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RESEARCH ARTICLE

Benefit From Smoking Cessation on COPD Patients Undergoing Stereotactic Body Radiation for Lung Cancer Functional Evaluation a Cohort Study

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Abstract

Introduction: Tobacco is the major risk factor for obstructive pulmonary disease (COPD) and lung cancer. Therefore stopping smoking is the most effective way of halting or slowing the progress of this disease.

Medically inoperable patients with early stage lung cancer with central or peripheral lesions could be safely treated by stereotactic radiotherapy (SBRT).

This case-control study aims to investigate the role of smoking cessation on functional variations after radiotherapy and the impact on response rate.

Methods: Forty-five smokers patients with moderate COPD and affected by non-small cell lung cancer stage T1-3N0M0 were progressively enrolled. They underwent successful smoking cessation program with varenicline or NRT (nicotine replacement therapy), at the time stereotactic body radiotherapy (SBRT) was undertaken.

It is a cohort not randomized study

Twenty smokers' patients without quitting affected by early stage lung cancer were recruited for comparison. The baseline characteristics of the two groups were comparable. Adenocarcinoma was the prevalent histo-type in both groups.

Follow up of six months was completed.

Patients performed the Fagestrom dependence nicotine test (FTND), spirometer with plethymography technique with detection of post-bronchodilator forced expiratory one second volume (FEV1) obtained by salbutamol 400 µg, 6 minute walking test, hemogasanalysis, and carbon monoxide exhaled test at baseline and after 6 months.

Endpoints: to detect differences in lung function decline after SBRT, between the two groups

Outcomes

Self-reported smoking cessation confirmed by measurement of exhaled CO. Comparison of FEV1 and forced vital capacity (FVC) level after SBRT between groups

Results: After radiotherapy, a minimal decline in lung function in the study group (quitters patients) compared with patients who not quit. Specifically FEV 1 was reduced by only 4 mm differently from the control group that reduced by 160 ml. FVC was also reduced less than control group (8 ml vs 250 ml). The Forced Expiratory Flow (FEF) 25-75 dropped down more in control group by 11%. 6-minute walking test(WT) was also reduced more in control group in terms of walking distance. PaO_2 didn't change significantly in the study group in comparison with control and dyspnea test modified Medical Research Council (mMRC) changed only in control group.

Conclusions: Smoking cessation is confirmed as an effective therapeutic presidium leading a good clinical response to stereotactic body radiation and good tolerance in COPD and lung cancer patients. SBRT along with smoking cessation should be considered for patients with lung cancer stage I-II, who are no fit for surgery.

Key words: Smoking cessation, lung cancer early stage, lung function tests, stereotactic radiotherapy

Running Head: smoking cessation plus bronchodilators and lung function

Abbreviations: COPD: Coronary Obstructive Pulmonary Disease; SBRT: Stereotactic Body Radiotherapy; FDNT: Fagestrom Dependence Nicotine Test; FEV1: Forced Expiratory One Second Volume; FVC: Forced Vital Capacity

Introduction

Worldwide, tobacco use causes nearly 6 million deaths per year [1]. Cigarette smokers die about 10 years younger than non-smokers [2-3] and nearly one million people around the world die every year from tobacco-related illnesses [4]. Among

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the pathologies caused by smoke, cardiovascular diseases are responsible for roughly 40% of smoking-related deaths, lung cancer accounts for 20% and chronic obstructive pulmonary disease (COPD) accounts for another 20% of all smoking-related mortality [5-6]. Symptoms of pulmonary disease smoke-related are sputum, cough, dyspnoea and exercise intolerance with exertional dyspnea.

COPD has been defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a "preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases" The major risk factor for COPD, particularly in developed countries, is cigarette smoking [7]

Patients affected by early stages lung cancer account for about 20-25% of cases and can undergo surgical resection. Another 20-30% of patients with early stage lung cancer are not surgical candidates or are unwilling to undergo surgery [8]:the median survival is 13 months for patients with surgically untreated T1 lung tumors and 8 months for untreated T2 tumors [9].

Stage I or II NSCLC patients with lesions ≤ 5 cm in diameter, who have no lymph-node involvement, who are medically inoperable for comorbidities, constitute the target population for SBRT [10-11]. Retrospective studies demonstrated the safety of SBRT in medically inoperable early-stage NSCLC patients with COPD undergoing long-term domiciliary oxygen therapy (LTOT) [12]. After SBRT it has also been showed that although FEV1 and DLCO are generally reduced and can decrease further over time, this has no impact on patient quality of life or survival [13]. Only a low body mass index, a high lung volume receiving ≥20 Gy of SBRT, and a high pre-treatment FVC seems to be predictors of a decline in FVC of more than 10% [14].

