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Role of Postoperative Radiotherapy for Patients with Pathological Stage III Non-Small-Cell Lung Cancer after Curative Resection

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Purpose: To evaluate the outcomes and prognostic factors of postoperative radiotherapy (PORT) for patients with pathological stage III non-small-cell lung cancer (NSCLC) at a single institution.

Materials and Methods: From 2000 to 2007, 88 patients diagnosed as having pathologic stage III NSCLC after curative resection were treated with PORT. There were 80 patients with pathologic stage IIIA and eight patients with pathologic stage IIIB in the AJCC 6th staging system. The majority of patients (n=83) had pathologic N2 disease, and 56 patients had single station mediastinal LN metastasis. PORT was administered using conventional technique (n=76) or three-dimensional conformal technique (n=12). The median radiation dose was 54 Gy (range, 30.6 to 63 Gy). Thirty-six patients received chemotherapy. Radiation pneumonitis was graded by the Radiation Therapy Oncology Group system, and other treatment-related toxicities were assessed by CTCAE v 3.0.

Results: Median survival was 54 months (range, 26 to 77 months). The 5-year overall survival (OS) and disease free survival (DFS) rates were 45% and 38%, respectively. The number of metastatic lymph nodes was associated with overall survival (hazard ratio, 1.037; p-value=0.040). The 5-year locoregional recurrence free survival (LRFS) and distant metastasis free survival (DMFS) rates were 88% and 48%, respectively. Multiple stations of mediastinal lymph node metastasis was associated with decreased DFS and DMFS rates (p-value=0.0014 and 0.0044, respectively). Fifty-one relapses occurred at the following sites: 10 loco-regional, 41 distant metastasis. Grade 2 radiation pneumonitis was seen in three patients, and symptoms were well tolerated with anti-tussive medication. Grade 2 radiation esophagitis was seen in 11 patients. There were no grade 3 or more severe complications associated with PORT.

Conclusion: Our retrospective data show that PORT for pathological stage III NSCLC is a safe and feasible treatment and could improve loco-regional control. The number of metastatic lymph nodes and stations of mediastinal lymph node metastasis were analyzed as prognostic factors. Furthermore, efforts are needed to reduce distant metastasis, which is a major failure pattern of advanced stage NSCLC.

Key Words: Post-operative radiotherapy, Pathological stage III non-small cell lung cancer

Introduction

The overall survival rate of patients with advanced stage non-small-cell lung cancer (NSCLC) is disappointing even if patients had complete resection.[1] To reduce local and/or regional recurrence and to improve survival, postoperative radiotherapy (PORT) has been explored as treatment option for many years. In 1998, PORT Meta-Analysis Trialists Group concluded that PORT had detrimental effect for patients with completely resected early stage NSCLC.[2] However, there was no clear evidence of detrimental effect of PORT for patients with N2 disease. Another retrospective analysis of Surveillance, Epidemiology, and End Results Database reported that PORT was associated with increase in overall survival significantly for patients with N2 disease.[3] Despite of traditional

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radiotherapy technique, these results suggested that PORT had survival benefit to locally advanced NSCLC. However, PORT is still a controversial issue. Benefit of PORT might be clearer, if the results of current radiotherapy technique were analyzed.[2~6]

Several studies published that administration of adjuvant cisplatin-based chemotherapy increase overall survival compared with surgery alone.[7,8] However, when patients received adjuvant chemotherapy combined with radiotherapy, it is not certain whether it leads to increase overall survival. Keller et al.[4] reported that adjuvant chemotherapy (cisplatin+etoposide) combined with radiotherapy did not reduce intrathoracic recurrence nor increase survival for patients with completely resected stage II or IIIA disease. Radiation Therapy Oncology Group (RTOG) conducted phase II trial of adjuvant chemotherapy (paclitaxel+carboplatin) combined with radiotherapy for patient with resected stage II and IIIA NSCLC. By contrast with report of Keller, the result of RTOG trial concluded that adjuvant chemo-radiotherapy improved overall and progression-free survival.[5]

Although it has not been proven in randomized trial using modern treatment techniques, many physicians expect that PORT may improve local control and overall survival for patients with locally advanced stage NSCLC. Thus this retrospective study was performed to evaluate the role of PORT in patients with stage III NSCLC.

