A Predictive Model for Lung Fibrosis after Irradiation

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- ABSTRACT -

A Predictive Model for Lung Fibrosis after Irradiation

Purpose: Radiation in amounts over the threshold dose produces lung fibrosis, resulting in reduction of lung function. Lung fibrosis volume can be predicted from a dose volume histogram (DVH), and the long-term change in lung function after radiation therapy can be correlated with lung fibrosis volume. The purpose of this study was to create a predictive model for lung fibrosis using DVH.

Methods and Materials: From January 2003 to January 2007, we enrolled 98 patients with non-small cell lung carcinoma who received postoperative radiation therapy. We excluded patients with recurrent cancer and those treated with chemotherapy. Forty-eight patients were enrolled for fibrosis volume measurement, and all patients were treated with 3D treatment planning. The V5-V50 percentages at 5 Gy intervals and mean lung dose (MLD) were calculated from DVH, and lung fibrosis volumes were measured from the most recent follow-up CT scans taken at least 6 months after completion of radiation therapy. Simple linear regression analysis was performed to estimate the association between the V5-V50 statistics and fibrosis volume.

Result: Fibrosis volume was correlated significantly with DVH between 30 Gy and 50 Gy as assessed by simple linear regression analysis. The correlation coefficients (r values) for V30, V35, V40, V45 and V50 were respectively 0.733, 0.741, 0.717, 0.775 and 0.710 ($p<0.0001$). Below 25 Gy, the correlation was weak and less significant. Fibrosis volume (ml) was found to fit with V30, V40 and V50 according to the following rules: 0.4 x (V30 –

80); 0.5 x (V40 – 70); and 0.9 x (V50 – 10). MLD correlated with fibrosis volume according to the Boltzmann model. The coefficient of determination (r^2 value) was 0.617 for the equation $Vf = 211.5 - 218.2/(1+ e^{(MLD-24.5)/5.34})$. Patient factors such as sex, age, tobacco use, comorbid lung disease, tumor site, pre-radiation forced expiratory volume in one second(FEV1) or symptomatic radiation pneumonitis were not significantly correlated with fibrosis volume by the t-test. Although the association between fibrosis volume and reduction of lung function did not achieve statistical significance, there was a tendency toward a decrease in function with increasing fibrosis.

Conclusion: Lung fibrosis volume after radiation therapy is predictable using V30-V50 measurements from DVH or MLD.

Key words : lung cancer, lung fibrosis, radiation-induced fibrosis, radiotherapy

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I. Introduction

Radiation therapy (RT) is used for patients with lung cancer in order to improve survival and relieve symptoms (Perez *et al.*, 1986). However, irradiation of the thorax can lead to radiation-induced lung damage in patients, many of whom present with compromised lung function. Radiation pneumonitis and radiation pulmonary fibrosis are well known complications of radiation therapy for lung cancer that can have important clinical consequences. They limit the therapeutic ratio and compromise the life quality of long-term survivors.

Pulmonary fibrosis is the clinical syndrome in which permanent scarring of lung tissue occurs within 6 to 12 months in response to initial radiation therapy and leads to permanent non-oxygenated shunting. It decreases pulmonary function and induces various symptoms including varying degrees of dyspnea, orthopnea, cyanosis, respiratory failure and *cor pulmonale* (McDonald *et al.*, 1995; Stone *et al.*, 1956).

Surprisingly, clinical studies evaluating the correlation between pulmonary function and radiation-induced pulmonary fibrosis have been rare. Generally, the incidence and severity of pulmonary fibrosis depends on several clinical factors including total radiation dose, dose per fraction, dose rate, treatment period, irradiated lung volume, and combination of radiation with chemotherapy (Mah *et al.*, 1994; McDonald *et al.*, 1989; McDonald *et al.*, 1995; Yan *et al.*, 1991).

In lung surgery, pulmonary function parameters such as FEV1, FVC and carbon monoxide diffusion capacity (DLCO) are widely used as predictors of post-operative residual lung function (Beccaria *et al*., 2001; Giordano *et al*., 1997; Markos *et al*., 1989).

