ORIGINAL ARTICLE

Screening with Low-Dose Computed Tomography Does Not Improve Survival of Small Cell Lung Cancer

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ABSTRACT

Introduction: Small cell lung cancer (SCLC) constitutes a distinct component of symptomatic or advanced-stage lung cancers in clinical practice and in lung cancer screening trials. The purpose of this study was to describe the outcome of SCLC in lung cancer screening trials and compare the frequency of SCLC in our cohort with that in the major lung cancer screening trials.

Methods: Subjects with a diagnosis of SCLC were selected from two lung cancer screening trials by low-dose computed tomography (LDCT), and their demographic characteristics, clinical parameters, tumor stage at diagnosis, therapy, and survival times were recorded. Survival curves were estimated using the Kaplan-Meier method.

Results: Ten cases of SCLC were reported in 45,141 person-years (22 in 100,000 person-years), representing the 6% of all lung cancer cases. Cumulative tobacco consumption was 82 pack-years compared with 39 and 46 pack-years for the overall study population and subjects with non-SCLC, respectively. Most of the neoplasms were in an advanced stage (seven in stage IV and one each in stages IIIb, IIIa, and Ia). Two subjects were treated with lobectomy for curative purposes and died of diffuse metastasis within 2 years of diagnosis. The median overall survival time in the LDCT arms was 20.6 months, with no survivors remaining at 3 years.

Conclusions: Subjects in whom SCLC develops are a subgroup of smokers with extremely high cumulative tobacco consumption. Consequently, the frequency of SCLC in our population was lower than in other screening populations, with higher cumulative tobacco consumption. Screening for lung cancer by LDCT does not improve survival of SCLC, with no survivors remaining at 3 years after diagnosis.

Keywords: Small cell lung cancer; Screening; Early detection of cancer; Mean survival time; Smoking cessation

Introduction

Small cell lung cancer (SCLC) accounts for approximately 13% of all lung cancers[1] and its prevalence is directly related to cigarette smoking.[2] Only 30% of SCLC is diagnosed as limited-stage SCLC (LS-SCLC), whereas the majority of cases show extensive-stage SCLC (ES-SCLC) related to either massive thoracic involvement or systemic diffusion.[3] The 5-year survival rate for SCLC in Europe ranges from 2.2% to 3.7%, which is consistently lower than the 10.8% to 14.0% survival rate for non–small cell lung cancer (NSCLC).[4] A trivial increase in survival of LS-SCLC compared with ES-SCLC is seen.[2,5,6]

The frequency of SCLC has been described within lung cancer screening trials using low-dose computed

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tomography (LDCT).[7–9] It varies between different screening programs, with an incidence of 26 cases in 100,000 person-years in Europe[7] and 83 cases in 100,000 in the United States.[8] Because of its aggressive biology, SCLC constitutes a consistently large percentage of the cases of symptomatic interval cancers or asymptomatic diffuse disease that are discovered during yearly LDCT screening.[8] To date, there has been no report about the outcome of SCLC with lung cancer screening.

The purpose of this study was twofold: to describe the outcome of SCLC in lung cancer screening trials and compare the frequency of SCLC between our cohort and those of the major lung cancer screening trials.

Materials and Methods

For the purpose of this study, we retrospectively reviewed data from two lung cancer screening trials based in Milan. The details of these screening programs were described elsewhere.[10,11] In brief, in 2000 a 5-year prospective pilot trial offering yearly LDCT to 1035 volunteers who were currently or formerly heavy smokers, had a smoking history of 20 or more pack-years, and were at least 50 years old was launched.[10] Five years later, the Multicentric Italian Lung Detection (MILD) trial started with prospective enrollment of 4099 volunteer heavy smokers with the same characteristics as those of the volunteers in the previous trial. Volunteers were randomly assigned to a control arm or an early detection arm; the subjects in the latter group were randomly assigned to either annual or biennial LDCT.[11] Furthermore, primary prevention was offered to all participants through a smoking cessation program. For the present analyses, the follow-up lasted until August 2015.

Subjects with a diagnosis of SCLC were selected and their demographics and clinical parameters were collected from the database. The results of the diagnostic work-up of each subject were recorded, and stage of the disease was assessed at the time of diagnosis. In particular, stage of disease was assessed according to both the tumor, node, and metastasis (TNM) staging system[12] and an SCLC-dedicated two-stage clinical system (e.g., LS-SCLC and ES-SCLC),[13] the latter being the standard method for clinical management. Descriptions of therapeutic management were retrieved from clinical records, and follow-up was conducted through active telephone contact and record linkage with national administrative databases. Cause of death was collected for all deceased subjects, and overall survival was calculated as index of outcome.

Statistical Analyses

Continuous variables were presented as median values and ranges, and categorical variables were reported as numbers and percentages. Survival curves were estimated using the Kaplan-Meier method. Statistical analyses were performed using STATA statistical software (version 11; StataCorp, College Station, TX).

Results

A total of 5134 subjects were recruited and followed up for a median time of 8.3 years, with 45,141 person-year of clinical follow-up. Ten cases of SCLC were reported, with an incidence of SCLC of 22 cases in 100,000 person-years. SCLC accounted for 10 of all 164 lung cancer cases (6%) diagnosed in the screening. SCLC was diagnosed in 3 of 1643 women and 7 of 3385 men; their median age at diagnosis was 65 years (range 53 to 73 years) compared with 57 years for the overall population (range 50 to 75 years). Their cumulative tobacco consumption was 82 pack-years (range 30 to 113 pack-years) as compared with 39 pack-years (range 20 to 216 pack-years) for the overall study population and 46 pack-years (range 21 to 162 pack-years) for the subjects with NSCLC. Eight subjects were current smokers at the time of SCLC diagnosis, and two subjects were ex-smokers with a diagnosis of SCLC at 2 and 6 years after they had quit smoking quitting, with cumulative tobacco consumptions of 84 and 80 pack-years during their 42 and 40 years of smoking history at their age of diagnosis (63 and 66 years), respectively.

Eight cases of SCLC were reported in the LDCT arms (three in a pilot study, two in the annual LDCT arm of MILD, and three in the biennial LDCT arm of MILD [Table 1]), and two were reported in a control group. Six of the eight SCLC cases reported in the LDCT arms were detected by LDCT before onset of symptoms (Fig. 1). In addition, two SCLC from the LDCT arms were not detected by scan, one of which was assigned to an annual arm and the other to an biennial arm (Fig. 2). The two subjects were referred for medical care for symptoms during the sixth and ninth intervals between screening rounds.

Two subjects had previous malignancies, namely, epidermoid NSCLC (diagnosed within the annual LDCT arm of MILD) or cutaneous melanoma. Three subjects had a family history of lung cancer. None of the 10 subjects with SCLC showed signs of paraneoplastic syndrome. Nine subjects underwent clinical staging by ^{18}F-fluorodeoxyglucose–positron emission tomography (^{18}FDG-PET). The median standard uptake value for SCLC was 10 (range 5.5 to 14.4).

According to the clinical TNM classification, all but one of the cases of SCLC were at an advanced stage at the time of diagnosis, specifically, seven cases with stage IV disease, one case with stage IIIb disease, one case with stage IIIa disease, and 1 case with stage Ia disease. In particular, four of the seven cases of stage IV SCLC were either from the control group (two cases) or cases from