Postoperative Radiation Therapy in Non-Small-Cell Lung Cancer

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Sixty patients with proven lung cancer were retrospectively studied to determine whether postoperative radiation therapy improves survival. Patterns of treatment failure and 5 year survival were assessed according to extent of tumor spread, histology, type of operation, positive resection margin and radiation dose.

Of the 60 patients, excluding 5 patients who received incomplete treatment or poor pulmonary function, 55 patients received postoperative radiation therapy following curative resection. The overall survival at 5 years was 39%. The hilar and mediastinal lymph node involvement had an influence on survival. The authors recommend that patients with resectable lung cancer involving the hilar and mediastinal lymph nodes may require postoperative radiotherapy to reduce the local recurrence and improve survival.

Key Words: Postoperative radiation therapy, Lung cancer, Lymph node

INTRODUCTION

The 5 year survival rate for patients treated with lobectomy and pneumonectomy varies from 20 to 50 percents, depending on the indication for the surgical procedure and the careful pathologic staging of the disease. When a lung cancer has been completely resected, and regional lymph nodes are free of tumor, the value of post-operative radiation therapy has not been demonstrated. However, the incidence of involvement of regional lymph nodes by metastatic carcinoma of the lung has been in the range of 30-60% in surgical series[1]. From the historical data, the survival rate of those patients with metastatic regional lymph nodes has been very poor, with a range of 0 to 20%[3,6~9].

While some of this decrease in survival is no doubt due to systemic metastasis, a significant portion of it is due to local failure.

Matthews reported that the incidence of microscopic residual carcinoma in the mediastinal lymph node was 52% for patients who had died within 30 days of a curative resection[1]. Because of this potential for residual disease, it is thought that postoperative radiation therapy to the tumor bed and regional lymph nodes would sterilize any residual disease and potentially offer the patient increased local control and possible increased benefit in survival.

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Most of the retrospective series concerning postoperative radiation therapy in node positive lung cancer patients showed the gamut between benefical effect and no survival difference. Two series of prospective randomized study showed the local benefit of adjuvant radiation therapy but no significant survival benefit[2,3].

This study was undertaken to analyze the prognostic factors with respect to the stage, histologic type of the tumor, and radiation dose on which a success or failure of the treatment depends.

MATERIALS AND METHODS

From Mar. 1979 to Feb. 1986, sixty patients were referred to Department of Therapeutic Radiology, Seoul National University Hospital, with pathological findings of regional lymph node involvement or positive resection margin and visceral pleural involvement.

Of these, 5 patients who had incomplete treatment or poor pulmonary reserve were excluded for this analysis. The minimum follow-up period was 24 months.

There were 34 patients (62%) with squamous cell carcinoma, 13 patients (24%) with adenocarcinoma, and 8 patient (14%) with other histology. (3 mixed carcinoma, 3 adenosquamous cell carcinoma, 1 large cell carcinoma and 1 alveolar carcinoma. (Table 1)

By the TNM system [4], eleven patients had stage I, 13 stage II, and 31 stage III.

Table 1. Patient Characteristics

	No. of pts
Age	
< 40	6
40 – 49	13
50 – 59	25
60 – 69	11
Sex	
Male	45
Female	10
Histology	
Squamous	34
Adenoca.	13
Others	8
Stage	
I	11
II	13
III	31
T-Stage	
T1	4
T2	31
T3	20
N-Stage	
N0	13
N1	24
N2	18
Operation	
Pneumonectomy	25
Lobectomy	30

Twenty five patients underwent a pneumonectomy, 24 had a lobectomy and 6 had a bilobectomy. Resection was believed to be complete in 49 patients, and incomplete in 6.

Treatments were delivered with Co-60 teletherapy unit or 6X or 10X linear accelerator and directed to mediastinum, medial halves of both SCL including bronchial stump with 2-2.5Cm margin. A midplane dose of 4,500-5,500 cGy was planned and boost dose of 500-1,000 cGy was added to high risk area (e.g. chest wall invasion, incompletely resected margin) at a rate of 180-200 cGy per treatment.

Statistical methods were the life table method for actuarial survival and the log-lank test for comparison.

RESULTS

1. Survival

The overall 5 year actuarial and disease free survival rate of 55 patients were 39% and 29% (Fig. 1).

According to stage, survival rates and disease free survival rates were 73% and 49%, 24% and 28 %, 20% and 20% for stage I, II and III respectively, showing marginally significant differences (P=0. 07) (Fig.2).

Retrospective series showed the different results of postoperative radiation therapy, a benefit for squamous cell carcinoma only[5],a benefit for adenocarcinoma only[6], and a benefit for all histology[7].

