T^{0.11}) (N^{0.24}).

All follow-up data are based on the date of initiation of radiation therapy. The follow up time was ranged from 1 to 37 months with the median follow up time of 15 months. The survival rate was calculated using life table method and the statistical significance was analysed by the Chi-square

Table 2. Patients Characteristics (N=102)

| Characteristics | No. of Patients (%) |
|------------------------------|---------------------|
| Age | |
| 30 – 39 | 2 (2.0) |
| 40 – 49 | 13 (12.7) |
| 50 – 59 | 42 (41.2) |
| 60 – 69 | 30 (29.4) |
| > 70 | 15 (14.7) |
| median age | 58 years |
| Sex | |
| Male | 91 (89.2) |
| Female | 11 (10.8) |
| Histology | |
| Squamous cell | 91 (89.1) |
| Adenocarcinoma | 8 (7.9) |
| Large cell, undifferentiated | 3 (3.0) |
| Tumor location | |
| RUL | 27 (26.5) |
| RML | 9 (8.8) |
| RLL | 18 (17.6) |
| LUL | 32 (31.4) |
| LLL | 16 (15.7) |

test.

RESULTS

102 patients with non-small cell lung cancer were treated with curative aim by radiotherapy and this accounted for 59% of all patients who referred for the radiotherapy with a diagnosis of non-small cell lung cancer.

Patients characteristics was shown in Table 2. The median age was 58 years and the proportion of patients older than the 50 years of age was 71%. In the entire population, the male to female ratio was 8.3:1. The squamous cell carcinoma was 89% (91/102).

The median survival was illustrated according to the stage and performance status (Table 3).

The actuarial 1 and 2 year survival rate of all the patients was 28% and 5%, respectively. The survival rate according to the clinical stage was analyzed (Fig. 1). The actuarial 2 year survival rate was 12.5% for stage II, 12.1% for stage IIIA, and 0% for stage IIIB, respectively.

The survival was analyzed according to the performance status (Fig. 2). Patients with good performance status showed better survival than patients with poor performance status. The 1 and 2 year survival rate of group I, II, III was 49% vs 18%, 23% vs 3%, and 20% vs 0%, respectively.

The radiation dose was represented by NSD (ret). We grouped them into two, below and above 1500ret (Table 4). The patients receiving irradiation

Table 3. Survival According to Stage and Performance Status

| Performance Status* | No. of Patients (%) | Survival (months) | |
|---------------------|---------------------|-------------------|--------|
| | | range | median |
| I (0 – 1) | 26 (27.7) | 2–37 | 9 |
| II (2) | 40 (42.5) | 2–16 | 5 |
| III (3 – 4) | 28 (29.8) | 1–15 | 4 |
| Stage# | | | |
| II | 8 (9.7) | 2–37 | 10 |
| IIIA | 26 (31.3) | 1–33 | 6 |
| IIIB | 49 (59.0) | 1–16 | 9 |

* 8 patients were not included due to inadequate information.

Information was not sufficient for the restaging in 19 patients.

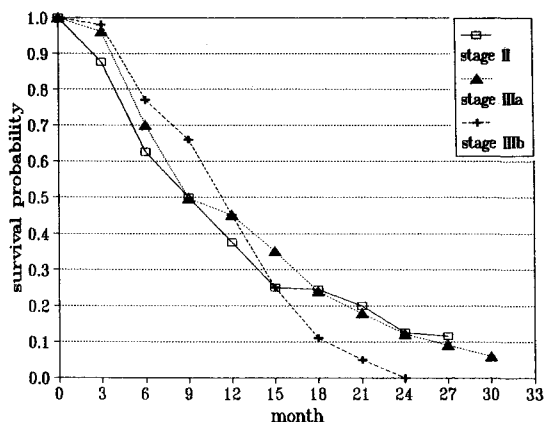


Fig. 1. Survival by stage.

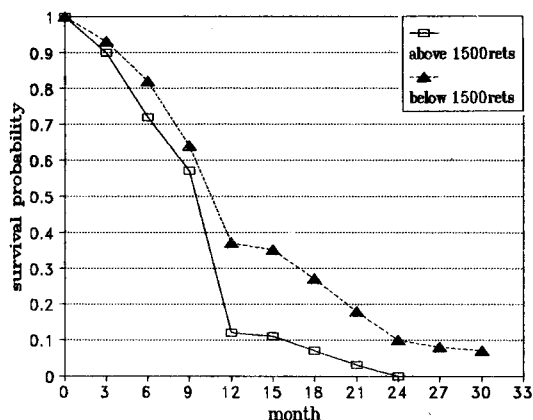


Fig. 3. Survival by radiation dose.

