

Outcomes after Radiotherapy in Inoperable Patients with Squamous Cell Lung Cancer

Sung-Ja Ahn, M.D.^{*}, Woong-Ki Chung, M.D.^{*}, Byung-Sik Nah, M.D.^{*},
Tack-Keun Nam, M.D.^{*}, Young-Chul Kim, M.D.[†] and Kyung-Ok Park, M.D.[†]

^{*}Department of Therapeutic Radiology, [†]Pulmonology,
Chonnam University Medical School, Gwang-ju, Korea

Purpose : We evaluated retrospectively the outcomes of inoperable squamous cell lung cancer patients treated with radiotherapy to find out prognostic factors affecting survival.

Materials and methods : Four hundred and eleven patients diagnosed as squamous cell lung cancer between November 1988 and December 1997 were the basis of this analysis. The planned dose to the gross tumor volume was ranged from 30 to 70.2 Gy. Chemotherapy was combined in 72 patients (17.5%) with the variable schedule and drug combination regimens. Follow-up period ranged from 1 to 113 months with the median of 8 months and survival status was identified in 381 patients (92.7%). Overall survival rate was calculated using the Kaplan-Meier method.

Results : Age ranged from 23 years to 83 years with the median 63 years. The male to female ratio was about 16:1. For all 411 patients, the median overall survival was 8 months and the 1-year survival rate (YSR), 2-YSR, and 5-YSR were 35.6%, 12.6%, and 3.7%, respectively. The median and 5-YSR were 29 months and 33.3% for Stage IA, 13 months and 6.3% for Stage IIIA, and 9 months and 3.4% for Stage IIIB, respectively ($p=0.00$). The median survival by treatment aim was 11 months in radical intent group and 5 months in palliative, respectively ($p=0.00$). Of 344 patients treated with radical intent, median survival of patients (N=247) who received planned radiotherapy completely was 12 months while that of patients (N=97) who did not was 5 months ($p=0.0006$). In the analyses of the various prognostic factors affecting to the survival outcomes in 247 patients who completed the planned radiotherapy, tumor location, supraclavicular LAP, SVC syndrome, pleural effusion, total lung atelectasis and hoarseness were statistically significant prognostic factors both in the univariate and multivariate analyses while the addition of chemotherapy was statistically significant only in multivariate analyses. The acute radiation esophagitis requiring analgesics was appeared in 49 patients (11.9%) and severe radiation esophagitis requiring hospitalization was shown in 2 patients (0.5%). The radiation pneumonitis requiring steroid medication was shown in 62 patients (15.1%) and severe pneumonitis requiring hospitalization was occurred in 2 patients (0.5%). During follow-up, 114 patients (27.7%) had progression of local disease with 10 months of median time to recur (range : 1-87 months) and 49 patients (11.9%) had distant failure with 7 months of median value (range : 1-52 months). Second malignancy before or after the diagnosis of lung cancer was appeared in 11 patients.

Conclusion : The conventional radiotherapy in the patients with locally advanced squamous cell lung cancer has given small survival advantage over supportive care and it is very important to select the patient group who can obtain the maximal benefit and to select the radiotherapy technique that would not compromise the life quality in these patients.

Key Words : Survival, Radiotherapy, Squamous cell lung cancer

percent of the patients with NSCLC are not candidates for surgery because of advanced disease or poor general condition, and radiotherapy remains the treatment of choice in these patients which only can lead to poor outcomes with respect to local tumor control and survival.^{1, 2)} Thoracic radiotherapy, however, plays an important role in advanced stage lung cancer patients in aspect of symptom relief and improvement of life quality rather than survival gain.^{3, 4)}

Even though there are numerous publications about broad clinical experiences, many controversies exist in the radiotherapy of inoperable NSCLC with either radical or palliative intent regarding the patient selection, the optimal total radiation dose, the fractionation schedule, and the target volume definition. Moreover, Erkert et al⁵⁾ recently reported that certain patient and disease characteristics were more important than the type of therapy with respect to the outcomes.

We previously reported our short-term experience of the NSCLC patients treated by radiotherapy alone⁶⁾ The purposes of this retrospective analyses are, first to review the outcomes of conventional radiotherapy in inoperable squamous cell lung cancer patients, and, second, to identify the patients' characteristics significant in determining the intensity and duration of radiotherapy.

