

## Postoperative Radiotherapy for Non-Small Cell Lung Cancer

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**Purpose** : To evaluate effect of postoperative radiotherapy on survival and local control for patients with non-small cell lung cancer (NSCLC).

**Materials and Methods** : Ninety two NSCLC patients with N1 or N2 involvement who were treated with postoperative radiotherapy following surgery with curative intent from May 1987 to October 1999 were retrospectively analyzed. Age of the patients was ranged from 32 to 78 years. According to TNM Stage, 35 patients had Stage II and 57 had Stage III disease. There were 49 patients with N1 involvement and 43 patients with N2 involvement. Fifty six patients were noted to have T1~2 tumors and 36 patients to have T3~4 tumors. Delivered total dose was ranged from 40 to 60 Gy. Majority of patients received 50 Gy or 50.4 Gy. Follow-up period was ranged from 9 month to 7 years with median follow-up of 26 months.

**Results** : Overall survival rates at 3 and 5 years for entire group of patients were 46% and 38%, respectively. Corresponding disease free survival rates were 44% and 36%. There was significant difference in survival between patients with Stage II and Stage III disease (50% vs 28% at 5-year). Five year survival rates for N1 and N2 patients were 52% and 20%, respectively ( $p < 0.05$ ). These were 40% and 34% for patients with T1~2 tumors and T3~4 tumors. There were documented local relapses in 13% of the patients. For patients with N1 and N2 Stage, local relapse rates were 8% and 18%, respectively.

**Conclusion** : Our study confirms that postoperative radiotherapy for patients with non-small cell lung cancer improves local control. However, influence of postoperative radiotherapy on long-term survival is less clear. More effective systemic treatment to prevent distant metastasis should be investigated in future study to improve long-term survival.

**Key Words** : Postoperative radiotherapy, Non-small cell lung cancer

### INTRODUCTION

Lung cancer is one of the main causes of cancer deaths. Approximately 80% of lung cancer is non-small cell lung cancer. The standard management for patients with resectable non-small cell lung cancer (NSCLC) without distant metastases is curative resection. However, only 30% of patients with NSCLC confined to the chest are considered as surgical candidates. Also long-term survival is greatly reduced if the mediastinal lymph nodes are involved.<sup>1)</sup> The 5-year survival rates after complete surgical resection are over 60% for patients with T1N0 tumors. This survival rate drops to less

than 30% for patients with N1 (hilar nodes) and 10% for those with N2 (mediastinal nodes) disease. Although high probability of distant metastases is a challenging issue in these patients, local recurrence has remained a significant problem even after curative surgery.<sup>2~4)</sup>

Thoracic postoperative radiation for NSCLC still remains a controversial issue but it represents challenge for radiotherapist. Radiation dose to control microscopic residual disease has to be delivered without exceeding the tolerance of many normal and vital organs such as lung, heart or spinal cord.<sup>3)</sup> A small benefit in terms of survival or local control may be outweighed by an increase in radiation induced late damage.

Several retrospective studies claimed to show benefit to patients with mediastinal node metastases from postoperative radiotherapy<sup>4~8)</sup> but the studies dealt with generally small group of patients and involved unreliable comparison with historical control or other series. Herein, we report the retrospective analysis of 92 NSCLC patients treated with

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postoperative radiotherapy in single institution and evaluate the effect on survival and local control as well as tolerance of the treatment.

## MATERIALS AND METHODS

Total of 96 NSCLC patients with N1 or N2 involvement were treated with postoperative radiotherapy following surgery with curative intent at our institution from May 1987 to October 1999. Of those 96 patients, 4 patients refused treatment or did not complete planned radiotherapy and excluded from the study. Records of remaining 92 patients were retrospectively analyzed. Patients treated with preoperative or postoperative chemotherapy were excluded from present study. Patients characteristics are shown in Table 1. Seventy patients were male and 22 patients were female with male to female ratio of 3.2:1. Age of the patients was ranged from 32 to 78 years with median age of 57 years. According to TNM Stage, 35 patients had Stage II and 57 had Stage III disease. There were 49 patients with N1 involvement and 43 patients with N2 involvement. Fifty six patients were noted to have T1~2 tumors and 36 patients to have T3~4 tumors. All of the patients in present study had histologically proven non-small cell cancers: 62 were squamous cell carcinoma, 28 were adenocarcinoma and 2 were undifferentiated large cell carcinoma. All of the patients underwent surgery with curative intent. Fifty eight patients underwent lobectomy and 34 did pneumonectomy.