Similarly, in this study we evaluated the correlation of pulmonary fibrosis, pulmonary function and dose volume histogram(DVH). We also aimed to predict the degree of reduction in pulmonary function after lung irradiation by evaluating the correlation between the volume of radiation fibrosis and DVH.

The hypothesis of this study was, (1) The long-term change in lung function after RT is correlated with the lung fibrosis volume. (2) The lung fibrosis volume is correlated with the lung volume receiving the threshold radiation dose. (3) Therefore, the long-term change in lung function after RT can be predicted by the volume of threshold radiation dose. We have attempted to establish a predictive model of long-term change in lung function after RT by analyzing lung dose distribution. In current practice almost all patients with NSCLC are treated with chemoradiation, so although more complete study is needed that includes the factor of chemotherapy, we here present an analysis of the effects of radiation alone in order to make these data available to the medical community immediately.

Ⅱ. Materials and Methods

A. Patient eligibility

Between January 2003 and January 2007, 98 patients with NSCLC received postoperative RT at Ajou University Hospital. We excluded patients with recurrent cancer and those had received chemotherapy. Forty-eight patients were enrolled for fibrosis volume measurement, and all patients were treated with 3D treatment planning. The average age was 63 (range 24-78), with 41 men and 7 women. Thirty-nine patients had smoked cigarettes prior to treatment. Thirty-five patients were treated with lobectomy and 13 with pneumonectomy, and thirteen patients had comorbid lung disease such as pulmonary tuberculosis and/or emphysema.

Irradiation was performed with 10 to 15MV photon beams, with an average total prescribed radiation dose of 50.4 Gy (range 44-65 Gy) given in fractions of 1.8-2 Gy per day. Radiation therapy was stated at a median time of five weeks after operation. Thirty-seven patients took the pre-RT pulmonary function test, and 29 patients were tested for post-RT pulmonary function.

Table 1. Patient characteristics

	Distribution
Age (Y)	
Range (median)	24-78 (63)
Sex (n)	
M/F	41/7
Stage (n)	
I/II/III	3/16/29
Tumor site (n)	
RUL/RML/RLL	8/3/6
LUL/LLL	11/15
RM,RLL/RU,RML	4/1
Histologic feature (n)	
Squamous cell carcinoma	31
Adenocarcinoma	12
Others	5
Tobacco use (n)	
Y/N	39/9
Operation type (n)	
Lobectomy/Pneumonectomy	35/13
Comorbid lung disease (n)	
Y/N	13/35
RT dose (Gy)	
Range (median)	44-65(50.4)
Pre-RT PFT (n)	
Y/N	37/11
Post-RT PFT (n)	
Y/N	29/19

Abbreviations: RT = radiotherapy; PFT = pulmonary function test; RUL = Right upper lobe; RML = Right middle lobe; RLL = Right lower lobe

B. Fibrosis measurement / three-dimensional treatment planning

Lung fibrosis volumes were measured from last follow-up CT scans taken six months after the completion of RT, because the change in fibrosis volume was small after that time. The change in fibrosis volume was measured in 12 patients that underwent several follow-up CT scans after RT (Table 2). Volume measurements were performed at the same window setting for the CT scan for all patients (window width 1400, level -500) (Fig. 1). The measurement of fibrosis and the analysis of data were taken separately for each side of the lung. The volume of fibrosis ≥grade 1 was measured according to the Radiation Therapy Oncology Group (RTOG)/European Organization for the Research and Treatment of Cancer (EORTC) late radiation morbidity scoring system: Grade 0, no abnormal radiographic density; Grade 1, slight radiographic appearances; Grade 2, patchy radiographic appearances; Grade 3, severe dense radiographic change (Cox *et al.*, 1995).

All patients were treated with 3D treatment planning during the entire RT period. CT scans including the entire lung volume were obtained from the patients while breathing freely. The lung DVH was obtained from 3D treatment planning, and the V5-V50 statistics at 5 Gy intervals were calculated from DVH. The V-dose was defined as the percent of lung volume that received at least the specified dose.