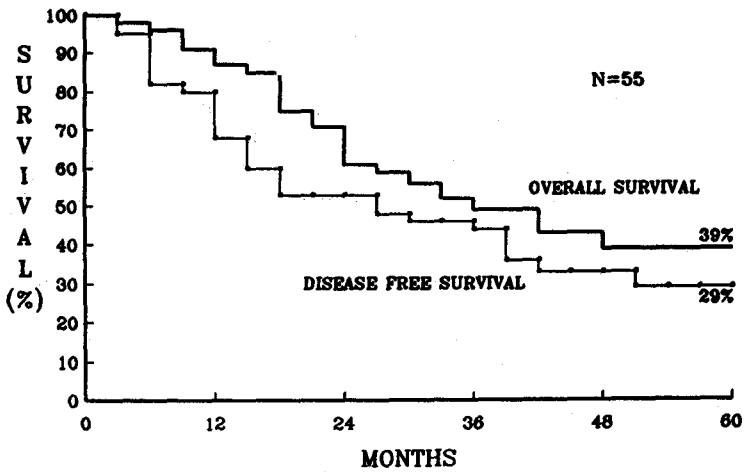

Fig. 1. Overall and Disease Free Survival.

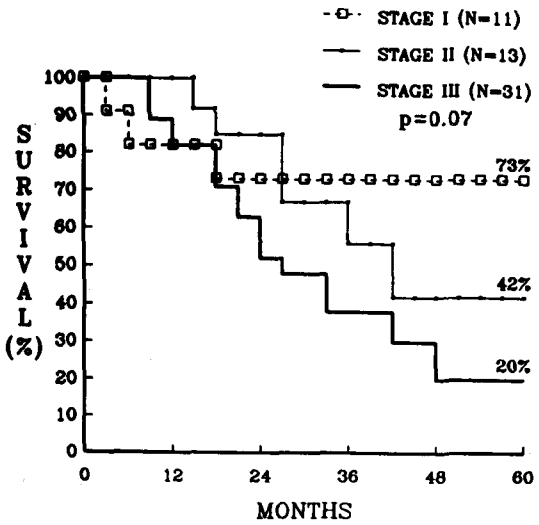

Fig. 2. Survival by Stage.

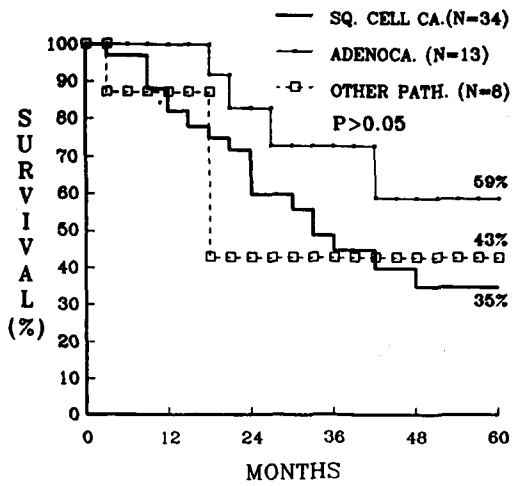

Fig. 3. Survival by Histology.

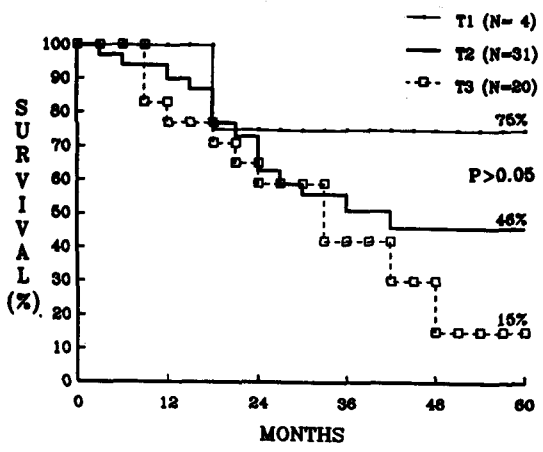

Fig. 4. Survival by T-stage.

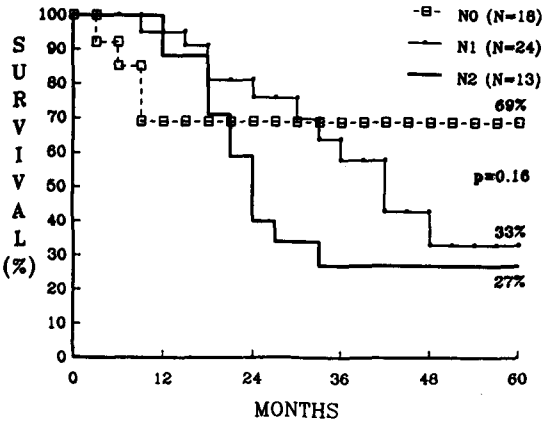

Fig. 5. Survival by N-stage.