The most important therapy for chronic bronchial obstruction is smoking cessation according to GOLD guidelines [7,15]. Smoking cessation can be achieved with non-pharmacological and pharmacological treatments. The benefits are immediately noteworthy: within 24 hours from smoking cessation there are significant improvements in blood pressure and heart rate, and exhaled carbon monoxide normalized in a few hours.

The Lung health study demonstrated that patients with COPD who gave up smoking and remained abstinent improved their FEV1 in the year after quitting; the study also showed a subsequent age-related decline in FEV1 that was half the rate among the continuing smokers. Furthermore intermittent quitters had only limited benefit of partial smoking reduction since the course of their lung function loss was closer to that of the continuing smokers. Moreover smoking cessation is associated with a 32% reduction in all causes of mortality at 6 months of follow-up [16, 17].

The mechanisms smoking-related inducing lung cancers were also deeply displayed [18] and the importance of smoking status in lung cancer was already shown. Indeed, a good effect of smoking cessation on cancer risk factors and lung function were found in both wild type and in EGFR mutated patients [19, 20].

Moving to smoking dependence issue and its treatment, some drugs indicated as first line therapy may help smoker to quit smoking. The effectiveness of the treatment with varenicline versus placebo on smoking cessation has already been demonstrated. Varenicline is an α4-β2 partial agonist of nicotinic-acetylcholine receptors that induces a complete abstinence rate up to 42% of all patients at three months and improve the post-bronchodilator FEV1 [11,16,17]. Varenicline displayed superiority compared with bupropion and nicotine replacement therapy (NRT) [21]. However NRT is a first-line therapy that could be feasible and useful [21].

In our report we analyzed 39 smokers patients affected by NSCLC stage T1-3N0 and moderate COPD undergoing SBRT and smoking cessation who quit compared with 15 subjects who didn't quit: the aim of the study was to highlight the effects of smoking cessation on lung function decline after SBRT comparing group of quitters with non-quitters over a short period of observation.

Patients and Methods

Study Design

From December 2015 to November 2016, 45 patients suffering from non-small cell lung cancer with T1-3 N0M0 and with moderate COPD (FEV1/FVC<70%, FEV1<60% of predicted) were referred to our outpatients service and prospectively [22-32] enrolled for smoking cessation and SBRT treatment (Table 1). Inclusion criteria were: age major than 20, smoking habit of more than 10 cigarettes per day with a pack-year value of at least 20 with a basal spirometer showing a moderate COPD

Characteristics patients at baseline	quitters	No quitters
Total patients	45	20
Cigarette daily consumption	24.3±3.4	23.5±5.6
Age	63±3.5	60±6.7
% male	20	25
Body mass index	23.2 ±3.4	21.5±5.1
ECOG performance status	0	1
CO ppm	15±3.0	12±3.5
PaO_2	67±3.5	68±2.5
Fagestrom test(FTND)	4.0±0.5	4.5±1.5
Location		
Peripheral	50%	55%
Central location	50%	45%
Histology squamous		
40%		35%
Histology adenocarcinoma	60%	65%

Table1: Patient characteristics Fisher Exact test for categorical variables Mann Whitney test for continuous variables

(60%> FEV1 >50% of predicted value) and early stage lung cancer.

20 patient's non-quitters who were also early stage disease undergoing SBTRT were considered for comparison.

Exclusion criteria were major depression, pregnancy, and recent heart disease. Pulmonary function tests were measured (Tiffenau index <70 %,) according to the ERS-ATS guidelines [33]. There were 18 males and 10 females in the study group. The mean age was 63 years for the first group and 60 years for the comparison group. The schedule dosage of varenicline was 0.5 mg per day for three days, then 0.5 twice a day for 4 days, up to 1 mg twice per day. Nicotine patch was also used at dosage of 21 mg every 24 hours

Information's regarding the patients were recorded including age, gender, present and past diseases, body mass index expressed as body weight in kilograms divided by the square of height in meters. Demographic baseline data represented by smoking habit, location of main lesion and histology are shown in (Table 1). SBRT

Chest computed tomography was used to visualize the target volume. The target planning volume was determined by adding a margin of 6 mm to the target volume of 29 ml through IGRT technique (imaging guide therapy) 6 MV photon energy.

It was performed with 50 Gy in five fractions through a dynamic conformal irradiation.

A consent written form was provided by each subject

Endpoint: difference in lung function decline after SBRT, between the two groups

Outcomes: Self-reported smoking cessation confirmed by measurement of exhaled CO.FEV1 and FVC and other spirometer values after SBRT in both groups.