Table 2. The change of fibrosis volume

Duration after RT	Vf / last Vf (mean±SD)
2-4months	82.1 ± 45.1
6-7months	98.3 ± 8.1
11-13months	99.4 ± 3.0
≥15months	100

Abbreviations: RT = radiotherapy; Vf = fibrosis volume; SD = standard deviation

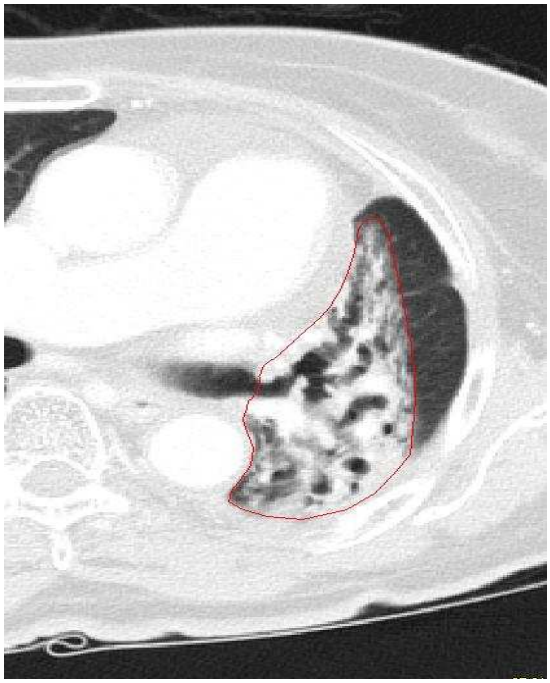

Figure 1. Delineation of fibrosis volume

C. Statistical analysis

Simple and multiple linear regression analyses were performed to estimate the associations between dosimetric parameters and fibrosis volume. Patient variables including age, sex, disease site, smoking status, comorbid lung disease, dose fraction, treatment period, pathology and pre-RT FEV1 were analyzed by t-test to investigate their association with fibrosis volume. In patients with pre-RT and post-RT PFT, analysis was performed to estimate the association between fibrosis volume and reduction in pulmonary function. Analysis was carried out using SPSS 12 (Superior Performing Software System) and Origin 6.0.

Ⅲ. Results

A. DVH and fibrosis volume

The DVH parameters were significantly correlated with fibrosis volume as assessed by simple linear regression analysis. Comparatively, V30-V50 showed the strongest correlation, with the correlation coefficients for V30, V35, V40, V45 and V50 equal to 0.733, 0.741, 0.717, 0.770, and 0.710, respectively ($p<0.0001$) (Fig 2). Below V25, the correlation was less significant. The correlation coefficients for V5, V20 and V25 were -0.083, 0.535 and 0.644, respectively. Fibrosis volume (ml) was found to fit with DVH according to the following rules: 0.4 x (V30 – 80), 0.5 x (V40 – 70) and 0.9 x (V50 – 10) (Table 3).

B. MLD and fibrosis volume

The mean lung dose (MLD) was also correlated with the fibrosis volume by simple linear regression analysis, with a correlation coefficient of 0.772 ($p<0.0001$) (Fig. 3a). The MLD was also correlated with the fibrosis volume by the Boltzmann model (Fig. 3b). The coefficient of determination (r^2 value) was 0.617 and fit the following equation:

