Original Article

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Evaluation of Changes in Pulmonary Function in Concurrent Chemoradiation in Non Small Cell Lung Cancer

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Abstract

Aim: To evaluate the changes in pulmonary function with concurrent chemoradiation. *Materials and Methods:* We analyzed 60 patients who had received ≥60 Gy radiotherapy, chemotherapy for primary NSCLC who had undergone pulmonary function tests (PFTs) before and within one year after treatment. Before every cycle of chemotherapy, pulmonary function tests were done. Post-radiation PFT values (percentage of predicted) were evaluated amongst individual patients compared to the same patient's pre-radiation value at the following time intervals: 0 to 4 months, 5 to 8 months, and 9 to 12 months. *Results*: Lung diffusing capacity for carbon monoxide (DLCO) is reduced in the majority of patients along the 3 time periods after radiation, whereas the forced expiratory volume in 1 second per unit of vital capacity (FEV1/VC) showed an increase and decrease after radiation in a similar percentage of patients. There were baseline differences (stage, RT dose, concurrent chemotherapy) among the radiation technology groups. On multivariate analysis, the following features were associated with larger post treatment declines in DLCO: pretreatment DLCO, gross tumor volume (GTV), Only pretreatment DLCO was associated with larger posttreatment declines in FEV1/VC. *Conclusions*: DLCO is reduced in the majority of the patients after chemoradiation.

Keywords: Radiotherapy; Chemotherapy; pulmonary function tests (PFTs).

Introduction

Lung cancer accounts for nearly 13% of all new cancers diagnosed in both sexs combined. Lung cancer is the most commonly diagnosed malignancy in developed countries after prostate and breast malignancies. It is the leading cause of death in men and it surpassed breast cancer in women in early 1990's. In developing countries, the death rates continue to accelerate. It appears that squamous cell carcinoma and small cell carcinoma have distinct dose response relation with increasing tobacco consumption. However, adenocarcinoma appears to be increasing especially in women, despite the fact it does not have any relationship with smoking. Prognosis is poor for patients with Carcinoma lung, in spite of advances in surgical, Radio-therapeutic technique and chemotherapy regimens. Surgery and Radiotherapy have been used independently to obtain loco-regional control of the primary tumor and regional lymphatic drainage. Until recently chemotherapy has been used in an attempt to prolong symptoms free life, in patients with metastatic disease.

In the last 20 years however combined modality therapies have become much more prevalent. But at the same time synergistic activity and shortening of treatment duration. But at the same time it is having disadvantages like increased toxicity and treatment breaks due to complications arise by combining chemotherapy and radiotherapy. Pulmonary function tests are important predictors of patients ability to undergo surgical resection and radical radiotherapy. As patients with lung cancer present with compromised lung function, the effects of chemo radiation on lung carcinoma results in removal of both air passages and parenchymal lung tissue.

A majority of the lung cancer patients present with compromised lung function because of smoking which leads to COPD. Ventilatory function can be evaluated by FEVI, vital capacity (FVC) and Maximum breathing capacity (MBC) by using spirometer. The

pulmonary volumes measured by spirometer can be shown by graphical method the changes of volume of gases under different conditions known as" spirogram". Gas exchange can be evaluated by PO2, PCO2, A-Ado2, DLCO (Diffusion).

Reproducibility of FEV1, FVC helps to ensure that the results truly represent the patients lung function, which will be focused on 3 key parameters, FEV1, FVC, FVC%. Many international studies have taken these parameters to assess the base line pulmonary function and in follow up, along with DLCO. Aim is to evaluate the changes in pulmonary function with concurrent chemoradiation

Materials and Methods

This is a prospective study conducted at MNJIO and RCC to evaluate the changes in pulmonary fuctions before and after concurrent chemo radiation in locally advanced , unresectable non small cell lung cancers. Total 60 patients were enrolled.

Inclusion Criteria

Age 40-70 years, KPFS >70 score, squamous , large cell, adenocarcinoma of 3 rd A,B patients with weight loss< 5% for 3 months before study entry(AJCC), median pre RT, PFTs,% predicted(range), FEV1 -67(24-121), FVC-72(45-116), No prior treatment, normal LFT/RFT, no distant metastases.