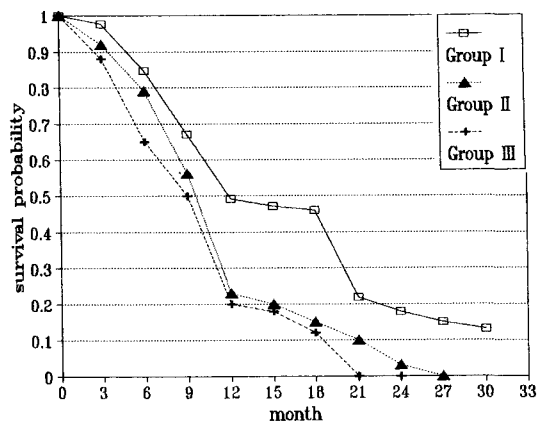


Fig. 2. Survival by performance status.

Table 4. Distribution by Total Radiation Dose

| Nominal Standard Dose | No. of Patients (%) |
|-----------------------|---------------------|
| below 1500 ret | 35 (34.3) |
| above 1500 ret | 67 (65.7) |
| Total | 102 (100.0) |

dose below 1500 ret was 34%. The survival rate according to the radiation dose was shown in Fig. 3.

The treatment failure was identified in 32 patients and crudely classified into the locoregional and distant failure (Table 5). The distant failure was 72% and the most common metastatic site was the bone.

Table 5. Patterns of Treatment Failure

| Failure | No. of Patients (%) |
|----------------------------|---------------------|
| Locoregional | |
| Primary | 2 (6.3) |
| Supraclavicular lymph node | 2 (6.3) |
| Superior Vena Cava | 5 (15.5) |
| Distant | |
| Bone | 12 (37.5) |
| Brain | 7 (21.9) |
| Liver | 2 (6.3) |
| Spine | 1 (3.1) |
| Bone + CBD | 1 (3.1) |
| Total | 32 (100.0) |

CBD : Common Bile Duct

DISCUSSION

Lung cancer is the third most common malignant disease with men in Korea and the incidence is annually increasing⁹. In women, it constitutes only 2.5% of the female cancer, but the incidence shows increasing tendency also^{1,9,10}.

The age, sex, and histologic distribution of our patients are not notably different from the recent reports from the several institutes^{1,4,10,11}.

In non-small cell lung cancer, the relative lack of survival correlation with histologic type is noted in the recent study^{10,12~15}. But, the natural history of the untreated patients with squamous cell carcinoma of the lung is prolonged when compared with

other histologic types^{12,15}). The pattern of failure after high-dose radiotherapy for carcinoma of the unresectable lung cancer seems to be dependent on tumor histology. For the squamous cell cancer, the primary and regional lymphatic areas are the most common sites of failure, and for adenocarcinoma it is the brain or bone^{4,5,16}).

Assessment of the physiologic and performance status is critical in order to determine the patient's ability to tolerate the aggressive therapy, and closely related to the survival^{12,14,17}). In our study, the actuarial 1 year survival rate according to the performance status was 49% with group I, 23% with group II, 20% with group III, respectively and there was no survivor living more than 15 months in group III.

The primary therapeutic approach to the non-small cell lung cancer is the surgery. However, the eligibility for surgical removal is very low and the status of many patients are not appropriate for the surgical removal¹⁹). In addition, patients with carcinoma of the lung often have additional medical problems, such as chronic obstructive pulmonary diseases or heart problems, making them medically inoperable¹⁹). In our study, the stage III comprised the 89% of the total patients with the curative radiotherapy. From this fact we know that most of the patients referred for the primary radiotherapy are in advanced disease status.

The high-dose radical radiotherapy produces a two-year survival of approximately 20% and a five-year survival of approximately 6% in patients with inoperable carcinoma²⁰). This should not be compared with surgical results because patients selected for the radiotherapy are less favorable cases than those selected for the surgery. The median survival of our patients for stage II and III was 10 months and 7 months, respectively and the actuarial 2 year survival rate of all the patients was 5%.

For the unresectable non-small cell lung carcinoma without clinically demonstrable distant metastases, there are two different major views of the role of radiation therapy¹⁶). The main school advocates an aggressive approach, using radiation dose more than 50Gy with a probability of cure of about 5%~10%. The other school advocates a conservative approach that is, no immediate treatment until the patient becomes symptomatic. Despite extensive experience and numerous reports, the role of radiation therapy in the management of unresectable or medically inoperable bronchogenic carcinoma remains undefined¹⁴).