$$Vf = 211.5 - 218.2/(1+ e^{(MLD-24.5)/5.34}) \quad \text{(Eq1)}$$

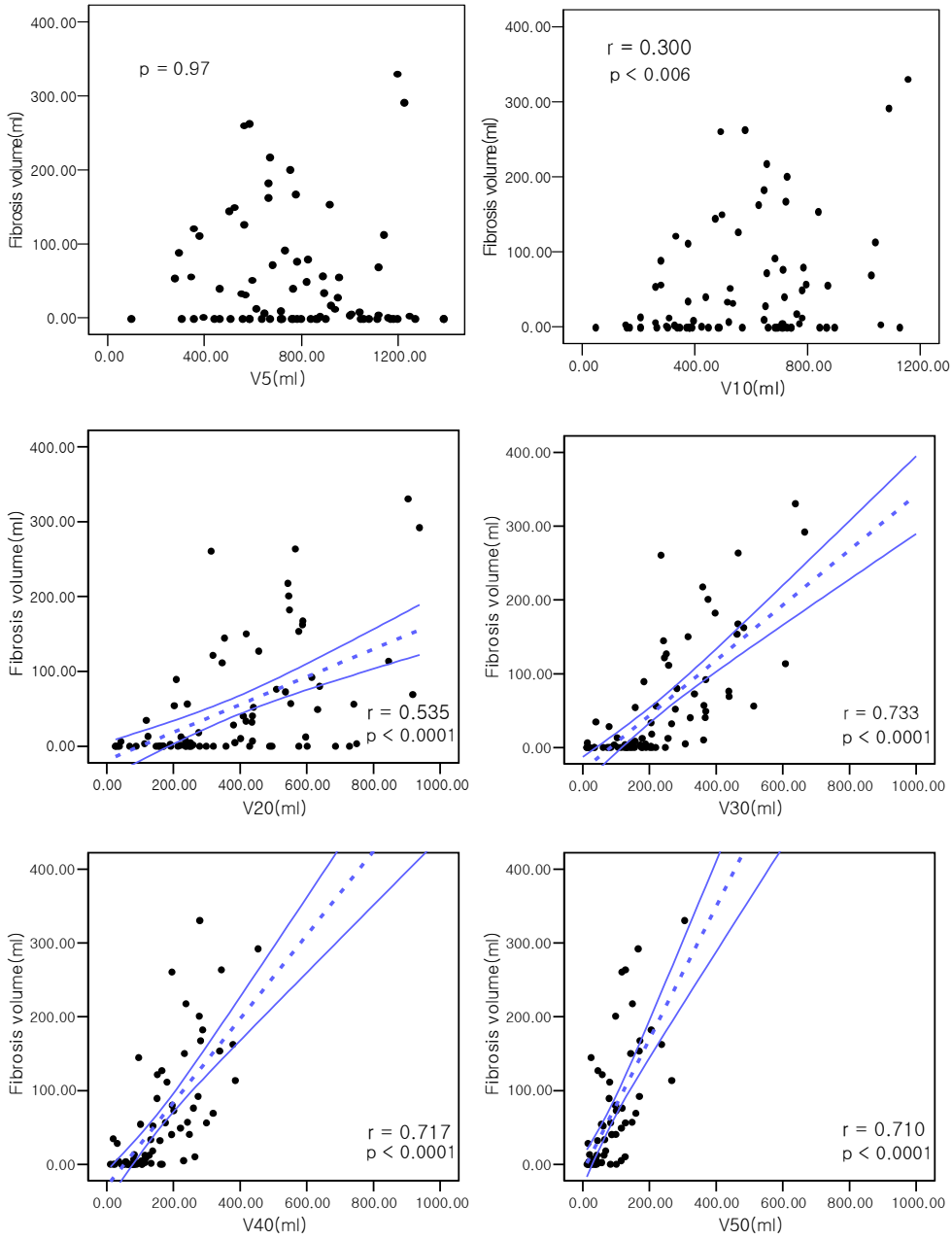

Figure 2. Correlation between fibrosis volume and DVH. Linear regression lines are dotted. Dark lines indicate the estimated upper and lower limits of the 95% confidence interval.