Materials and Methods

1. Patients' identification

From 2000 to 2007, 120 patients had PORT after curative operation for NSCLC at our institution. Among these patients, 88 patients with pathologic stage III NSCLC were reviewed in this study. There were 80 patients with stage IIIA, 8 patients with stage IIIB in AJCC 6th staging system.[9] According to AJCC 7th staging system, 5 patients had been reclassified from IIIB to IIIA.[10] At diagnosis, median age was 59 years (range, 31 to 81 years) and median follow-up duration for all patients and survivors was 30 months and 50 months, respectively.

The characteristics of 88 patients are summarized in Tables 1 and 2. Preoperative staging was determined by bronchoscopy, computed tomography (CT) and/or fluorine-18 fluorodeoxyglucose positron emission tomography (PET). Mediastinoscopic LN biopsy was not routine staging process during the study period in our institution. According to mediastinal LN staging using CT and/or PET-CT, 35 patients had preoperative N2 disease. Of them, 21 patients had single station mediastinal LN metastasis. After surgical resection, 83 patients were diagnosed as N2 disease; 56 patients with single station and 27 patients with multiple stations mediastinal LN metastases. Median number of metastatic lymph node was 3.5 (range, 1 to 41).

Table 1. Patient's Characteristics

Variable	No. of patients (%)
Age (yr)	Median 59 (range, 31~81)
Sex	
Male	66 (75)
Female	22 (25)
Performance status	
ECOG1*	80 (91)
ECOG2	8 (9)
Histology	
Squamous cell carcinoma	34 (39)
Adenocarcinoma	49 (56)
Large cell carcinoma	3 (3)
Other	2 (2)

*Eastern Cooperative Oncology Group.

Table 2. Patients' Characteristics-Stage

Variables		Preoperative stage	Postoperative stage	
			AJCC 6th staging system	AJCC 7th staging system
T stage				
T1	T1a	30 (34)	17 (19)	7 (8)
	T1b			10 (11)
T2	T2a	49 (56)	57 (65)	42 (48)
	T2b			10 (11)
T3		3 (3)	6 (7)	14* (16)
T4		6 (7)	8 (9)	5 (6)
N stage				
N0		45 (51)	0 (0)	0 (0)
N1		8 (9)	5 (6)	5 (6)
N2		35 (40)	83 (94)	83 (94)
Stage				
IA		18 (21)		
IB		22 (25)		
IIA		2 (2)		
IIB		7 (8)		
IIIA		33 (37)	80 (91)	85 (96)
IIIB		6 (7)	8 (9)	3 (4)

*3 patients: T4→T3 (multiple tumor nodule in same lobe), 5 patients: T2→T3 (greater than 7 cm in tumor size).

2. Surgery

Only patients who had surgery for curative aim were eligible in this study. Curative operation included pneumonectomy (n=14), bilobectomy (n=14), or lobectomy (n=60) with mediastinal lymph node dissection (MLND; n=73) or multilevel mediastinal lymph node sampling (n=15). Most patients had complete resection whereas four patients had resection margin involved by tumor microscopically.

3. Radiotherapy

Radiotherapy was administered with 6 or 10 MV photons from linear accelerator. Median time to radiotherapy after surgery was 4 weeks (range, 2.5 to 25 weeks). Duration of radiotherapy was median 42 days (range, 26 to 75 days).