Roswet et al²¹). reported that even though the difference in survival between the irradiated group and the control group was statistically real (22% vs 16% of 1 year survival rate, respectively), the actual prolongation of life was discouragingly small. Durrant et al²²). found no evidence that treatment by irradiation led to prolongation of survival or to prevention of incapacitating symptoms in patients with inoperable carcinoma of the bronchus. Because distant metastases undetectable by the current screening methods often determine the course of the disease despite the effectiveness of local and regional treatment such as radiotherapy or surgery, the real value of radiotherapy as a curative procedure for patients with truly localized lung cancer continues to be underestimated until a reliable screening test become available for microscopic distant metastases¹⁶). Survival alone may not be a reliable indicator of therapeutic efficacy and intrathoracic tumor control must be carefully evaluated.

Hellman et al²⁷). described residual microscopic primary tumor in 17 of 24 patients treated with 5500 ~6000 cGy prior to thoracotomy, and Bromley and Szur¹⁵) observed that localized lung cancer could be eradicated in about 40% of group of patients given mean doses of 4700 cGy. Above a dose of 1450 ret, no correlation between increasing ret dose and increasing local control is observed and 6000 cGy is said to be optimum dose for the tumor sterilization¹⁹).

There are many dissimilar opinions about the relationship between the radiation dose and the survival^{4,14,17,19~21,23}). Pierquin et al²⁸) observed somewhat better survival for patients given doses of over 4000 cGy tumor dose, as compared with those given 1500~3000cGy and that however, with doses as high as 7500cGy, the survival rate did not improve significantly. In our study the survival difference by the radiation dose (below vs. above 1500 ret) was not statistically significant.

Choi et al¹⁶). found that the comprehensive coverage of the regional lymphatics might have been an important factor for the improved survival as well as better local control. He also suggested that the target volume of the high-dose en-bloc radiotherapy including the entire regional lymphatics in addition to the primary tumor was necessary because 91% of patients had involvement of mediastinal lymph node with or without ipsilateral supraclavicular lymph node.

Stanely et al¹⁸). described a variety of factors which affect the response to irradiation and survival

of those patients like these; 1) patients characteristics such as initial performance status and weight loss in the six months prior to diagnosis, 2) tumor characteristics such as the clinical stage, size of the lesion and histologic type, 3) technical parameters relative to the delivery of irradiation, such as the tumor dose and the volume treated.

Bleehen et al³⁰⁾ suggested the conditions of patients who are deemed eligible for radical radiotherapy with curative intent like these; 1) lesions are limited to one hemithorax including the supraclavicular nodes, 2) no evidence of distant metastases or malignant pleural effusions, 3) performance status of Karnofsky 60~70% or better and adequate pulmonary function, 4) exclusion of tumors in excess of 8cm either in the primary or metastatic nodes, and those invading the chest wall.

In this study, we had the difficulty in defining the radiation response and failed to analyze the significance of the local control which may affect the long-term survival. So we are planning to proceed the work for that and form the complement to this results.

Physiologic change after radiation treatment revealed decreased residual volume and diffusing capacity and further decreases in the pulmonary capillary blood flow in areas initially affected³¹⁾. So careful evaluation of pulmonary function is recommended before patients are subjected to the definitive radiotherapy and sophisticated treatment planning and careful delineation of radiation ports must be adopted. In this study, we did not experience any severe pulmonary complication by irradiation.