A. B.

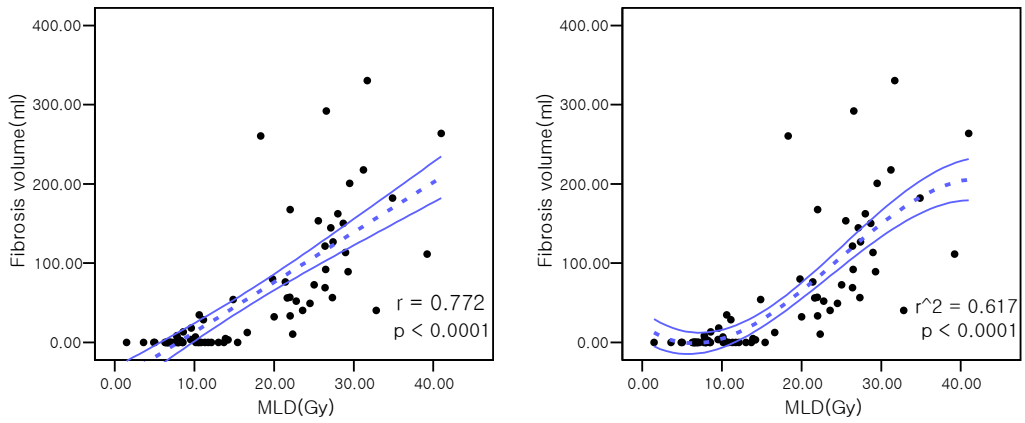

Figure3. Correlation between fibrosis volume and mean lung dose(MLD). Linear regression lines (A) and sigmoidal fitting (B) are dotted. Dark lines indicate the estimated upper and lower limits of the 95% confidence interval.

Table 3. Correlation between fibrosis volume and DVH

	Fibrosis Volume (Vf)	r-value	p-value
V5		-0.005	0.97
V10		0.300	0.006
V15		0.484	<0.0001
V20	Vf = -20 + 0.19 V20	0.535	<0.0001
V25	Vf = -27 + 0.28 V25	0.644	<0.0001
V30	Vf = -30 + 0.37 V30	0.733	<0.0001
V35	Vf = -34 + 0.47 V35	0.741	<0.0001
V40	Vf = -34 + 0.47 V40	0.717	<0.0001
V45	Vf = -26 + 0.69 V45	0.770	<0.0001
V50	Vf = -9 + 0.89 V50	0.710	<0.0001
MLD	$Vf = 211.5 - 218.2/(1+ e^{(MLD-24.5)/5.34})$	0.617 (r^2 value)	<0.0001

Abbreviations: Vf = fibrosis volume; MLD = mean lung dose

C. Patient factors associated with fibrosis volume

The parameter Vf/V30 was used to compare each variable. Although the total dose, pre-RT FEV1 and symptomatic radiation pneumonitis (RP) all showed some trends, no patient factors achieved any significant correlation with fibrosis volume by t-test. The mean Vf/V30 values for each variable are given in Table 4.

D. Fibrosis volume and reduction of pulmonary function

In twenty-nine patients with pre-operative and post-RT PFT, the correlation between Vf and the reduction in pulmonary function was analyzed by simple linear regression. Pulmonary function parameters such as FEV1, forced vital capacity (FVC) and FEV1/FVC were analyzed for association. Because the types and sites of operations were variable, a correction was performed by following a simple segment counting equation: predicted postoperative FEV1 = preoperative FEV1 x (1 – segment of lung to be resected/19) (Bolliger *et al.*, 2002). The correlation coefficient for the reduction of FEV1 was -0.521 (p=0.004) (Fig. 4). Although there was not a significant correlation, the analysis revealed a slight tendency toward reduction. The parameters FVC and FEV1/FVC failed to show any association.

Table 4. Patient factors associated with fibrosis volume

	Fibrosis/V30 (mean)	p-value
Age		
<70/≥70	0.16/0.21	0.319
Smoking		
non/<60py/≥60py	0.27/0.17/0.10	0.153
Radiation pneumonia Hx		
Y/N	0.24/0.15	0.161
Comorbid lung disease		
Y/N	0.16/0.18	0.856
Site		
upper/lower	0.23/0.19	0.466
Total dose (Gy)		
≤50.4/≥54	0.15/0.22	0.240
Pre-RT FEV1 (%)		
<60/≥60	0.20/0.09	0.667

Abbreviations: RT = radiotherapy; FEV1 = forced expiratory volume at the first second