Postoperative radiotherapy was administered 3~5 weeks

after radical operation. Linear accelerator producing 6 MV or 10 MV photons was employed to treat all of the patients. Parallel opposed anteroposterior (AP-PA) fields were used covering bronchial stump, ipsilateral hilum and most of the mediastinum. Typical field of the mediastinum was 6 cm wide. Oblique fields were used to take off the spinal cord after 40 Gy. Either enlarged AP-PA field or different field arrangement was used to irradiate the primary site in patients with chest wall invasion. Supraclavicular fossae were not routinely irradiated.

Treatment was given once a day, five times a week. Dose of daily fraction was 1.8 Gy or 2.0 Gy. Delivered total dose was ranged from 40 Gy to 60 Gy. Table 2. showed the distribution of patients according to dose. Only 3 patients received less than 45 Gy. Majority of patients in present study received 50 Gy or 50.4 Gy. In selected patients with T3~4 lesions, dose of 55-60 Gy was delivered to primary site with coned down boost field. Six out of 8 patients with T4 lesions underwent incomplete resection.

All of the patients were followed by us or their referring physicians. Follow-up period was ranged from 9 months to 7 years with median follow-up of 26 months. After radiotherapy, local control was assessed by means of chest radiographs at 2~3 month intervals, with the use of computed tomography reserved for patients with clinical findings suggestive of recurrence. Local recurrence was defined as ipsilateral hilum relapses, mediastinal lymph nodes metastasis and/or primary site relapses. Survival was calculated from day one of radiotherapy. Kaplan-Meier method and log-rank test were used to compare the survival rates.

Table 1. Patients Characteristics

Number of patients	92
Male	70 (76%)
Female	22 (24%)
Median Age	57 (32~78)
Stage	
II	35 (38%)
III	57 (62%)
N Stage	
N1	49 (53%)
N2	43 (47%)
T Stage	
T1~2	56 (61%)
T3~4	36 (39%)
Histology	
Squamous	68 (74%)
Adenoca	22 (24%)
Large Cell	2 ( 2%)

## RESULTS

### 1. Survival

Overall survival rates at 3 and 5 years for entire group of patients were 46% and 38%, respectively. Corresponding disease free survival rates were 44% and 36%. This result is

Table 2. Distribution of Patients according to Delivered Dose

Dose	Number of Patients
<45 Gy	3
45~50 Gy	4
50~55 Gy	78
55~60 Gy	7
Total	92

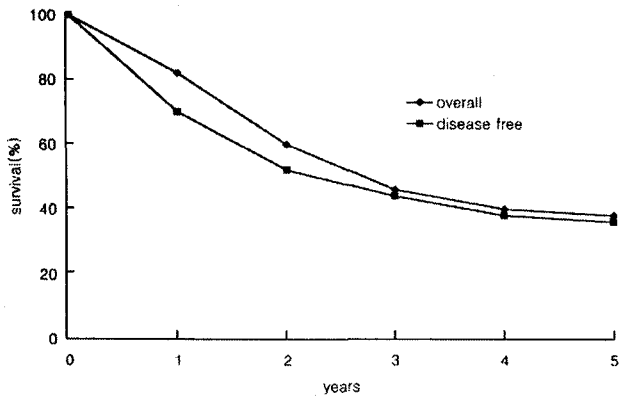


Fig. 1. Overall and disease free survival rates for entire group of patients.

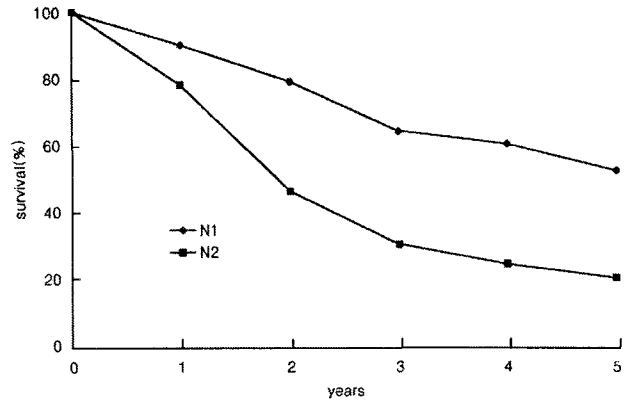


Fig. 3. Survival rates according to N-Stage.