MATERIALS AND METHODS

Between November 1988 and December 1997, 1024 patients with primary lung cancer were referred to the Department of Radiotherapy, Chonnam National University Hospital for radiotherapy (Table 1). Four hundred eleven patients with

inoperable squamous cell lung cancer who diagnosed in our hospital and received thoracic radiotherapy were the basis of the current retrospective analyses.

All patients underwent evaluations including physical examination, chest radiographs, computed tomography (CT) scans of the chest and upper abdomen, bronchoscopy with detailed anatomic mapping of endobronchial lesions, and pulmonary function test. The ^{99m}Tc-whole body bone scan and brain CT or MRI were performed when clinically indicated. The patients underwent bronchoscopic or transthoracic needle aspiration biopsy for the histologic diagnosis. The blood chemistry and sputum examination against tuberculosis were done routinely in all patients. Stage assignment was done using the AJCC/UICC system (1997), based on the clinical informations (Table 2).

Radiation was delivered with 6 MV (Meatron, Siemens Co., Germany) or 10 MV (Clinac 1800, Varian Co., USA) X-rays. Initially we used the parallel opposing AP-PA fields and then reduced it one to three times to boost the gross tumor volume in addition to limit the critical normal tissue dose within the tolerance dose. The daily dose of 1.8 or 2 Gy was delivered 5 times a week and prescribed to intersection of the central axis of the treatment fields. No lung correction was used in the dose calculations. The planned dose to the gross tumor volume was usually 64.8 Gy (range : 1.8 70.2 Gy, mean : 50.85 Gy). In the palliative radiotherapy, the daily dose was 3 Gy and the planned dose was 30 Gy (range : 0 58.4 Gy, mean : 28.45 Gy). Simulation was performed using planning CT scan in the treatment position using 10 mm slice interval in 157 patients (38%).

Table 1. Tumor Registry of Primary Lung Cancer : Chonnam National University Hospital (1988. 11 - 1997. 12)

Classification	No. of Patients	
Small Cell Lung Cancer (SCLC)	145 (14.2%)	
Nonsmall Cell Lung Cancer (NSCLC)	765 (74.7%)	
	Postoperative Radiotherapy	Primary Radiotherapy
	87 (11.4%)	678 (88.6%)
squamous cell ca.	58	506
adenocarcinoma	21	125
adenosquamous cell ca.	2	34
large cell ca.	3	9
undifferentiated	-	3
adenosquamous cell ca.	-	1
others	3	-
Not Verified	114 (11.1%)	
Total	1024 (100%)	

In the remaining patients, the planning was performed in the conventional simulator. The median number of treatment planning was 3 times with the range of 1 to 5.

Chemotherapy was combined in 72 patients (17.5%) with the various schedules and combination regimens. Of those, 35 patients (8.5%) had neoadjuvant chemotherapy, 18 (4.4%) had concomitant chemotherapy, 16 (3.9%) had postradiation adjuvant chemotherapy, and 3 had mixed regimen. Chemotherapy regimens were variable with EC (Etoposide, Carboplatin; N=20), EP (Etoposide, Cisplatin; N=14), daily concurrent Cisplatin (N=10), CAP (Cyclophosphamide, Adri-

amycin, Cisplatin; N=9), MVP (Methotrexate, Vinblastine, Cisplatin; N=8), etc. The number of chemotherapy cycle ranged from 1 to 10, and daily concurrent regimen was given in 10 patients.

Survival status was identified in 381 patients (92.7%) by medical records or mail. The survival time was calculated from the first day of the radiotherapy to the date of death or the last follow-up. The actuarial survival rate was calculated according to the Kaplan-Meier method and their survival curves were compared using the Log-rank test. Cox proportional hazard model was used for multivariate analysis. All statistical analyses were performed using the SPSS for Windows Version 10.0 statistical software.

Table 2. Patients Characteristics (N=411)

Parameters	No. of Patients (%)
Age(years)	
range	23-83
mean	62.3
median	63
Sex	
male	387 (94.2)
female	24 (5.8)
Stage	
IA	3 (0.7)
IB	10 (2.4)
IIA	0 (0)
IIB	23 (5.6)
IIIA	102 (24.8)
IIIB	222 (54.0)
IV	45 (10.9)
Unknown	6 (1.5)
Aim of Radiotherapy	
curative	344 (83.7)
palliative	67 (16.3)
Completion of Radiotherapy	
no	118 (28.7)
yes	293 (71.3)
Chemotherapy	
no	339 (82.5)
yes	72 (17.5)

RESULTS

Four hundred and eleven patients were the basis of this study. These patients' characteristics are shown in Table 2. The median age was 63 years (range, 23-83 years). The male to female ratio was about 16:1. Three hundred and forty-four (83.7%) patients were treated with radical intent and 67 patients with palliative intent and the planned therapy was completed in 293 (71.3%) patients. Stage IIIA (N=102) and Stage IIIB (N=222) comprised of 78.8% of all patients population. Thirty-two patients with operable lesions underwent radiotherapy due to patient's refusal of surgery or combined medical illness.