Exclusion Criteria

Age>70 years, KPFS<70, stage-4, small cell carcinoma, patient with weight loss> 5% before study entry, pre RT PFTs (% predicted)F EV1<24, FVC<45, patient received chemo/RT prior to study entry , abnormal LFT/RFTs, patients with distant mets.

All patients underwent a thorough clinical examination and baseline pulmonary function tests, and necessary work up before being included in the study.

Special investigations done like PFT tests before starting treatment, after completion of 44 gy+2.

Cycles of chemotherapy every 3 months upto 12 months.

All 60 patients received initially 44 Gy external beam RT in 22 fractions with 200CGy/fraction, treated daily along with 2 cycles of chemotherapy, Cisplastin and Etoposide once in 3 weeks. Chemotherapy started on the same day along with external beam RT, 3 cycles were given with full doses of chemotherapy after calculating dose according to BS.

Inj CDDP-100mg/m^2–D1

Inj ETOPOSIDE-100mg/m^2D1-3

Before every cycle of chemotherapy , CBP with PC, RFT, LFT were done after completion of 44 gy+ 2cycles of chemotherapy, pulmonary function tests were done. At the end of 66 gy + 3 cycles of chemotherapy again pulmonary function tests were done.

The two characteristics of pulmonary function that were the focus of this study were diffusing capacity and obstruction. On the basis of the American Thoracic Society and the European Respiratory Society recommendations [8], the DLCO (percentage of predicted value) was used as a measure of diffusion capacity and the forced expiratory volume in 1 second per unit of vital capacity (FEV1/VC) was used as a measure of obstruction. All patients included in this study had undergone both evaluations.

Post-radiation PFT values (percentage of predicted) were evaluated amongst individual patients compared to the same patient's pre-radiation value at the following time intervals: 0 to 4 months , 5 to 8 months, and 9 to 12 months. In patients that had more than one post-treatment PFT value within a time period, the lowest value within that time period was used for analysis and compared to the baseline value. Each time period was used for analysis and compared to the individual's baseline value. We used the linear regression model for the PFT evaluation at different time intervals. Additionally, we used the logistic regression model to evaluate predictors of major changes in pulmonary function after RT

Results

In our study a total of 60 patients were studied to evaluate the changes in pulmonary function before and after concurrent chemoradiation. We have taken patients characteristics and pulmonary function tests which were prognostically important. All patients were ideally received ideally RT dose 66 GY and received chemotherapy cisplatin and etoposide in full doses concurrently.

All patients had good performance status (Karnofsky performance score ≥70) and. treatment approaches included induction chemotherapy followed by radiation (n=30), induction chemotherapy followed by concurrent chemotherapy and radiation (n=30), concurrent chemotherapy and radiation without induction treatment (n=60).

Advanced disease stage, pretreatment DLCO ≤ 50%, twice-daily radiotherapy fractionation and

Table 1: Patients characteristics

Characteristic	3CRT (n = 30)	IMRT (n=30)	All patients (n=60)
Sex			
Male	12(40)	14(47)	26(43)
Female	18 (60)	16'(53)	34(57)
Age, years			
mean +SD	56+12	58+11	57+11
Range	44-68	47-69	46-68
Respiratory disease history			
Yes	17(57)	15(50)	32(53)
No	13 (43)	15(50)	28 (47)
Cardiovascular disease history			
Yes	18(60)	17 (57)	35(58)
No	12 (40)	13 (43)	25 (42)
Disease stage			
I, II	13 (43)	11(37)	24(40)
III, IV	17(57)	19(63)	36(60)
Karnofsky performance score			
>80	9(30)	15(50)	24(40)
70-80	21(70)	15(50)	36(60)
Concurrent CRT			
No	9(30)	15(50)	24(40)
Yes	21(70)	15(50)	36(60)
Mean lung dose			
Median	20 Gy	18 Gy	17 Gy/GyE
Range	4-29 Gy	3-27 Gy	3-29 Gy/GyE
Baseline DLCO, % of predicted			
Median	65	67	66
Range	22-128	20-148	20-148
Baseline FEV1, % of predicted			
Median	63	74	68
Range	19-106	26-127	19-127