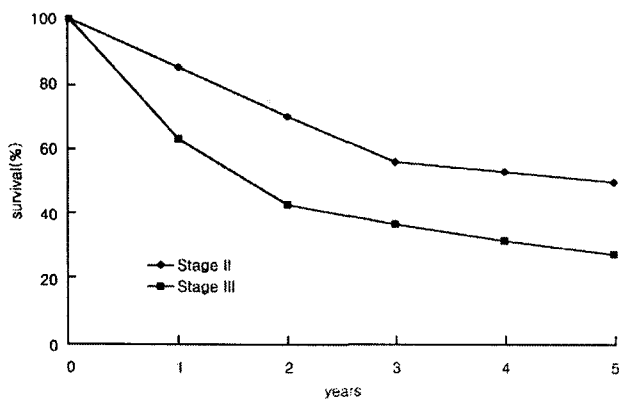


Fig. 2. Survival rates according to TNM-Stage.

shown in Fig. 1. Also survival rates according to TNM Stage, N-Stage, T-Stage were examined. There was significant difference in survival between patients with Stage II and Stage III disease. Three and five year survival rates for Stage II patients were 56% and 50% and corresponding survival rates for Stage III patients were 37% and 28% (Fig. 2).

Compared with T-Stage, lymph node involvement (N-Stage) implicated more significant impact on survival in univariate analysis. Five year survival rates for N1 and N2 patients were 52% and 20%, respectively ( $p < 0.05$ ) as shown in Fig. 3. For patients with T1~2 tumors and T3~4 tumors, these were 40% and 34% ( $p > 0.05$ ). Five year survival rate for 56 patients with squamous cell carcinoma was 43% and this was 21% for 22 patients with adenocarcinoma. Of 2 patients with large cell carcinoma, one patient died at 27 month after the treatment and one patient is alive without evidence of disease.

## 2. Failure

There were documented local relapses in 13% of the patients. Local relapse was defined as ipsilateral hilum relapses, mediastinal lymph nodes metastasis and/or primary site relapses. Only 8% of Stage II patients and 16% of Stage III patients developed local relapse. For N1 and N2 Stage patients, local relapse rates were 8% and 18%, respectively. These were 12% and 19% for T1~2 and T3~4 tumors. There were 48% distant metastases.

## 3. Complications

Most of the patients developed mild to moderate esophagitis during the treatment. However, none of the patients had treatment break because of acute reactions. Two patients complained of generalized fatigue and had to cease the treatment at 40 Gy. These patients were not excluded from the study. Severe late complications requiring surgical procedures were not noted in any patient.

## DISCUSSION

Postoperative radiotherapy has been used to prevent local failure and possibly improve long-term survival of patients with NSCLC for past decades. However, the role of postoperative radiotherapy in non-small cell lung cancer still remains controversial. There is no benefit to postoperative radiotherapy in patients with completely resected Stage I NSCLC,<sup>9-11)</sup> but the role of postoperative radiotherapy in patients with N1, N2 disease is less clear.

Van Houtte et al reported the results of randomized trial showing that survival of patients with N0 disease was better

in non-irradiated group,<sup>9</sup> compared to those receiving postoperative radiotherapy (43% vs 24% at 5 years). In patients with N1~2 disease, randomized trial accomplished in different institutions showed different results.

The Lung Cancer Study Group reported that there was no evidence that postoperative radiotherapy improves survival, although local recurrence rate was significantly lower in this group.<sup>12</sup> Paterson and Russell documented similar results in a randomized trial of 202 patients, showing no difference in survival between patients treated with or without postoperative radiotherapy.<sup>13</sup> However, Mayer et al reported better local control rates and higher overall and disease free survival (30% and 27%) in patients receiving postoperative radiotherapy, compared to patients treated with surgery alone (20% and 16%).<sup>14</sup> Thus, influence of postoperative radiation on survival in patients with N1 or N2 non-small cell lung cancer still remains to be clarified.