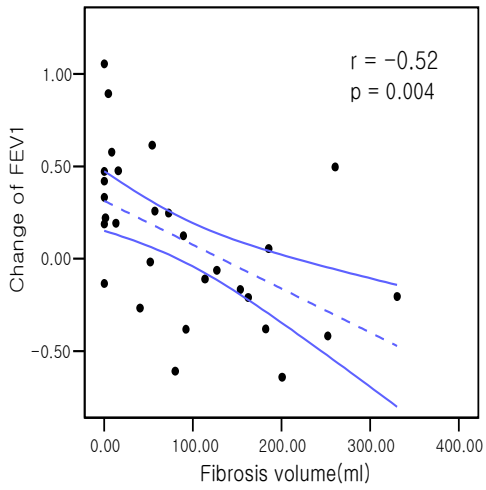

Figure 4. Correlation between fibrosis volume and change in FEV1. The linear fitting lines are dotted. Dark lines indicate the estimated upper and lower limits of the 95% confidence interval.: FEV1 = forced expiratory volume at the first second

Ⅳ. Discussion

Past studies have mostly attempted to analyze correlations between RP and various predictive factors. Generally age, smoking, tumor site, chemotherapy exposure, performance status, pre-RT PFT, total radiation dose, fraction size, and number field size have been implicated as important in RT-induced RP. V5, V20, V30, Veff, mean lung dose (MLD), and normal tissue complication probability (NTCP) have been identified as the best predictors of RP (Hernando *et al.*, 2001; Kong *et al.*, 2006; Kwa *et al.*, 1998). Studies of radiation fibrosis, however, are rare. Radiation fibrosis can induce long-term reduction of pulmonary function, especially in postoperative NSCLC patients for whom long-term survival is expected, the reduction of lung function by pulmonary fibrosis is more important than RP as an indicator of quality of life (QOL).

Pulmonary fibrosis differs from RP in histologic presentation, radiographic appearance, clinical symptoms, and molecular regulation. Lung fibrosis consists of sclerosis of the alveolar wall, endothelial damage, loss of capillaries, and encroachment by fibrotic tissue into normal alveolar spaces (McDonald *et al*., 1995; Rosiello and Merrill, 1990). Fibrosis after irradiation is a consequence of the local release of cytokines and is limited to the area of irradiation (Abratt and Morgan, 2002).

On the basis of the results of several studies, it seems that although the predictors of symptomatic fibrosis (Grade≥2) are similar to those of RP, they are less useful than RP for risk prediction (Kong *et al*., 2006). It is known that total dose, fractionation, dose rate and lung volume have effects on radiation fibrosis (McDonald *et al.*, 1989; McDonald *et al*., 1995; Yan *et al*., 1991; Lingos *et al*., 1991). We analyzed the correlation between radiation

fibrosis and DVH in order to extract a predictive model. Clinical symptoms such as dyspnea, cough, and fever were not evaluated in these studies.

Usually, permanent changes resulting from radiation fibrosis evolve over 6-24 months and remain stable after two years. We used the most recent follow-up CT scans taken six months after completion of RT as our end point, because in our research fibrosis volume was found to be little changed after six months (Table 2). The delineation of fibrosis was performed by a single researcher to eliminate interobserver variability. Although residual normal lung volume must be measured in order to analyze the reduction of lung function with pulmonary fibrosis, the volume was variable because planning CT was performed during free breathing. We assumed that the fibrosis volume is constant and on that basis we tried to calculate residual normal lung volume by measuring the pulmonary fibrosis.

A report from the M.D. Anderson Cancer Center classified fibrosis density into grades 1-3 (Rosen *et al.*, 2001). However, we did not employ this classification system. Measuring fibrosis volumes using CT images was subjective, and the boundaries of areas of fibrosis density were vague. Morgan *et al*. suggested that sporadic radiation pneumonitis is mediated through the induction and release of tissue cytokines (Morgan and Breit, 1995). However, in our study, out-field fibrosis was almost never found in follow-up CT scans.

We excluded patients with recurrent disease or who were treated with chemotherapy during their follow-up period in order to reduce tumor effects and bias due to chemotherapy. To estimate the effect of radiation alone, we selected those patients who were treated by radiation alone after their operations. However, in current practice few patients are treated in this manner. Most patients receive radiation combined with chemotherapy, with the exception of patients limited by old age or comorbid disease. Because the cohort of patients

was limited, we started our analysis even though we knew that the study was not robust in numbers.