Measurements

Patients underwent a mMRC dyspnea test and then a 6-minute walking test (WT), during which the oxygen saturation and the distance covered were recorded (Nonin pulsoxymeter, USA). A fall of oxygen saturation higher than 4% was considered indicative of exercise intolerance. An arterial blood sample was performed for detection of PaO_2 (arterial pressure partial oxygen)with GEM system (USA) .

The exhaled CO measurement was detected by smokerlyzer with electrochemical sensor (Bed font, USA). Tobacco smoking abstinence was considered in case of eCO<7ppm.

Spirometer by means of body plethymography (Jaeger system master screen, Germany) was performed before smoking cessation and six months later, after therapy. Briefly, flows and dynamic volumes were measured with the pneumo-tacographic method and volumes and resistances with the body plethymography method. Data considered were Forced Vital Capacity (FVC), Post-bronchodilator Forced Expiratory Volume in one second (FEV1), total resistances (tRaw).

The predicted FEV1 and FVC were calculated according to the standard values of the Global Initiative for Chronic Obstructive Lung disease (GOLD) and the patients with COPD were diagnosed according to the GOLD criteria.

Bronchodilator test was performed administering salbutamol 400 μg by metered dose inhaler (MDI). Tests were performed before and 24 hours after wash-out from bronchodilators and data were collected, as post-bronchodilator determination, at the beginning of the treatment for smoking cessation and again six months later (Table 2). The techniques followed the American Thoracic Society and European Respiratory Society task force 2005 guidelines [33].

Bronchial resistances (tRaw) are expressed as cmH20 /l/sec, mMRC dyspnea score test ranging score from 0 to 5 (0 absence, 5 maximum of dyspnea), FEV1 and FVC were expressed in liters, and FEF 25/75 (Forced expiratory flow at 25/75% of forced vital capacity) in liters/second.

CT scan for chest evaluation was also performed at 6 months check

Follow Up

The measures were detected at basaline and after 6 months from recruitment.

Statistical Analysis

All values were expressed as mean plus standard deviation.

Local control rate was determined following RECIST 1.1 criteria [34].

The Wilcoxon signed- rank test was applied to compare the pre

	quitters	Non quitters	p
FEV1 baseline	1.29±0.8	1.26±1.2	NS
FEV1 check	1.25±1.1	1.10±0.4	<0.01
FVC baseline	2.58±1.1	2.35±0.7*	<0.01
FVC check	2.50±2.5	2.10±3.4	<0.001
eCO baseline*	15±3	12±3.5	<0.01
eCO check	6.5±1.5	10±2.5	<0.001
FEF 25-75 baseline	40±2.1	45±2.5	NS
FEF 25-75%predicted	35.7±2.5	34.6±3.5	NS
mMRC baseline	1.5	2.5	<0.01
mMRC check	1.5	2	<0.01
6-minute WT distance m postSBRT bas*	350±2.5	310±2.1**	NS
6-minute WT distance m postSBRT	320±3.1	220	<0.001
PaO_2 mmHg baseline	67±2.7	68±2.5	NS
PaO_2 mmHg	65.5±5.6	62.2±6.1	NS
Resistances baseline	118±2.9	110±3.5	<0.01
Resistances %	120±6.1	119±5.2	NS
Variations according to GOLD criteria			

Table2: Lung function test after SBRT: Univar ate analysis: Wilcoxon test for comparison within groups continue data and Fisher exact test for categorical data. Mann Whitney for comparison between groups Resistances mmHg/ml/min, PaO2 mmHg, WT meters, eCO ppm
*<0.01 **<0.001

and post SBRT continues variables. The Fisher's exact test was applied to detect differences regarding categorical variables.

Mann Whitney analysis was applied to detect differences after SBRT between quitters and non-quitters.

P value of<0.05 was considered statistically significant.

Statistical analysis was performed using SAS software (version 9.2, SAS Institut, Cary, NC).

Results

The socio-demographic and histology characteristics of the patients are reported in (Table 1). No significant differences were observed, regarding body mass index, age, performance status. Adenocarcinoma was the prevalent histotype equally located in peripheral and central bronchi. The location of lesions and histology were also similar.

No significant differences in baseline data were taken with Fisher exact test, as well. A moderate level of obstruction was found in the two samples. (Tiffenau index <70% and FEV1 less then 70% predicted).

At six months of follow up all the patients in the study group were still without smoking.