Before 2005, PORT was administered using conventional technique in our institution (n=76). For patients treated with conventional technique, radiation target volume was defined as entire mediastinum, ipsilateral hilar region, and bronchial stump, and then boost to tumor bed was done. Initially 23.4~56 Gy (median, 45 Gy) was administered to mediastinum and bronchial stump with parallel opposed AP-PA field arrangement. And then tumor bed and involved nodal area received additional 3.6~23.4 Gy (median, 9 Gy) with lateral or oblique field arrangement to prevent a spinal cord from receiving more than 45 Gy. Most patients did not electively received irradiation of supraclavicular lymph node area, except seven patients. In our institution, 3D-conformal radiotherapy was used since 2005 (n=12). For 3D-conformal therapy, CT simulation with free breathing was done. Radiation target volume and planning were based on CT scan. CTV was defined as involved mediastinal lymph node stations (according to pathologic report), ipsilateral hilar node region, and bronchial stump. Uninvolved mediastinum and supraclavicular area did not receive irradiation. Most patients had boost to tumor bed (range, 5.4 to 18 Gy).

For all patients, median radiation dose was 54 Gy (range, 30.6 to 63 Gy); 59 patients received 54 Gy or more, 29 patients received less than 54 Gy. One patient had incomplete treatment of 30.6 Gy, because of patient's refusal, not treatment-related complications. One patient received 63 Gy, because surgeon notified that there might be residual disease, despite of negative resection margin on pathology report.

4. Chemotherapy

Thirty six patients received chemotherapy; 5 patients with neoadjuvant aim, 17 patients with adjuvant aim, and 14 patients with both aim. Of 19 patients who had neoadjuvant chemotherapy, 18 patients had preoperative N2 stage and 1 patient had preoperative T4N0 stage. Patients with preoperative N2 stage had tendency to receive adjuvant chemotherapy (p-value=0.03). The stations of involved mediastinal lymph node did not affect use of adjuvant chemotherapy (p-value=0.471). Adjuvant chemotherapy was administered sequentially with radiotherapy; 11 patients received chemotherapy before radiation, 20 patients received chemotherapy after radiation. Combination of chemotherapy was variable, such as paclitaxel+cisplatin, paclitaxel+carboplatin, gemcitabine+cisplatin, or navelbine+cisplatin.

5. Adverse effects

Radiation pneumonitis was graded according to RTOG Acute and Late Lung Morbidity Scoring Criteria.[11] Other treatment related toxic effects were assessed by Common Terminology Criteria for Adverse Event CTCAE v 3.0 (CTCAE-v 3.0).

6. Statistical analysis

Survival rates were estimated by Kaplan-Meier method. Survival rates were analyzed on the basis of age, sex, performance status, mediastinal LN metastasis level (single or multiple stations), MLND, total radiation dose and chemotherapy to determine prognostic factors. The univariate analysis was used to evaluate prognostic factors by log-rank test. The multivariate analysis was performed using Cox-proportional hazards model. Loco-regional recurrence and distant metastasis were defined as first recurrent site.

Results

1. Survival

Median survival was 54 months for all patients (range, 26 to 77 months). The 5-year overall survival (OS) rate and disease-free survival (DFS) rate were 46% and 38%, respectively (Fig. 1). Fig. 2 showed the survival rates according to stage. The 5-year OS rate of old stage IIIA, old stage IIIB,

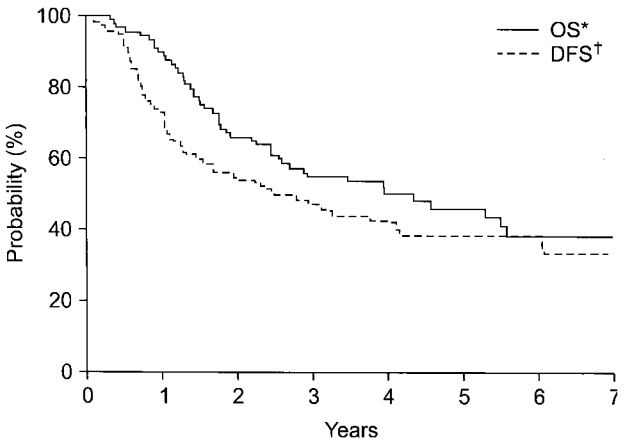

Fig. 1. Overall survival and disease-free survival of all patients. The 5-year overall survival rate and disease-free survival rate were 46% and 38%, respectively. *overall survival, †disease free survival.