For all 411 patients, the median overall survival was 8 months and the 1-year survival rate (YSR), 2-YSR, and 5-YSR were 35.6%, 12.6%, and 3.7%, respectively (Fig. 1). The survival outcomes by stage were shown in Table 3. The median and 5-YSR were 29 months and 33.3%, for Stage IA, 13 months and 6.3% for Stage IIIA, and 9 months and 3.4% for Stage IIIB, respectively ($p=0.0000$). The median survival periods by the treatment aim were 11 months in

Table 3. Survival Results by Stage in All 405 Patients with Squamous Cell Lung Cancer

Stage	No. of patients	MS (months)	1-YSR (%)	2-YSR (%)	5-YSR (%)	p value (%)
IA	3 (3)	29 (29)	100 (100)	100 (100)	33 (33)	0.001 (0.21)
IB	10 (8)	7 (14)	50 (63)	30 (38)	0 (0)	
IIB	23 (17)	15 (15)	50 (59)	10 (12)	0 (0)	
IIIA	102 (71)	12 (15)	46 (55)	14 (19)	6 (7)	
IIIB	222 (130)	8 (12)	33 (44)	11 (13)	3 (4)	
IV	45 (14)	5 (7)	16 (29)	9 (14)	2 (7)	

() represent data of patients who completed the planned radical radiotherapy (N=243)
MS : median survival, YSR : year survival rate

radical intent group, and 5 months in palliative ($p=0.0000$). Of patients with radical intent radiotherapy, the median survival of patients who completed the planned radiotherapy ($N=247$) was 12 months while that of patients who did not ($N=97$) was 5 months ($p=0.0006$).

We separately analyzed the various prognostic factors that might have affected the survival outcomes in 247 patients who completed the planned radical radiotherapy. Table 4 summarized the results of the univariate and multivariate analyses. Tumor location (upper lobe vs others), supraclavi-

cular lymphadenopathy (LAP), superior vena cava (SVC) syndrome, pleural effusion, total lung atelectasia, hoarseness were statistically significant adverse prognostic factors in the univariate analyses. These variables were examined further with multivariate analyses to determine the importance of each factor in the presence of all other factors. Tumor location (upper lobe vs others), supraclavicular LAP, SVC syndrome, pleural effusion, total lung atelectasia, and hoarseness were also statistically significant. The addition of chemotherapy were statistically significant favorable factor only in multivariate analyses.

The acute radiation esophagitis requiring analgesics appeared in 49 patients (11.9%) and severe radiation esophagitis requiring hospitalization occurred in 2 patients (0.5%). The radiation pneumonitis requiring steroid medication occurred in 62 patients (15.1%) and severe pneumonitis requiring hospitalization occurred in 2 patients (0.5%). During follow-up, local progression was observed in 114 patients (27.7%) with the time range of 1 and 87 months (median : 10 months)

and the distant failure was in 49 patients (11.9%) with the time range of 1 to 52 months (median : 7 months). Second malignancy, before or after the diagnosis of lung cancer was observed 11 patients.

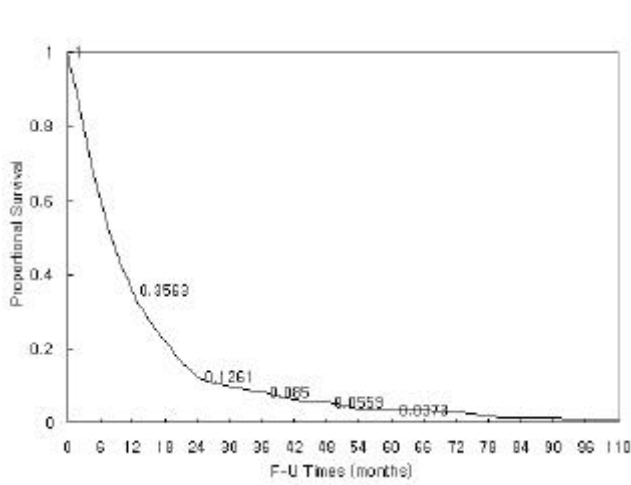


Fig. 1. The actuarial survival rate if unoperable squamous cell lung cancer patients treated with radiotherapy ($N=411$).

