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Comparison of survival of chronic obstructive pulmonary disease patients with or without a localized non-small cell lung cancer

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ABSTRACT

Objectives: Chronic obstructive pulmonary disease (COPD) and non-small cell lung cancer (NSCLC) are often co-existing diseases with poor prognosis. The aim of this study was to compare survival in COPD patients with localized NSCLC treated with stereotactic body radiotherapy (NSCLC group) with COPD patients without a malignant diagnosis (non-malignant group).
Materials and methods: The NSCLC group was prospectively recorded at the Department of Oncology from 2007 to 2013. The non-malignant group was selected among patients referred to the Department of Respiratory Medicine from 2005 until 2011 suspected of thoracic malignancy but without the malignant diagnosis maintained.
Results: In a propensity score matched comparison the median overall survival was 53 vs. 71 months in the NSCLC and non-malignant groups, respectively ($p < 0.001$). Subgroup analyses showed survival for patients with mild/moderate COPD was affected statistically significant with a higher mortality rate by a diagnosis of localized NSCLC with hazard ratio = 2.62 (95% CI: 1.47–4.68) while an insignificant higher mortality rate with hazard ratio = 1.22 (95% CI: 0.71–2.08) was found in patient with severe/very severe COPD.
Conclusion: Despite the serious prognosis of COPD, a localized NSCLC diagnosis negatively affects survival in COPD patients. However, stereotactic body radiotherapy should still be considered for COPD patients diagnosed with localized NSCLC.

1. Introduction

Danish lung cancer patients diagnosed in 2009–2013 have a poor prognosis with an estimated overall 5-year survival of 11% and 16% for males and females, respectively according to the NORDCAN website [1]. Patients staged non-small cell lung cancer (NSCLC) T1-2N0M0 may be cured by surgical resection [2]. However, some patients are unfit for surgery due to poor lung function, comorbidities, poor performance status, or advanced age. Despite the lack of randomized trials, stereotactic body radiotherapy (SBRT) has emerged as a curative treatment modality for localized NSCLC for patients not having surgery.

The cause of death for NSCLC patients treated with SBRT is often the comorbid conditions that made the patients inoperable [3,4]. Lung cancer is diagnosed most frequently among smokers [5] and approximately 50% of lung cancers is diagnosed among persons aged 70 years or more [6]. Smoking and advanced age increases the comorbid conditions.

The main reason for inoperability in patients with localized NSCLC is chronic obstructive pulmonary disease (COPD), and is present in up to 70% of lung cancer patients at the time of diagnosis [7]. COPD is the fifth leading cause of deaths worldwide [8]. In Denmark with a population of 5.4 million, approximately 10% of

Abbreviations: COPD, chronic obstructive pulmonary disease; NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiotherapy; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GTV, gross tumour volume; PTV, planning target volume; CCI, Charlson comorbidity index; PSM, propensity score matching; HR, hazard ratio; CAO, chronic airways obstruction; GLI, global lung function initiative.

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persons aged 45 or older have COPD, and it is believed that almost 50,000 patients suffer from severe or very severe COPD [9]. The GOLD classification using four categories based on FEV1 in percent of predicted (FEV1%pred) is the main method to describe the severity of COPD [10]. Patients with COPD have a high annual mortality rate and the mortality rate increases with the severity of the GOLD criteria [11]. Many patients with localized NSCLC treated with SBRT have severe COPD [12]. Given the higher mortality rates associated with COPD increases stepwise for GOLD 1–4, the diagnosis of a localized NSCLC may not affect the already poor prognosis for all COPD patients.

The purpose of this study was to compare survival in COPD patients with localized NSCLC treated with SBRT (NSCLC group) with COPD patients suspected for thoracic malignancy but with a malignant diagnosis subsequently ruled out (non-malignant group).

2. Materials and methods

The analysis was constructed as a descriptive observational study. Two cohorts of patients with COPD were established.

2.1. Setting

Data of the NSCLC group were obtained from prospectively recorded consecutive patients with histologically or cytologically proven localized NSCLC treated with SBRT in the period of January 2007 to December 2013 at the Department of Oncology, Odense University Hospital (OUH). The non-malignant group was retrospectively selected from a group of patients from the local area of Funen with suspected thoracic malignancy consecutively referred to and prospectively registered in the Department of Respiratory Medicine at OUH from January 2005 until June 2011.