In our study, 5 year survival rates for N1 and N2 disease were 52% and 20%, respectively and overall survival rate at 5 year was 38%. This result is similar to series reported by others.<sup>7, 12, 14, 15</sup> Also local relapse rate of 13% is comparable to other studies.<sup>12-15</sup> Baldini et al. reported improved local control rate as well as improved survival in postoperative radiation group.<sup>16</sup> Although present study is not a randomized trial, our study demonstrates that local relapse rate is lower, comparing to results reported in surgery alone series.<sup>4, 12</sup> As shown in other studies,<sup>7, 12, 17</sup> survival rate in our study is similar to data obtained from surgery alone. Thus, we might conclude that postoperative radiotherapy for patients with NSCLC significantly improves local control. However, influence of postoperative radiotherapy on long term survival is still to be examined in the future.

Compared with T-Stage, lymph node involvement (N-Stage) implicated more significant impact on survival. Five year survival rates for N1 and N2 patients in our study were 52% and 20%, respectively. However local relapse rates for N1 and N2 patients were 8% and 18%. This result suggest that N2 Stage patients are more likely to have microscopic disease in distant organ at the time of surgery and eventually develop distant metastases. There was significant difference in 5-year survival rates between patients with squamous cell carcinoma and those with adenocarcinoma. Five year survival rate for 56 patients with squamous cell carcinoma was 43%. On the contrary, this was only 21% for 22 patients with adenocarcinoma. This was probably due to

the fact that patients with adenocarcinoma presented with more N2 disease, comparing with patients with squamous cell carcinoma.

Based on results in our study, we confirm that postoperative radiotherapy for patients with non-small cell lung cancer improves local control. However, influence of postoperative radiotherapy on long-term survival is less clear. Although local relapse rate was significantly reduced with postoperative radiotherapy, high probability of distant metastases in these tumors made adverse impact on survival. Therefore, more effective systemic treatment to prevent distant metastasis should be investigated in future study to improve long-term survival.

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국문 초록

비소세포성 폐암의 수술 후 방사선치료

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**목적 :** 비소세포성 폐암 환자에서 수술후 방사선치료가 생존율 및 국소제어율에 미치는 효과를 평가하고자 함이 본 연구의 목적이다.

**재료 및 방법 :** 1987년 5월부터 1999년 10월까지 근치적 수술후 외부 방사선치료를 시행한 N1 및 N2 병기의 비소세포성 폐암 환자 92명을 대상으로 후향적으로 분석하였다. 환자 나이의 분포는 32세부터 78세이었다. TNM 병기에 따른 환자분포는 35명이 제 2 병기, 57명이 제 3 병기이었다. N1 병기의 환자는 49명이었고 N2 병기의 환자는 43명이었다. 56명은 T1~2 병기의 종양에 속하였고 36명은 T3~4 병기의 종양에 속하였다. 총 방사선 조사량은 40 내지 60 Gy이었으며 대부분의 환자는 50 Gy 또는 50.4 Gy의 방사선을 조사 받았다. 추적기간은 9개월 내지 7년이었으며 중앙값은 26개월이었다.

**결과 :** 전체 환자에서 3년 및 5년 생존율은 46% 및 38%이었다. 3년 및 5년 무병생존율은 각각 44% 및 36%이었다. 제2 병기 환자와 제3 병기의 환자에서 5년 생존율에 유의한 차이가 있었다(50% vs 28%). N1 병기 및 N2 병기 환자의 5년 생존율은 각각 52% 및 20%이었다. T1~2 병기 및 T3~4 병기 환자에서는 각각 40% 및 34%이었다. 전체 환자에서 국소 재발율은 13%이었고, N1 병기 및 N2 병기 환자에서의 국소 재발율은 각각 8% 및 18%이었다.

**결론 :** 본 연구는 비소세포성 폐암 환자에서 수술후 방사선치료가 국소 제어율을 향상시킴을 확인하였다. 그러나 수술 후 방사선치료가 생존율을 향상시키지는 못하였다. 원격 전이를 예방하여 궁극적으로 생존율을 증가시킬 수 있는 보다 효과적인 전신요법에 관한 연구가 필요할 것으로 생각된다.

**핵심용어 :** 수술 후 방사선치료, 비소세포성 폐암