In the study from the M.D. Anderson cancer center, radiographic lung fibrosis in SCLC following RT increased with an increasing dose greater than the threshold of 30-35 Gy (Rosen *et al*., 2001). The result of Geara *et al.* similarly established a threshold dose of 30-40 Gy (Geara *et al*., 1998). We aimed to also estimate the threshold dose and to determine the predictive equation associated with measurement of the radiation-induced fibrosis volume. Our study showed that the fibrosis volume correlated significantly with DVH between V30 and V50. The V45 statistic had the most significant correlation coefficient ($r=0.770$, $p<0.0001$), but the value of the coefficient was similar throughout the range between V30 and V50. Equations relating DVH to fibrosis volume were extracted by linear fitting (Table 3). The fibrosis volumes fit with DVH according to the following equations: 0.4 x (V30 – 80); 0.5 x (V40 – 70); and 0.9 x (V50 – 10). Sigmoidal fitting proved to be less correlated than linear fitting.

A recent study from the University of Michigan reported that symptomatic fibrosis correlates with V20, MLD and normal tissue complication probability (NTCP) *(Kong et al*., 2006). In our study, V20 was less correlated ($r=0.535$, $p<0.0001$) than V30-V50. However, in general MLD was shown to be significantly correlated with fibrosis volume, as in the University of Michigan study. Although they found sigmoidal fitting ($r^2=0.617$, $p<0.0001$) to be more significantly correlated than linear fitting($r=0.772$, $p<0.0001$), the difference was small. Their equation relating MLD and fibrosis volume by sigmoidal fitting was: $Vf = 211.5 - 218.2/(1+ e^{(MLD-24.5)/5.34})$.

In a study by Geara and colleagues, total dose and fractionation schedule were identified

as significant and independent determinants of radiographic lung fibrosis (Geara *et al*., 1998). Kong *et al*. demonstrated that lung volume and FVC may be associated with symptomatic fibrosis (Kong *et al*., 2006). In our analysis, patient factors such as age, smoking status, RP history, comorbid lung disease, tumor site, total radiation dose and pre-RT lung function were analyzed by t-test (Table 4). Although pre-RT FEV1, symptomatic RP history, and total dose showed some trends, we did not find any statistically significant patient factors associated with fibrosis volume. We believe that this lack of statistical power is due to our low patient numbers, however.

Many studies have attempted to predict radiation-induced reduction in pulmonary function, two of which have investigated the correlation between changes in pulmonary function and the irradiated volume of the lung (Choi *et al*., 1990; Choi and Kanarek, 1994; Curran *et al*., 1992). Although these studies discovered some correlation, the entire 3D radiation dose distribution was not obtained. Generally, pulmonary function tests are the most objective evaluation of late functional radiation-induced pulmonary toxicity. Reductions in DLCO reflect damage at the capillary-alveolar level, and FEV1 indicates bronchial obstruction after RT. FVC and total lung capacity (TLC) are an index of lung compliance. A decrease in lung compliance after irradiation results in a decrease in FVC and TLC and subsequently also in FEV1 (Abratt and Morgan, 2002).

In some studies, the largest decrease in lung function after radiotherapy has been observed with DLCO (Abratt and Willcox, 1995; Boersma *et al*., 1995; Mattson *et al*., 1987). Abratt and Willcox reported decreases in DLCO, FVC, TLC and FEV1 at six months in patients without progressive lung cancer (-14, -7, -6 and -2%, respectively) (Abratt and Willcox, 1995). In a study by Jaeger and co-workers, post-RT FEV1 decreased an average of