Table 2: Factors significantly associated with DLCO decrease

Variable	Time	Present		Significance (*P*)
		Yes	No	
Concurrent chemotherapy	0 to4 months	21	9	0.016
Intensity-modulated radiation therapy	5 to 8 months	11	19	0.04
Advanced disease stage (III, IV)	0 to 4 months	9	2	0.02
	5 to 8 months	10	6	0.027
	9 to 12 months	11	6	0.017
Lung V5 >median	5 to 8 months	10	4	0.047
	9 to 12 months	13	5	0.038
Lung V20 >median	5 to 8 months	12	2	0.001
Heart V40 >median	5 to 8 months	11	3	< 0.0001
	9 to 12 months	6	2	0.014
Gross tumor volume ≥100 cm^3	5 to 8 months	11	2	< 0.0001
	9 to 12 months	11	6	0.022
Baseline DLCO ≥50% of predicted	0 to 4 months	1	15	< 0.0001
	5 to 8 months	3	13	0.001
	9 to 12 months	2	14	0.009
Baseline FEV1 ≥60% of predicted	0 to 4 months	9	19	0.014

3DCRT were associated with larger posttreatment declines in DLCO during T2. Additionally, lung (MLD, $V_{5,}$ and V_{20}) and cardiac dosimetric parameters (MHD and V_{40}) also associated with the DLCO change.

Thirdly, GTV ≥100 cm^3, advanced disease stage, history of respiratory disease, and pretreatment DLCO ≤ 50% were associated with larger posttreatment declines in DLCO during T3. Moreover, the total radiation dose, lung $V_{5,}$ and heart V_{40} associated with the DLCO change after RT. MLD and lung V_{20} had

marginal significance (P =0.056 and P =0.052, respectively).

Pretreatment DLCO ≤ 50% was associated with larger posttreatment declines in FEV1/VC during T1; twice-daily radiotherapy fractionation in T2; and pretreatment FEV1 ≤ 60% in T3. We did not observe a significant FEV1/VC change difference at any time interval between the two groups. After adjusting by covariates, only pretreatment DLCO retained statistical significance during the initial time period, T1 (P=0.021). When evaluating the effect of predictors of major changes in the FEV1/VC after RT (decrement greater than the upper tertile), we did not find a significant association with any of the patient, tumor, treatment, and pre-RT PFT factors assessed.

Table 3: Factors significantly associated with FEV1/VC decrease (percent change from baseline) in univariate analyses

Variable	Time	Present		Significance (P)
		Yes	No	
Baseline DLCO ≥50% of predicted	0 to 4 months	-3	1	0.021
Twice-daily radiotherapy fractionation twice a day	5 to 8 months	1	-3	0.017
Baseline FEV1 ≥60% of predicted	9 to 12 months	-3	3	0.018

Discussion

In our study, we evaluated prospectively the changes of pulmonary function before and after concurrent chemo-radiation. 60 patients are enrolled in our study. Of these 57% patients are women. Most of them have stage -3,4.

We observed that DLCO was more often affected than obstruction, with a much larger percentage of patients experiencing a decline in DLCO after RT, regardless of technique. Several factors were associated with a decline in diffusing capacity, including GTV, pretreatment DLCO, and dosimetric data, consistent with prior studies [3,9]. Several prior studies have examined the effect of RT on pulmonary function with time [3,10,11].

Miller et al. [11] reported that by 1 year, the median FEV1 and forced vital capacity were similar as baseline and the median DLCO was 90% of baseline. Contrary to Henderson et al [10], we found that baseline pulmonary function predicted decreased pulmonary function after treatment. Those patients with pretreatment DLCO ≤ 50% were associated with larger posttreatment declines in DLCO.

Our finding that diffusing capacity is affected more often and to a greater extent by radiation therapy than airway obstruction, is consistent with those of others who have reported that the largest and most consistent changes in PFT values after RT occur in DLCO [3,4]. It may be that lung overexpansion, though affecting both FEV1 and DLCO, cannot compensate for the loss of functional alveolar surface area that is reflected in the DLCO [12,13]. In addition, we observed a parallel in terms of the pre-treatment DLCO value as prognosis factor for post-treatment pulmonary dysfunction between lung cancer patients receiving RT and those treated with surgery. It seems that in both cases, the pre-treatment DLCO plays an important role as prognosis factor for not only pulmonary dysfunction but also for postoperative lung complications [4,14].