In this study, there was no statistically significant difference among each histology (P>0.05).

As in figure 4, patients with T1 lesion achieved the best result, but the difference was not statistically significant because of small number of patients. They also had longer median survival time of 53 months than that of T2 or T3 patients (27 months and 23 months).

Sixty nine percents of patients without regional lymph node metastasis survived 5 years. In contrast, patients with hilar node and mediastinal node metastasis survived 33% and 27% at 5 year. N0 patients also showed higher disease free survival (59%, 21% and 18% for N0, N1 and N2 respectively) and longer median survival (37 months, 30.5 months and 22 months, respectively) than that of N1 and N2. Because of short follow up period and relatively small number of patients, there were no statistically significant differences (Fig. 5).

Age, sex, type of operation, resection margin involvement and radiation dose were not correlated with the prognosis in this study.

2. Failure Pattern

Among 55 patients, 33 patients had a failure identified and 14 patients are alive in the state of no evidence of disease, 5 lost in NED state and 3 died without intercurrent disease.

Stage III patients showed slightly higher locor-

egional failure and lower distant metastasis, but the difference was not significant as shown in Table 2.

In Table 3, we could not find any difference in failure pattern according to stage. Each histology has distant metastasis in about 60% of total failure.

Table 4 and 5 showed that T3 has slightly higher locoregional failure rate and node positive patients have higher distant metastatic rate.

The sites of locoregional failure were lung out of field in 4, lung in field in 3, ipsilateral SCL in 1, and pleura in 1 patient.

The common metastatic sites were bone in 8 patients, brain in 4, contralateral lung in 3, brain and bone in 2 and liver in 1 patients.

About one third of patients developed mild or moderate complications such as pneumonitis, esophagitis and clinicaly not significant pulmonary fibrosis. There were no myelopathy induced by irradiation.

Table 2. Failure Pattern by Stage

Stage	LR	LR+DM	DM	TOTAL
I	1 (25%)	–	3 (75%)	4/11
II	2 (20%)	1 (10%)	7 (70%)	10/13
III	6 (32%)	2 (10%)	11 (58%)	19/31

Table 3. Failure Pattern by Histology

APTH	LR	LR+DM	DM	TOTAL
Squamous	5 (26%)	2 (10%)	12 (63%)	19/34
Adenoca.	2 (22%)	1 (11%)	6 (67%)	9/13
Other	2 (40%)	–	3 (60%)	5/ 8

Table 4. Failure Pattern by T-Stage

T-Stage	LR	LR+DM	DM	TOTAL
T1	–	–	2	2/ 4
T2	5 (29%)	1 (6%)	12 (67%)	18/31
T3	4 (31%)	5 (15%)	7 (54%)	13/20

Table 5. Failure Pattern by N-Stage

N-Stage	LR	LR+DM	DM	TOTAL
N0	3 (60%)	1 (20%)	1 (20%)	5/13
N1	2 (13%)	1 (6%)	13 (81%)	16/24
N2	4 (33%)	1 (8%)	7 (59%)	12/18

DISCUSSION

1. Survival

The role of radiation therapy following surgery for lung cancer patients has been a subject of debate for many years.

On the basis of data from retrospective studies, the use of postoperative radiation therapy in patients with regional lymph node metastasis was the general trend. Therefore, the value of surgical adjuvant radiation therapy could be difficult to assess unless the strong prognostic factors were defined. Unfortunately, most of these studies were retrospectdive.

Patterson and Russel conducted a controlled study of postoperative radiation therapy following pneumonectomy. No improvement in survival was seen but they did not assess survival according to the stages of the tumor[8]. The studies by Kirsh et al, Green et al and Choi et al reported that postoperative radiation therapy improved survival in patients with positive mediastinal lymph node metastasis [5,7,9].

However, retrospective series cited above showed three different results of adjuvant radiotherapy according to the histologic types of the tumor. A benefit for squamous cell carcinoma, a benefit for adenocarcinoma and a benefit for all histology [5,7,9], therefore, it is difficult to appeal to this studies for guidance.

Two prospective randomized trials involving postoperative radiation therapy in lung cancer have been reported. Van Houtte et al in European trial reported on 224 patients receiving postoperative radiation therapy, in which there was no significant difference in survival between the control and the irradiated group; however, in this study many patients were without regional lymph node metastasis and had complete resection of the primary lesion[3].