6%, and reductions in DLCO averaged 14% (De Jaeger *et al*., 2003). A decrease of 20% in FVC and FEV1 was observed in patients with lymphoma following thorax irradiation by Boersma and colleagues (Boersma *et al*., 1995). Marks and co-workers reported that pre-radiation DLCO and CT-based NTCP were predictive for the development of RT-induced symptoms (Marks *et al*., 1997). In our study, although we did not achieve statistical significance, we found a trend toward correlation between fibrosis volume and reduction of FEV1. Post-operation/Pre-RT PFT was unstable due to the shortness of convalescence after operation. Conversely, the lung function after irradiation increased in most of our patients. We postulate that patients recover their lung function following operation after enough convalescence. We analyzed this result in terms of pre-operative PFT corrected by simple segment counting as follows: predicted postoperative FEV1 = preoperative FEV1 x (1 – segment of lung to be resected/19) (Bolliger *et al*., 2002). Although the accuracy was low, we could predict the postoperative FEV1 of each operation type with a moderate correlation ($r=-0.52$, $p=0.004$). There was no association with FVC or FVC/FEV1. Because very few patients took the DLCO test at our institution, we could not address DLCO.

The results of this study demonstrate that fibrosis volume following RT is correlated significantly with dosimetric parameters such as V30-V50 and MLD. Although the association between fibrosis volume and reduction in lung function is moderate, there is a tendency toward decreased function. We suggest that V30-V50 and MLD can be used as predictor of radiation-induced fibrosis and that the equations above can be valuable in predicting lung fibrosis volume from postoperative RT. Additional studies focused on DLCO, regional perfusion and biological factors are needed in order to predict reduction of lung function after RT with even better accuracy.

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- 국문요약 -

폐의 방사선치료 후 폐섬유화 용적 예측 모델

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연구목적: 폐의 방사선치료 후 발생하는 폐섬유화는 폐기능의 감소를 초래하지만 그 정도를 예측할수 있는 방법은 알려져 있지 않다. 본 연구자등은 방사선치료 계획상의 방사선량 용적(dose volume histogram)과 폐섬유화 용적의 상관관계를 규명하여 폐섬유화 용적 예측 모델을 개발하고자 하였다.

대상 및 방법: 2003 년 1 월부터 2007 년 1 월까지 폐암으로 완전절제 수술을 시행받고, 수술 후에 3 차원 입체조형 치료계획을 통해 수술 후 방사선치료를 시행받은 98 명의 환자 중에서 항암화학약물요법이 시행되거나 재발한 환자를 제외하고, 방사선치료 종료 후 6 개월 이후의 컴퓨터단층촬영 사진이 있어 폐섬유화 용적의 측정이 가능하였던 48 명을 대상으로 하였다. 방사선치료 계획상의 방사선량 용적에서 5, 10, 15, 20, 25, 30, 35, 40, 45, 50 Gy 용적을 구하였으며, 이와 컴퓨터단층촬영사진에서 측정한 폐 섬유화 용적과 비교하여 상관관계를 구하였다.

결과: 단순회귀분석을 시행한 결과 폐섬유화 용적(Vf)은 V30 부터 V50 까지의 방사선량 용적과 비교적 강한 선형 상관관계를 보여주었고, 이는 통계적으로도 유의하였다. 상관계수(r-value)은 V30, V35, V40, V45, V50 이 각각 0.733, 0.741, 0.717, 0.710 이었으며, V25 이하에서는 상관성을 찾을 수 없었다. 이를 식으로 나타내면 Vf = 0.4 x (V30 – 80), 0.5 x (V40 – 70), 0.9 x (V50 – 10)이었다. 중앙폐선량(mean lung dose)은 폐섬유화 용적과 S 자형 상관관계를 보여주었는데, 결정계수(r^2-value)는 0.617 이었고 볼츠만 모델에 의해 $Vf = 211.5 - 218.2/(1+ e^{(MLD-24.5)/5.34})$ 의 식을 도출할 수 있었다. 그외 폐섬유화 용적에 영향을 미치는 요인은 발견할 수 없었다. 방사선치료후 폐기능의 감소는 폐섬유화 용적과 선형 상관관계를 보여 주었으나 그 정도는 크지 않았다.

결론: V30 부터 V50 까지의 방사선량 용적과 중앙폐선량은 폐섬유화 용적과 비교적 규칙적인 상관관계를 보여주었는데, 이를 이용하여 방사선 치료후 발생할 수 있는 폐섬유화를 치료계획단계에서 보다 효과적으로 예측할 수 있을것으로 기대한다.

핵심어: 폐암, 폐섬유화, 방사선치료