2.2. Chronic obstructive pulmonary disease and smoking status

For the present study the patients were classified as having COPD if spirometry showed a ratio between forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) less than 70%. The predicted values of FEV1 were calculated from the European reference equations [13]. GOLD criteria were used to classify the severity of COPD (GOLD I; FEV1 $\geq$80% of predicted, GOLD II; FEV1 = 50–79% of predicted, GOLD III; FEV1 = 30–49% of predicted, and GOLD IV; FEV1 <30% of predicted). Patients who had stopped smoking for one year or more were defined as ex-smokers, while patients abstinent for less than one year were defined as current smokers.

2.3. Patients

A review of records identified 136 patients with localized NSCLC treated with SBRT. Thirty-four patients were not included since FEV1/FVC was $\geq$70%. Thus, 102 patients in the NSCLC group were included in the study. All patients were staged NSCLC T1-2aN0M0 according to the 7th edition of TNM Classification of malignant tumours. Seventy-seven patients were considered medically inoperable, 22 patients were considered best served by SBRT due to age, frailty or comorbidity, and three patients denied surgery. All were treated with SBRT as described previously [14]. In summary, SBRT consisted of three fractions of radiotherapy. Prior to October 2008, the gross tumour volume (GTV) was treated to a total dose of 45 Gy and the planning target volume (PTV) treated to 30 Gy. After October 2008, the GTV was treated to 66 Gy and the PTV treated to 45 Gy. The treatment duration was maximum nine days.

Patients for the non-malignant group were selected among 2672 patients with no previous diagnosed lung cancer referred to the Department of Respiratory Medicine. Of these, 2322 were 50 years of age or above corresponding to the minimum age of the SBRT treated group. 870 patients were not included as an up-front additional imaging excluded malignancy and these patients never attended the Department of Respiratory Medicine. 127 patients had pleural effusion drainage. Since pleural effusion may have had impact on lung function test these patients were not included. In total, 1325 patients without lung malignancy were candidates for a possible match to the NSCLC group. A review of records was made to detect if a spirometry was performed and if it indicated COPD. 645 patients did not meet the criteria for COPD and were not included together with 108 patients without a spirometry performed within 14 days before or 1 month after the first visit at the Department of Respiratory Medicine. Thus, the non-malignant group consisted of 572 patients.

Data from both groups of patients were obtained from patients' charts. The pre-treatment evaluation for patients in the NSCLC group included complete clinical examination, chest x-ray, and a CT scan of the chest and upper abdomen. Most patients in the non-malignant group had performed chest x-ray and CT-scan of chest and upper abdomen. Charlson Comorbidity Index (CCI) was retrospectively calculated by physician chart review with lung cancer diagnosis being excluded from the scoring. Any new comorbid conditions that developed after the date of the first visit at the diagnostic department were omitted from the CCI score calculations. Patients were grouped as 1 (COPD alone), 2–3, or 4+.

2.4. Follow-up

Follow-up for patients in the NSCLC group was performed five weeks after treatment, every third month in two years, and then every six-month for a total of five years follow-up. The follow-up included a medical history, clinical examination, chest x-ray and/or CT scan, and measurement of lung function. The patients in the non-malignant group did not have a planned follow-up since malignancy was ruled out.

2.5. Statistical methods

The primary endpoint of the study was overall survival. The survival rates were calculated from the date of the first visit at the diagnostic department after referral for suspected thoracic malignancy for both groups. Overall survival was defined as the time to death from any causes including lung cancer. All medical documentation for both groups was reviewed for survival status. Data cutpoint was 15th December 2015.

Univariate analyses were used to compare groups. Means/medians were then compared using T-test/Mann-Whitney test. Group proportions were compared using Fisher's exact test. Multivariable analyses used Cox regression to explore if any of the variables could have influence on overall survival. Propensity score matching (PSM) was performed to reduce confounding between the groups. The PSM was done utilizing the nearest-neighbour methodology without replacement. The survival analyses were calculated using the Kaplan-Meier method for both the unmatched and matched comparisons of patients. The log rank test was used for testing differences in survival rates. Secondary propensity score matching analyses stratified by GOLD criteria into to two groups (mild/moderate vs. severe/very severe) were performed.

In all the statistical analyses, a two-tailed p-value of <0.05 was considered to be statistically significant.

3. Results

572 patients in the non-malignant group and 102 patients in the NSCLC group were enrolled. The median potential follow-up time was 89 months (54–132 months) and 55 months (25–106 months)