In 1986, the Lung Cancer Study Group has performed prospective randomized study on 230 patients with resected stage II or III squamous cell carcinoma. The result was negative for the survival benefit of irradiation and just showed the increased local control rate[2].

We assessed the value of postoperative radiation therapy with regard to the determinants for survival: the local extent of tumor spread, the histologic type and the type of resection.

In this study, 13 out of 55 patients with negative lymph node were irradiated and the 5 year survival

for N0 patients was 59%. But this result was similar to those of other studies which were treated by surgery alone, showing that no advantage was found for this N0 group with postoperative irradiaton. The 5 year survival for N1 patients was 21 %, which was comparable to those of other studies with surgery alone ranging from 0 to 31%. But for N2 patients, the 5 year survival rate of 17% was somewhat higher than that of surgery alone, though the stratification of patients with respect to size of primary lesion, pathologic stage, performance status or histology were impossible.

According to histology, we observed a higher survival rate of 59% in patients with adenocarcinoma than patients treated with surgery alone ranging from 0 to 38%. But in patients with squamous cell carcinoma, we could not find any survival advantage with postoperative irradiation.

Lewin et al noted the prognostic significance of residual disease status in the study of Joint Center for Radiation Therapy with p-value of 0.03 or less[10]. Soorae et al reported that microscopic residual tumor was found at the cut margin in approximately 15% of resected specimen, and the overall 5 year survival rate was 22%[16].

In this study, the 5 year survival rate was 45%, showing that the involvement of resection margin by tumor did not decrease the survival rate and we think that it resulted from adding 500-1,000 cGy boost to this high risk area (Fig. 6).

Recently, the Lung Cancer Study Group reported on 172 patients with incompletely resected non-small-cell lung cancer in which postoperative radiotherapy combined with CAP chemotherapy

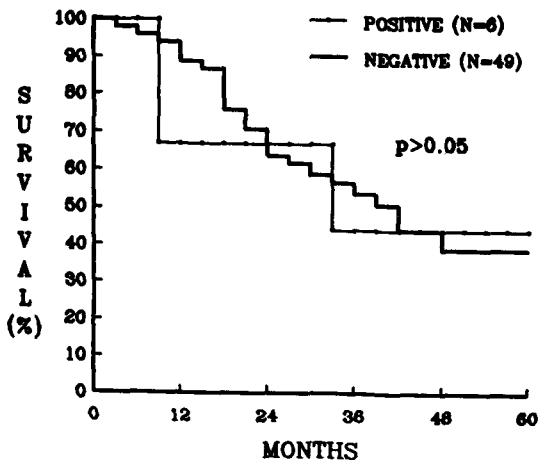

Fig. 6. Survival by Resection Margin.

arm showed significantly longer recurrence free survival (p=0.004), and decrease in distant metastasis with survival benefit of 14% at 1 year from randomization[11].

2. Prognostic Factors

Shields reported on 794 patients treated either surgery alone or surgery combined with postoperative radiotherapy, in which the tumor size and the presence of lymph node metastasis are the most important prognostic factors[12]. In our study, the most important factor affecting the prognosis was stage. Stage I patients showed 73% 5 year survival rate and median survival of 50 months in contrast to 20% survival and 23 months median survival in stage III, though the statistical significance was marginal (p=0.07). The results are slightly higher than that of other studies showing 5 year survival rates of about 50% in stage I, 30% in stage II and 15 % in stage III. But the small number of patients in each group and relatively short follow up period are the problems we should solve.

Another important factor was the node status. Kirsh et al reproted the 5 year survival of patients without nodal metastasis was 49.3%. It was 31.1% in N1 patients and 23.1% in N2 patients [2,3]. Green et al reported 27% for node negative patients and 35% for node positive patients[7].

In our study, node negative (N0) group showed much higher 5 year survival and disease free survival rates (69% and 59%) than that of node positive group (33% and 21% for N1, 27% and 18% for N2; p=0.16 and 0.09).

Median survival time was also longer in node negative patients. If the number of patients and follow-up periods is increased for the next few years, we are sure of the significance of the difference among each group.

We could observe that lower T-stage lesion had better survival than higher T-stage, indicating that locally advanced lesion has poorer prognosis.

The median survival time were 53 months in T1 patients, 20 months in T2 and 23 months in T3. But the absolutely small number of patients in T1 group obliterated the significance.

The nominal standard dose (NSD) of Ellis, age, sex and type of operation did not affect the survival at all.

Many authors demonstrated that patients with squamous cell carcinoma had a better chance for long term survival than patients with other carcinoma cell types[5,13,14], but in this study, we could

not observe any superiority of survival or disease free survival in patients with squamous cell carcinoma, rather poorer results was observed as in studies by Choi, Lewin, and Holms et al[6,10,15].