Continues variables obtained as post-bronchodilator, were reported comparing both groups after SBRT (Table 2). Going into depth exhaled CO and FTND were notably positively changed for quitters by 10 ppm and for non-quitters by only 2 ppm. No significant variation was observed about FEV1 and FVC parameters in quitters differently from non-quitters, with only 4 ml variation vs 160 ml (post FEV1 1.25 vs 1.10) that are pathognomonic of obstructive or restrictive disease, as well as mMRC dyspnea test that worsened in second group. FVC changed by 250 ml in control group and no significant variation was reported in quitters. Moreover FEF 25-75% changed less in quitters. Indeed, post-SBRT value was 35.7 and changed by 5%, whereas the same value declined by 10% in control group. Eventually PaO_2 did not changed significantly in quitters. PaO_2 declined in quitters by 6 mmHg. Resistances changed declining only in non-quitters

The response evaluation demonstrated a better response rate in the study group compared with the no-quitters group (Table 3). Partial response was considered according to RECIST criteria 1.1, as a reduction of the longest diameter of main lesion by at least 30%

Discussion

The aim of this study was to evaluate the effect of smoking cessation in moderate COPD patients affected by early stage lung cancer undergoing SBRT.

	Recist criteria 1.1		
Group 1	Responder (SD,PR,CR)	Non Responder (PD)	P<0.01
	32(82%)	7	
Group 2	5	1.1E+12	

Table 3: Response evaluation.

SBRT was applied using high dose fraction on small volume lesion. The study demonstrated smoke cessation to have a very important role in clinical outcome.

Smoking cigarettes has an undeniable role on lung cancer induction [20-22] and the positive effect positive of smoking cessation on lung nodule development and lung function was also observed in literature [19]. Furthermore varenicline is the most effective drug approved as first-line therapy for smoking cessation [21]. The effectiveness of smoking cessation in lung cancer patients harboring EGFR mutation was already showed [20]. The NRT, used in current study, also showed an activity on smoking cessation rate [23].

So far tobacco plays a role in dependence mechanism triggering the reward process by activation of α4β2 nicotinic receptor and the releasing of Neuro-molecules such as dopamine in the mesolimbic system [24]. Counseling combined with varenicline may lead to successful outcome, and the effects were demonstrated in various settings [25]. In a trial by Tashkin et al. the forced expiratory volume in one second (FEV1) declined by only 34 ml per year in COPD patients who stopped their habit, roughly half of decline compared to that of smokers who continued [17].

Moving to lung cancer issue, we consider that surgery may be detrimental and should be avoided in severe COPD because of frequent complications: a predicted FEV1 of less than 40% implies high risk of respiratory complications. Therefore SBRT is a very good choice in medically inoperable early stage non-small cell lung cancer patients. In a phase II trial SBRT demonstrated a survival rate of 55% at 3 years associated with negligible mortality and manageable toxicity [26].

In a surveillance trial it was found out that 12% of patients treated by SBRT showed recurrence of disease [27,26]. The present study showed a reduced risk in lung recurrences in patients who give up smoking compared with who did not: all patients in the quitting group were free of recurrences at 6 months of follow up.

The short effectiveness of smoking cessation is demonstrated on lung function and biological parameters. The data collected showed that an early therapeutic intervention leads to control the decline of lung parameters during the short period [28].

Smoking cessation has a pivotal role in limiting the functional decline of FEV1. In COPD patients drugs like indacaterol and other bronchodilators such as anti-cholinergic were seen to improve lung function reducing functional decline and re-exacerbations [29-30]. In the present study we also want to point out that a wide range of tests may be used to detect lung function variations [31,32], such as the 6-minute walk test and the dyspnea test represent the ability of the patient to successfully face his or her daily obligations. The 6-minute walk test expresses the fall of the oxygen saturation after effort and walking distance and represents an important parameter [31]. The improvement in dyspnea score indicates a better symptom perception.

In the present study it has been found a small decline in lung

function in the short period favored by smoking cessation despite radiotherapy treatment. No complications deriving from treatment were observed, irrespective of dose fraction. The response rate and functional tolerability are very notable and therefore quality of life and survival are improved especially in patients who quit smoking. Radiation pneumonitis is less common reported in SBRT treated patients as we can see in our report. A minimal reduction of pulmonary function is observed consistently with the literature [33].

We may also suppose a direct effect of Varenicline on airways since it maintains a stable values of obstructive parameters.

Conclusion

We may state that smoking cessation therapy appears to be effective by itself in patients with COPD and concurrent early stage lung cancer undergoing SBRT. Smoking cessation has great capacity to influence the natural history of COPD. Healthcare providers should encourage all patients who smoke to quit. The pharmacotherapy reliably increases long term smoking abstinence rate.

Hence, smoking cessation therapy is still very important in reducing the deterioration of lung function and could strengthen the effects of bronchodilators therapy in COPD patients.

SBRT has become a standard treatment option in patients with inoperable early stage, and it is associated with very low mortality rate. Small and not significant decline in lung function tests is registered after treatment. Therefore, SBRT should be considered in patients with severe and moderate COPD at baseline.

The response rate analysis tell us that quitters patients are favorite in prognosis compared to no-quitters and could improve their quality of life, suggesting an interference of smoking in cancer treatment.

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