REFERENCES

1. 최순호 : 폐암의 임상적 고찰. 대한흉부외과학회지 11:126-134, 1978
2. Silverberg E: Cancer Statistics. Cancer 33:19-25, 1983
3. Seydel HG: External beam irradiation of unresectable lung cancer. Int J Radiat Oncol Biol Phys 10: 573-576, 1984
4. 김일한, 하성환, 박찬일 : 비소세포성 폐암의 방사선 치료 성적. 대한치료방사선과학회지 2:203-211, 1984
5. Martini N, Beattie EJ: Results of surgical treatment in stage I lung cancer. J Thorac Cardiovasc Surg 4:499-506, 1977
6. American Joint Committee on Cancer: Manual for staging of cancer, 3rd Ed., Philadelphia: JB Lippincott, 1988, pp115-121
7. Zubrod CG, Schniderman M, Frei G, et al: Appraisal of methods for the study of chemotherapy of cancer in man: Comparative therapeutic trial of nitrogen mustard and triethylene thioposphoramide. J Chron Dis 11:7-33, 1960
8. Ellis F: Nominal standard dose and the ret. Br J Radiol 44:101-108, 1971
9. Cancer Research Program in the ROK: July 1, 1985 -June 30, 1986
10. 윤종철, 손승창, 서현숙, 전우기, 김동순, 손광현 : 비소세포 폐암의 방사선치료성적. 대한치료방사선과학회지 4:55-62, 1986
11. 성진실, 오원용, 서창옥등 : 비소세포 폐암의 방사선 치료. 대한치료방사선과학회지 2:213-218, 1984
12. Huber CM, DeGiorgi LS, Levitt SH, et al: Carcinoma of the lung: An evaluation of the scalene node biopsy in relation to radiation therapy of the supraclavicular region. Cancer 29:84-89, 1972
13. Lanzotti VJ, Thomas DR, Boyle LE, et al: Survival with inoperable lung cancer. An integration of prognostic variable based on simple clinical criteria. Cancer 39:303-313, 1977
14. Perez CA, Stanley 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 the lung: preliminary report by the Radiation Therapy Oncology Group. Cancer 45:2744-2753, 1980
15. Bromley LL, Szur L: Combined radiotherapy and resection for carcinoma of the bronchus: Experience with 66 patients. Lancet 2:937-941, 1955
16. Choi NCH, Doucette JA: Improved survival of patients with unresectable non-small cell bronchogenic carcinoma by an innovated high dose en-block radiotherapeutic approach. Cancer 48: 101-109, 1981
17. Perez CA: Radiation therapy for cancer of the lung: previous experience and definition of current issues. Cancer Chemother Rep Part 3 4:145-152, 1973
18. Stanley KE: Prognostic factors for survival in patients with inoperable lung cancer. J Natl Cancer Inst 65:25-32, 1980
19. Eisert DR, Cox JD, Komaki R: Irradiation for bronchial carcinoma: Reasons for failure. Cancer 37: 2665-2670, 1976
20. Sherman DM, Weichselbaum R, Hellman S: The characteristics of long-term survival of lung cancer treated with radiation. Cancer 47:2575-2580, 1981
21. Roswet B, Patno ME, Rapp R, et al: The survival of patients with inoperable lung cancer: A large-scale randomized study of Radiation therapy versus placebo. Radiology 90:688-697, 1968
22. Durrant KR, Berry RJ, Ellis F, et al: Compariosn of treatment policies in inoperable bronchial carcinoma. Lancet 1:715-719, 1971
23. Perez CA, Stanely 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. *Cancer* 50:1091-1099, 1982
24. **Rissanen PM, Tikka V, Holsti LR:** Autopsy findings in lung cancer treated with megavoltage radiotherapy. *Acta Radiol (Stockh)* 7:433-442, 1968
 25. **Perez CA, Stanley K, Rubin P:** Patterns of tumor recurrence after definitive irradiation for inoperable non-small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* 6:987-994, 1980
 26. **Choi NCH:** Curative radiation for unresectable non-small cell carcinoma of the lung: Indication, technique, results. In *thoracic Oncology*, edited by Choi NCH and Grillo HC, Raven Press, New York, 163-199, 1983
 27. **Hellman S, Kilgerman MM, Von Essen CF, et al:** Sequelae of radiotherapy of carcinoma of the lung. *Radiology* 82:1055-1061, 1964
 28. **Pierquin B, Gracis P, Gelle X:** Study of 688 cases of bronchial cancer treated by teleradiotherapy (200KV and 22MeV). *J Radiol Electr Med Nucl* 46: 201-216, 1965
 29. **Rubin P, Ciccin S, Setisarn B:** The controversial status of radiation therapy in lung cancer. In *proceedings of the 6th National Cancer Conference Philadelphia:JB Lippincott*, 855-865, 1970
 30. **Bleehen NH, Cox JD:** Radiotherapy for lung cancer. In *J Radiat Oncol Biol Phys* 11:1001-1007, 1985
 31. **German PA, Brady LW:** Physiologic changes before and after radiation treatment for carcinoma of the lung. *J Am Med Assoc* 206:809-814, 1968
 32. **Brady LW, German PA, Cander L:** The effects of radiation therapy on pulmonary function. *Radiology* 85:130-134, 1965

== 국문초록 ==

비소세포성 폐암의 방사선 치료 성적

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1985년 8월부터 1988년 10월까지 전남대학교병원 치료방사선과에서 근치목적의 방사선치료를 받은 비소세포성 폐암환자 102명에 대하여 후향적 분석을 시행하였다. 대상환자들에 대한 추적조사기간은 1개월에서 37개월이었고 중간값은 15개월이었다.

전체환자군의 1년 및 2년 생존율은 각각 28%, 5%였으며 임상적 병기별로 보면 II, IIIA, IIIB기 환자군의 평균생존기간은 각각 10개월, 6개월, 9개월이었고 2년 생존율은 각각 12.5%, 12.1%, 0%였다.

방사선치료후 치료실패가 확인된 32명에 대하여 분석을 하여보면 국소실패군이 28%(9명)였으며 원격실패군이 72%(23명)로 폐암환자의 사망의 대부분은 전신적인 원격전이에 의한 것을 알 수 있었다. 치료당시의 전신적 건강상태는 생존율에 유의한 영향을 주었으나($p < 0.01$), 방사선 치료선량에 따른 생존율의 유의한 차이는 보이지 않았다($p > 0.05$).