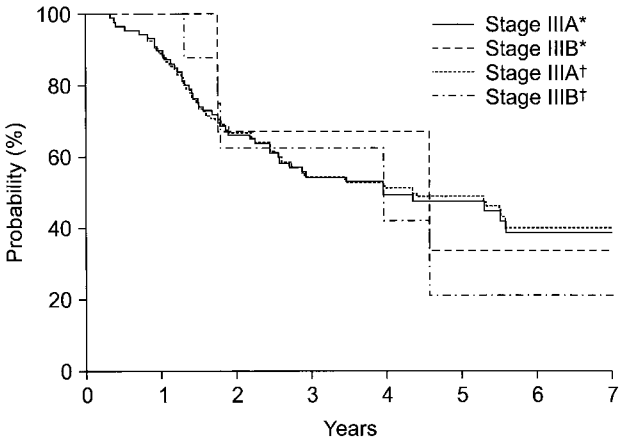

Fig. 2. Overall survival rate according to old and new stage. The 5-year OS rate of old stage IIIA, old stage IIIB, new stage IIIA and new stage IIIB were 48%, 21%, 47%, and 33% respectively. *AJCC 7th staging system, †AJCC 6th staging system.

Table 3. Univariate Analysis of Prognostic Factors

Variable	Overall survival (p-value)	Disease-free survival (p-value)
Age (<60 vs. ≥60)	0.2470	0.2626
Sex (male vs. female)	0.5851	0.2882
Performance status	0.0629	0.5615
Mediastinal lymph node dissection (yes vs. no)	0.9525	0.6771
Total radiation dose (<54 Gy vs. ≥54 Gy)	0.4160	0.3970
Adjuvant chemotherapy	0.8956	0.4575
Mediastinal lymph node metastasis (single vs. multiple stations)	0.1338	0.0014
No. of metastatic lymph node (≤3 vs. ≥4)	0.3813	0.0523

new stage IIIA, and new stage IIIB were 48%, 21%, 47%, and 33% respectively. There was no significant difference in OS and DFS according to MLND, total radiation dose (≥54 Gy) and adjuvant chemotherapy (Table 3). The 5-year DFS rate for patients with single station mediastinal LN metastasis was 50%, which was significantly better than those with multiple stations who had 5-year DFS of 8% (p-value=0.0014) (Fig. 3). However, overall survival rate was not significantly different between single station and multiple stations mediastinal LN metastasis (p-value=0.1338). Table 4 shows the results of multivariate analysis. The number of metastatic lymph node was associated with overall survival (hazard ratio, 1.037; 95% confidence interval, 1.002~1.074; p-value=0.040).

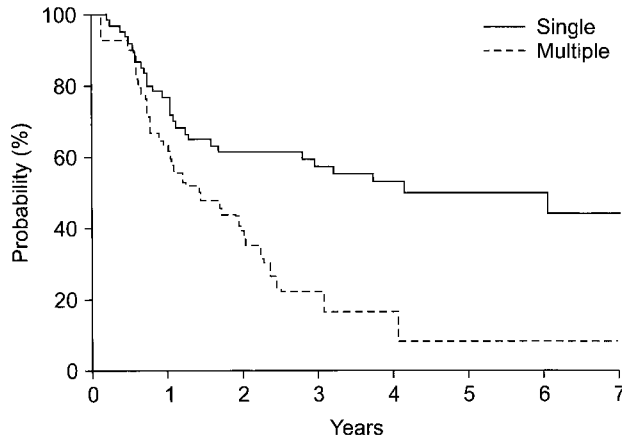

Fig. 3. Disease free survival according to mediastinal lymph node metastasis. The 5-year disease free survival rate for patients with single station mediastinal lymph node metastasis was 50%, which was significantly better than those with multiple stations who had 5-year disease free survival rate of 8% (p-value=0.0014).