Table 4. Survival Comparison in Patients with Complete Radical Aim Radiotherapy : Univariate and Multivariate Analysis ($N=247$)

Parameters	No. of patients	MS (months)	1-YSR (%)	2-YSR (%)	5-YSR (%)	p value
Age						
65	144	12	45.5	14.7	4.9	
>60	103	14	51.8	18.3	4.2	0.57
Gender						
male	239	12	48.5	15.9	4.9	
female	8	7	37.5	25.0	0	0.68
Smoking						
no	6	16	66.7	16.7	0	
yes	171	12	49.3	15.8	3.8	0.86
Tumor Location*						
Upper lobe	160	13	51.5	18.3	5.1	
Others	87	10	41.9	12.3	3.7	0.04
Hemoglobin (g/ dl)						
12	69	12	48.9	12.2	4.6	
>12	136	16	54.5	19.2	5.5	0.08
Coughing						
no	32	14	62.5	12.5	9.4	
yes	210	12	46.7	17.1	4.2	0.62
Hemoptysis						
no	121	14	53.2	15.8	7.0	
yes	116	11	43.9	16.6	1.4	0.45

Table 4. Continue

Parameters	No. of patients	MS (months)	1-YSR (%)	2-YSR (%)	5-YSR (%)	p value
Dyspnea						
no	97	15	58.6	15.8	5.6	
mild	57	12	45.4	17.8	5.9	
moderate	76	9	41.1	17.8	2.5	0.26
severe	10	7	50	10.0	0	
Fever						
no	199	12	48.7	16.6	4.1	
yes	44	14	50.1	15.8	7.2	0.72
SVC syndrome						
no	240	12	49.2	16.7	4.8	
yes	7	5	14.3	0	0	0.01
Hoarseness*						
no	222	13	50.6	17.5	5.2	
yes	25	9	25.9	4.3	0	0.01
Chest Pain						
no	141	12	49.8	15.8	3.3	
mild	62	14	52.2	14.8	3.7	0.91
severe	34	9	38.2	20.6	11.8	
Pleural Effusion*						
no	236	12	50.0	17.0	4.9	
yes	11	8	9.1	0	0	0.00
Total Lung Atelectasis*						
no	239	12	49.0	16.7	4.8	
yes	8	6	25.0	0	0	0.01
Lung to Lung Metastasis						
no	237	12	48.5	16.0	4.4	
yes	11	8	40.0	30	10	0.61
T stage						
T1	3	29	100	100	33.3	
T2	48	14	52.1	17.8	0	0.28
T3	103	13	51.0	14.3	5.7	
T4	90	11	40.7	14.4	5.6	
N stage						
0	24	15	58.3	29.2	0	
1	24	12	50.0	20.8	8.3	0.53
2	112	12	49.3	13.5	6.2	
3	83	12	43.6	14.4	2.6	
Subcarinal LAP						
negative	151	12	49.7	17.0	4.5	
positive	79	11	41.3	15.8	4.7	0.61
Supraclavicular LAP*						
no	220	13	50.7	17.2	4.7	
yes	26	8	28.2	8.0	4.0	0.00
Radiation dose (Gy)						
60	101	12	46.8	17.3	5.3	
>60	146	12	49.1	15.4	4.2	0.85
Chemotherapy*						
no	194	12	46.5	14.0	3.1	
yes	53	14	54.2	24.1	10.8	0.06

* statistically significant parameters in multivariate analysis
MS: median survival, YSR: year survival rate