We further found that DLCO is reduced in the majority of patients along the 3 time periods after radiation, whereas increased vs. decreased over time in a similar number of patients. Our findings suggest that interventions such as bronchodilators may have only modest effects on improving posttreatment pulmonary function and that patients with a substantial radiation dose to the lung would benefit instead from an intensive pulmonary rehabilitation program [15,16].

With respect to our final aim, we found several dosimetric factors to be associated with decreased pulmonary function after RT. Specifically, the mean dose to the lung and heart, as well as lung V_{20} and heart V_{40}, all correlated with posttreatment pulmonary function on univariate and multivariate analysis during the interval of 5 to 8 months after RT. However, the lung V_5 did not retain significance after adjustment by other covariates. Although the specific lung and heart variables that correlate most strongly with lung toxicity is still debated in the literature [17], both the lung and heart dose are important for predicting radiation-induced lung injury and its clinical sequelae [18-20].

Our current findings add to the increasing body of literature suggesting that lung injury is multifactorial and that radiation doses to the lung and heart influence long-term cardiopulmonary function. Moreover, while we certainly acknowledge the importance of both low- and high-dose radiation in contributing to posttreatment pulmonary complications, the current study found that V5 was not associated with significant DLCO impairment. We are currently assessing if posttreatment DLCO can be used as an objective measure of lung toxicity given its relationship to radiation pneumonitis.

Abratt & Wilcox evaluated the pulmonary function by mean of formal PFTs, FEV, FVC & DLCO. Based on this study, we also evaluated FEV1, FVC, at 44 gy+2cycles of chemotherapy, at 66gy+3cycles of chemotherapy, at 6 months. At 9 months, at 12 months. FEV1 is significantly affected in obstructive diseases & FVC is significantly affected in restrictive diseases. As carcinoma lung most commonly occurs in smokers, the impairment, in obstructive pulmonary function is not only by tumor it self , but also due to chronic obstructive pulmonary disease (COPD) changes in lungs due to smoking.

The results were evaluated on the basis of each study's percentage of predicted of normal value (i.e adjusted for age, gender & weight). So that serial studies will not be confounded by the effects of ageing. Each patient's sequential examinations are compared with their initial study and a percentage of the base line value is calculated. Changes in FEV1 after radiation to a portion of lung could be affected by fibrosis causing traction of bronchi, adjacent tissue. The decrease in FVC is relatively larger than FEV1 likely to indicate over all stiffening of the lungs, chest without bronchial obstruction.

The histological and result of radiation damage is fibrosis, thickening of alveolar septae and reduction of the fine vasculature & the most important target cell for radiation appear to be the capillary endothelium and type 2 pneumocytes.

Many factor such as constant lung disease associated COPD changes & radiation factors (dose, dose per fraction, tumor shrinkage), use of concurrent chemotherapy would affect the pulmonary function. More recently emphasis has placed on the importance of the DLCO in pre operative assessment of the lung function, as it is a best indicator of postoperative morbidity including respiratory failure and mortality.

Conclusions

In conclusion, we have found that, with definitive radiation therapy using modern techniques, diffusing capacity of the lung is reduced in the majority of the patients. We were able to elucidate several patient and treatment factors which were associated with greater reductions in lung function after treatment, including GTV and pre-radiation lung function, all of which could be used to estimate the impact of radiation therapy on an individual's respiratory status, possibly in the setting of objective models that could aid in counselling patients prior to treatment.

It is difficult to draw conclusions in this study because follows up till 1yr. Additional studies and pooling of data from multiple institutions may help to clarify better the long term impact of concurrent chemo-radiation.