2. Recurrence

The 5-year loco-regional recurrence free survival (LRFS) rate and distant metastasis free survival (DMFS) rate were 88% and 48%, respectively. The 5-year of DMFS for patients with single station mediastinal LN metastasis was 59%, which was significantly better than those with multiple stations who had 5-year DMFS of 16% (p-value=0.0044) (Table 5). Neither radiation dose greater than 54 Gy nor adjuvant chemotherapy reduce loco-regional recurrence and distant metastasis (p-value =0.6376, 0.7516 for loco-regional recurrence, and 0.3970,

0.5583 for distant metastasis, respectively) (Table 5).

Fifty-one relapses occurred at following site (as first recurrence); 10 patients in loco-regional area and 41 patients in distant metastasis. Of 10 patients with loco-regional recurrence, 6 patients recurred in radiation field. Among these 6 patients, three patients recurred in bronchial resection site which received radiation of 54 Gy, 54 Gy, and 63 Gy, respectively although resection margin was clear after surgery. Another three patients recurred in mediastinal LN which received radiation of 30.6 Gy, 45 Gy, and 54 Gy, respectively. Distribution of distant metastasis was as follows: 11 patients in lung, 11 patients in bone, 10 patients in brain, 3 patients in kidney, 1 patients in adrenal gland, 3 patients in non-regional lymph node, and 2 patients in liver.

Table 4. Multivariate Analysis of Prognostic Factors

Variable	Hazard ratio (95% CI)	p-value
Age (<60 vs. ≥60)	1.264 (0.691~2.311)	0.447
Sex (male vs. female)	0.858 (0.418~1.764)	0.678
Performance status	1.819 (0.648~5.110)	0.256
Mediastinal lymph node dissection (yes vs. no)	0.825 (0.388~1.756)	0.618
Total radiation dose (<54 Gy vs. ≥54 Gy)	1.187 (0.608~2.318)	0.616
Adjuvant chemotherapy	1.066 (0.542~2.097)	0.853
Mediastinal lymph node metastasis (single vs. multiple stations)	1.328 (0.661~2.668)	0.425
No. of positive lymph node	1.037 (1.002~1.074)	0.040

3. Complication

Table 6 showed radiotherapy-related toxicities. For patients treated with conventional radiation technique, radiation pneumonitis of any grade was seen in 54 patients. However, majority of patients (n=51) experienced minimal or mild symptoms during and after treatment, which did not need any medication. Three patients had radiation pneumonitis of grade 2, and the symptoms were well tolerated with antitussive medication. There were no patients greater than grade 3 radiation pneumonitis. For patients treated with three-dimensional conformal therapy, radiation pneumonitis of any grade was seen in 4 patients, and no patient of grade 3 radiation pneumonitis was seen.

At least 3 months after the treatment, chest radiographic

Table 5. Patterns of Recurrence

Variables	Loco-regional recurrence			Distant metastasis		
	Crude rate	5-yr LRFS* (%)	p-value	Crude rate	5-yr DMFS† (%)	p-value
Radiation dose (GY)			0.6376			0.3970
<54	4/29	84		12/29	59	
≥54	6/59	86		29/59	41	
Adjuvant chemotherapy			0.7516			0.5583
Yes	4/31	86		15/31	45	
No	6/57	86		26/57	51	
Mediastinal lymph node metastasis			0.4891			0.0044
Single	6/56	87		23/57	59	
Multiple	4/27	84		18/27	16	

*loco-regional recurrence free survival, †distant metastasis free survival.

Table 6. Treatment-related Toxicities

	Radiation pneumonitis		Radiation esophagitis	
	Conventional technique	3-Dimensional conformal technique	Conventional technique	3-Dimensional conformal technique
Grade 0	22 (29)	8 (66)	32 (42)	4 (33)
Grade 1	51 (67)	3 (25)	33 (43)	3 (25)
Grade 2	3 (4)	1 (9)	11 (15)	5 (42)
≥Grade 3	0 (0)	0 (0)	0 (0)	0 (0)
Total	76 (100)	12 (100)	76 (100)	12 (100)

Values are presented as number (%).

image was available for 85 patients, and pulmonary fibrosis associated with radiotherapy was seen in 59 patients. Most of patients did not have any symptoms related to pulmonary fibrosis and have minimal radiographic pulmonary fibrosis, but two patients had persistent cough and dyspnea on exertion due to pulmonary fibrosis. These two patients had received radiotherapy using conventional technique. One patient experienced radiographic progression of the pulmonary fibrosis until 1year after completion of treatment, although symptoms were not aggravated.