DISCUSSION

Radiation oncologists choose the way how they deliver the radiation to the patient depending on the stage of the disease and the patient's general condition. Jeremic et al⁷⁾ reported that the median and the 5-YSR were 33 months and 30%, respectively after hyperfractionated radiotherapy alone for clinical stage I NSCLC. They concluded that the results of their study were better than those of most previous studies employing conventional fractionated radiotherapy for stage I NSCLC. In our study, the survival outcomes were also good for Stage IA patients with the median survival of 29 months. As most of the NSCLC patients referred for radiotherapy were with their advanced disease status, the treatment results by radiotherapy alone were very poor, which is known already through many reports of the inside or outside the country.^{1, 2, 6, 8)} Advanced Stage IIIA and IIIB patients comprised about 80% of the whole patients in this study. The median and 5-YSR were 13 months and 6.3% for Stage IIIA and 9 months and 3.4% for Stage IIIB, respectively. It would be desirable if we could predict the outcome of patients in order to make more wise decision on treatment method and schedule. It is widely accepted that performance status and weight loss are the most significant prognostic indicators in advanced lung cancer patients.⁹⁾ But, we could not confirm the performance status and weight loss to be the significant prognostic factors, because the medical information were not perfect in many patients. The physical performance status of the patients including general condition and clinical signs and symptoms in addition to the anatomical tumor stage influenced on the determination of the treatment aim before initiation of the radiotherapy, and we followed the usual treatment guidelines commonly accepted in the treatment of the inoperable NSCLC patients. This analyses showed difference of survival by the treatment aim that the median survival of radical aim group and palliative aim group were 11 months and 5 months, respectively, which suggested that the patient's and tumor factors were more important to the treatment outcomes than the treatment technique itself.

We analyzed the various prognostic factors affecting the survival outcomes only in 247 patients who completed the radical intent radiotherapy. The age or the sex did not influence the survival, and the stage was not important pro-

gnostic factor in this group although the survival difference was significantly different by stage in all patients group. Upper lobe tumor location showed better survival outcomes than other locations, and this result can be explained by the fact that the high dose of radiation, which can be limited by the normal lung damage, can be delivered to the upper lobe area more easily than the other lobes. The poor prognostic clinical signs and symptoms were SVC syndrome, hoarseness, total lung atelectasis, and pleural effusion in this analysis. We confirmed the conclusion that the primary therapeutic decision-making in inoperable non-small cell lung cancer using decision-support system (DSS) or a prognostic index (PI) was as important as the therapeutic techniques.⁵⁾

Failure pattern studies of patients in RTOG 88-08/ECOG 4588 made it clear that control of the tumor within the field of irradiation was far from satisfactory.¹⁰⁾ A prospective study by Arriagada et al¹¹⁾ strictly evaluated local control with bronchoscopy in addition to chest CT scans and found local control in only 17% following 65 Gy radiation to the primary tumor. Our analysis also showed the result that the local progression of the disease appeared in about a half patients. It is clear from these data that further steps are needed to improve the control the primary disease in lung cancer. Recent results from the RTOG (protocol 83-11) using hyperfractionated radiotherapy(HFRT) to a total dose of 69.6 Gy are encouraging with 29% survival at 2 years in selected patients.¹²⁾ Improvement in local tumor control may be achieved by increasing the total radiotherapy dose and reducing the overall treatment time. But, in our study, the survival difference by the radiation dose was not shown with the same median survival of 12 months (< 60 Gy vs >60 Gy). Because local progression remains a predominant pattern of failure in NSCLC, future investigations aimed at improving local control should include dose escalation using conformal radiotherapy or combination of the chemotherapeutic agents with radiotherapy as a radiosensitizer. The randomized study has demonstrated the survival benefits of combined chemoradiotherapy as compared to radiotherapy alone in locally advanced NSCLC patients who had less than 5% weight loss and good Karnofsky performance status (70-100).¹³⁾ A recent meta-analysis including data from 22 trials showed a significant benefit in favor of chemotherapy administered in a sequential way: this was particularly true for a cisplatin-based chemotherapy with an absolute survival benefit of 4% at 2 years and 2% at 5 years.¹⁴⁾ Combination

chemoradiotherapy is now considered the standard for unresectable locally advanced NSCLC in good performance status patients. In this study, chemotherapy was combined in only about 20% of all patients analyzed and the survival result was better than that of radiotherapy alone group although survival differences among combination schemes of radiation and chemotherapy could not be identified. Since 1998, we usually have combined the chemotherapy to the radiotherapy in patients group who are appropriate candidates for more aggressive therapy. In these patients with more aggressive therapy we anticipate more improved treatment outcomes.

In conclusion, the conventional radiotherapy in the patients with locally advanced squamous cell lung cancer has given small survival advantage over supportive care and it is very important to select the patients group who can obtain the maximal benefit and to select the radiotherapy technique that would not compromise the life quality of the patients. In advance, we must take a positive attitude toward the radiotherapy in patients group with prolonged life expectancy.

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IA 5 29 33.3% , IIIA IIIB 13 , 6.3% 9 11

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