3. Failure Pattern

Chung et al noted that the overall incidence of local failure in patients treated with surgery alone was about three times of patients treated with surgery and irradiation (32% vs 10%)[14]. And for surgery alone group, patients with positive nodes are at a higher risk of local failure compared to those with negative nodes (48% vs 21%). He showed that postoperative irradiation siginificantly decreased the local failure rate in node positive group (48% vs 8%), but not in node negative group (21% vs 17%). In our study, we noted a locoregional failure rate of 22% which was much lower than that of surgery alone patients in other studies. In node negative patients, it was 31%, and 18% in node positive patients suggesting that locoregional failure rate was much decreased in node positive group with irradiation (Table 5).

Choi et al showed that for patients with early stages of carcinoma of the lung, the majority of failures are due to distant metastasis[3].

We also observed slightly higher proportion of locoregional failure in stage III patients and higher distant metestasis rate in stage I, though the significance was minimal due to small number of patients. (Table 2) For early stage cancer, it can be thought that local control is more easily achievable with the same dose of irradiation because of the completeness of tumor resection.

Matthews reported that there were differences in the frequency of metastasis for each of the histologic types. At autopsy, the frequency of extrathoracic metastasis were epidermoid 25% to 54%; adenocarcinoma 50% to 82%; large cell carcinoma 48% to 86%[16].

Choi also noted that locoregional relapse is the most common cause of failure for patients with locally advanced squamous cell carcinoma, and distant metastasis, especially brain, in the most common cause of failure for patients with adenocarcimoma[6]. Cox and Stanley showed that squamous cell carcinoma is more likely to develope local failure prior to distant metastasis than adenocarcinoma and large cell carcinoma as opposed to having distant metastasis in a much large proportion of patients. But our results did not show such tendency of failure by histology type[17,18] (Table 3).

We observed similar effect of T-stage on failure as in stage. Higher T stage had slightly higher locoregional failure and lower distant metastatic rate (Table 4). And by N stage, the results was contrary. Chung et al, Perez and many other authors noted that patients with metastatic regional lymph nodes have a higher risk of developing distant metastasis[9,19]. We also observed that positive mediastinal node patients had higher proportion of distant metastatic rate, and lower proportion of locoregional failure than node negative patients (Table 5).

The results showed that postoperative radiation therapy improved survival among patients with hilar and mediastinal lymph node metastasis of all histological types but did not improve survival among patients without node metastasis. The authors recommend that patients with resectable lung cancer involving the hilar and mediastinal lymph nodes should be treated by postoperative radiation therapy following curative resection.

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= 국문초록 =

비소세포성 폐암의 수술후 방사선 치료

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김 주 현

최근 폐암의 발생빈도는 높아지고 있으나, 아직까지 만족할 만한 치료 성적은 제시되지 않고 있으며, 현재로서는 가능한 한 초기에 발견하여 수술을 시행후 국소재발 위험군의 경우 방사선 치료를 시행하는 것이 최선의 방법으로 알려져 있다. 이에 저자들은 1979년 3월부터 1986년 2월까지 서울대학교 병원에서 비소세포성 폐암 진단하에 근치적 절제수술 시행후 방사선 치료를 받은 60명의 환자를 대상으로 수술후 방사선 치료의 효과 및 예후인자에 대한 분석을 시행하여 다음과 같은 결과를 얻었다.

전체 환자 60명중 방사선 치료를 불완전하게 시행한 5명을 제외한 55명을 분석한 결과 전체 환자의 5년 생존율은 39%였으며 무병생존율은 29%였다. 환자의 예후를 결정하는 주요인자로서는 병기 및 국소 임파절 전이 여부였고, T 병기와 병리조직학적 분류 및 나이, 성별, 방사선 조사선량과 수술시 절제면의 종양 침범 여부는 예후에 큰 영향을 미치지 못하였다. 수술 시행후 방사선 치료를 받은 환자군의 생존율은, 문헌상에 나타난 수술 단독 시행 환자군의 생존률과 비교해 볼때 국소 임파절 전이가 있는 환자군에서 더 높은 결과를 보였으며, 임파절 전이가 없는 환자군에서는 큰 차이를 발견할 수 없었다.

국소 재발율도 임파절 전이가 있는 환자군에서는 수술 단독 시행 환자군보다 현저히 낮은 결과를 보여 수술후 방사선 치료가 임파절 전이가 있는 환자에게는 생존율의 증가 및 국소재발 억제의 효과를 나타냄을 관찰할 수 있었다.