During radiotherapy, radiation esophagitis of grade 2 was seen in 16 patients. No patients had experienced severe esophagitis of grade 3 or more, which requiring intravenous fluid, tube feeding or total parenteral nutrition.

Discussion and Conclusion

For many years, several studies concluded that PORT could improve local control and might increase survival of patients with completely resected NSCLC, especially in pathologic N2 disease. In our study 5-year OS rate is 46%, which is comparable to the results of other studies.[5,6] Also, the patients achieved 5-year LRFS of 88%. Furthermore, this study showed that PORT was safe and feasible treatment modality for patient with surgical resection for locally advanced NSCLC.

As adjuvant aim, radiotherapy has a role to sterilize micrometastasis, which can cause loco-regional recurrence or distant metastasis. Therefore, many clinicians expect that there may be dose-response relationship in PORT for NSCLC. However, this study did not show that radiation greater than 54 Gy reduced recurrence and improved overall survival. Possible explanation is that most of patients received PORT using conventional technique, which might result inadequate dose distribution. To the best of my knowledge, there were no randomized trials designated to determine the benefit of higher dose of PORT. On the other hand, there were some studies reported that radiation dose escalation has survival benefit in case of curative aim.[12~14] If patients have received precise higher dose of PORT, there would be expected more benefit of PORT for lung cancer. To increase dose of PORT with better sparing residual lung function, conformal radiotherapy technique should be used. Also, to show benefit of higher dose of PORT, further study using modern technique is needed.

In the era of conformal therapy, radiation target definition is critical problem. However, there was lack of consensus of target delineation for PORT of NSCLC. Recently Spoelstra et al.[15] reported that there were interclinician variations of PORT target delineation, upto threefold between some clinicians. After the use of Lung Adjuvant Radiotherapy Trial (ART) study protocol, variations of target contouring were decreased. Because target delineation of PORT for lung cancer has largely variation in each institution, consensus of guidelines for target contouring should be needed.

In our study, 41 (46%) patients had distant metastasis as first site of failure and adjuvant chemotherapy did not reduce distant metastasis. Because distant failure is common failure pattern of completely resected locally advanced NSCLC, appropriate postoperative combined modality treatment is needed. Although several studies concluded that postoperative chemotherapy improve survival, postoperative chemotherapy combined with radiotherapy still remains controversial. Keller et al.[4] reported that postoperative chemotherapy combined with radiotherapy for completely resected stage II or IIIA NSCLC did not improve survival. However, RTOG 9705 phase II trial concluded that combined chemo-radiotherapy improve overall and progression-free survival.[4,5] Further randomized trial using new chemotherapeutic agent combined with radiotherapy is needed to determine role of postoperative chemoradiation.

In current AJCC staging system, number or levels of mediastinal LN metastasis are not considered as nodal stage, so stage III NSCLC is heterogenous presentation such as bulky tumor and/or single or multiple stations mediastinal LN metastasis.[9,10] Several studies showed a significantly better survival of patients with single station mediastinal LN metastasis[16~18] and our results also showed that number or level of metastatic lymph node were prognostic indicator of survival rate.

Patients with multiple stations mediastinal lymph node metastasis had tendency to develop distant metastasis. However, loco-regional recurrence was not different between single and multiple stations. Therefore, reduction of DFS in multiple stations mediastinal lymph node metastasis was resulted from distant metastasis. Several studies showed that PORT can reduce local recurrence and improve overall survival or disease free survival for patients with multiple station mediastinal

lymph node metastasis.[19,20] Our study also showed that PORT could achieve excellent local control for patients with multiple station mediastinal lymph node metastasis, who had 5-year LRFS of 84%. Therefore, to increase survival, combined modality treatment such as adjuvant chemotherapy are needed in addition to PORT.