References

1. Cerfolio RJ, Talati A, Bryant AS. Changes in pulmonary function tests after neoadjuvant therapy predict postoperative complications. Ann Thorac Surg. 2009;88:930–935. discussion 935-936. [PubMed]
2. Semrau S, Klautke G, Fietkau R. Baseline cardiopulmonary function as an independent prognostic factor for survival of inoperable non-small-cell lung cancer after concurrent chemoradiotherapy: a single-center analysis of 161 cases. Int J Radiat Oncol Biol Phys. 2011;79:96–104. [PubMed]
3. Gopal R, Starkschall G, Tucker SL, et al. Effects of radiotherapy and chemotherapy on lung function in patients with non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2003;56:114–120. [PubMed]
4. Takeda S, Funakoshi Y, Kadota Y, et al. Fall in diffusing capacity associated with induction therapy for lung cancer: a predictor of postoperative complication? Ann Thorac Surg. 2006;82:232–236. [PubMed]
5. Liao ZX, Komaki RR, Thames HD, Jr, et al. Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2010;76:775–781. [PubMed]
6. Fang LC, Komaki R, Allen P, et al. Comparison of outcomes for patients with medically inoperable Stage I non-small-cell lung cancer treated with two-dimensional vs. three-dimensional radiotherapy. Int J Radiat Oncol Biol Phys. 2006;66:108–116. [PubMed]
7. Zinner RG, Komaki R, Cox JD, et al. Dose escalation of gemcitabine is possible with concurrent chest three-dimensional rather than two-dimensional radiotherapy: a phase I trial in patients with stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2009;73:119–127. [PubMed].
8. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. European Respiratory Journal. 2005;26:948–968. [PubMed].
9. Theuws JC, Muller SH, Seppenwoolde Y, et al. Effect of radiotherapy and chemotherapy on pulmonary function after treatment for breast cancer and lymphoma: A follow-up study. J Clin Oncol. 1999;17:3091–3100. [PubMed].
10. Henderson M, McGarry R, Yiannoutsos C, et al. Baseline pulmonary function as a predictor for survival and decline in pulmonary function over time in patients undergoing stereotactic body radiotherapy

for the treatment of stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2008;72:404–409. [PubMed]

11. Miller KL, Zhou SM, Barrier RC, Jr, et al. Long-term changes in pulmonary function tests after definitive radiotherapy for lung cancer. Int J Radiat Oncol Biol Phys. 2003;56:611–615. [PubMed]
12. Jaen J, Vazquez G, Alonso E, et al. Changes in pulmonary function after incidental lung irradiation for breast cancer: A prospective study. Int J Radiat Oncol Biol Phys. 2006;65:1381–1388. [PubMed]
13. McDonald S, Rubin P, Phillips TL, Marks LB. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. Int J Radiat Oncol Biol Phys. 1995;31:1187–1203. [PubMed]
14. Takamochi K, Oh S, Matsuoka J, Suzuki K. Risk factors for morbidity after pulmonary resection for lung cancer in younger and elderly patients. Interact Cardiovasc Thorac Surg. 2011;12:739–743. [PubMed]
15. Nazarian J. Cardiopulmonary rehabilitation after treatment for lung cancer. Curr Treat Options Oncol. 2004;5:75–82. [PubMed]
16. Riesenberg H, Lubbe AS. In-patient rehabilitation of lung cancer patients--a prospective study. Support Care Cancer. 2010;18:877–882. [PubMed]
17. Dehing-Oberije C, De Ruysscher D, van Baardwijk A, et al. The importance of patient characteristics for the prediction of radiation-induced lung toxicity. Radiother Oncol. 2009;91:421–426. [PubMed]
18. Huang EX, Hope AJ, Lindsay PE, et al. Heart irradiation as a risk factor for radiation pneumonitis. Acta Oncol. 2011;50:51–60. [PMC free article] [PubMed]
19. Kong FM, Ten Haken R, Eisbruch A, Lawrence TS. Non-small cell lung cancer therapy-related pulmonary toxicity: an update on radiation pneumonitis and fibrosis. Semin Oncol. 2005;32:S42–54. [PubMed]
20. Mehta V. Radiation pneumonitis and pulmonary fibrosis in non-small-cell lung cancer: pulmonary function, prediction, and prevention. Int J Radiat Oncol Biol Phys. 2005;63:5–24. [PubMed]