In some institutions including our institution, patients with resectable clinical stage III NSCLC receive curative operation. Because mediastinal lymph node biopsy using EBUS or mediastinoscopy was not routine staging procedure during study period, approximately 50 patients had experienced upstage of nodal stage. When considering operability of NSCLC, accurate staging procedure should be essential, especially status of mediastinal lymph node, although standard treatment is definitive concurrent chemo-radiotherapy at present time. Because criteria for "resectability" are discrepancy according to each of institution and/or surgeons, further definition of resectability for stage III NSCLC is required.

This study has limitations due to retrospective analysis. First, selection of patients who received higher radiation dose or adjuvant chemotherapy had bias. Second, majority of patients had irradiation using conventional technique. These limitation might cause uncertainty of anlysis of prognostic factors.

Our retrospective data showed that PORT for locally advanced stage NSCLC was safe and feasible treatment and could improve loco-regional control, although consensus of target volume definition of PORT for lung cancer is not yet defined. Also, our study showed that number of metastatic lymph node and stations of mediastinal lymph node metastasis were analyzed as prognostic factors. Furthermore, efforts are needed to reduce distant metastasis, which is major failure pattern of advanced stage NSCLC.

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국문초록

근치적 절제술 후 병기3의 비소세포성 폐암에서 수술 후 방사선 치료의 역할

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목 적: 본 연구는 근치적 절제술 후 병기 3의 비소세포성 폐암에서 방사선 치료의 결과와 이에 영향을 주는 예후 인자를 분석해 보고자 하였다.

대상 및 방법: 2000년부터 2007년까지 88명의 환자가 비소세포성 폐암으로 근치적 절제술 후 병기3기로 진단받았고, 수술 후 방사선 치료를 시행 받았다. 이중 80명의 환자가 병기 3A였으며, 8명의 환자가 병기 3B였다. 83명의 환자는 림프절 병기 N2였으며 이들 중 56명은 단일 부위(single-station)의 종격동 림프절 전이였다. 76명은 2차원, 12명은 3차원 입체조형치료로 수술 후 방사선 치료를 받았다. 총 선량은 30.6에서 63 Gy 였으며 중앙값은 54 Gy 였다. 36명의 환자가 항암치료를 시행받았다.

결 과: 생존기간은 26~77개월이었다(중앙값, 54개월). 5년 생존율 및 무병생존율은 각각 45%, 38%였다. 전이된 림프절개수가 생존율에 영향을 미치는 인자로 분석되었다(hazard ratio, 1.037; p=0.040). 5년 국소제어율 및 원격전이제어율은 각각 88%, 48%였다. 종격동 림프절 부위의 전이가 단일 부위(single-station)인 경우가 무병생존율(p=0.0014)과 원격전이제어율(p=0.0044)을 의미 있게 증가시켰다. 총 51명의 재발이 발생하였으며 국소구역 재발은 10명, 원격전이는 41명이었다. 10명의 국소구역 재발 중에 6명은 방사선 치료 범위 내에서 재발하였다. Radiation Therapy Oncology Group (RTOG) 2도의 방사선 폐렴은 3명의 환자에서 보였으며 증상은 진해성 약제만으로도 조절이 잘 되었다. CTCAE 2도의 방사선 식도염은 11명의 환자에서 관찰되었다. 수술 후 방사선 치료로 인한 3도 이상의 심각한 부작용은 관찰되지 않았다.

결 론: 본 연구에서 국소 진행 비소세포성 폐암에서 근치적 수술 후 방사선 치료는 안전하고 임상적으로 적용 가능한 치료법이며, 국소제어를 증가시킬 수 있는 것으로 분석되었다. 예후인자로는 전이된 림프절 개수와 종격동 림프절 부위가 생존율에 영향을 미치는 것으로 분석되었다. 또한 국소 진행 비소세포성 폐암의 대부분의 재발 형태인 원격 전이를 감소시키기 위한 추가적인 노력이 필요할 것으로 생각된다.

핵심용어: 수술 후 방사선 치료, 국소 진행 비소세포폐암