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

Table 1. Characteristics and Smoking History of Subjects with SCLC in the LDCT Arms[a]

Parameter	Subjects with SCLC in LDCT Arms (n = 8)
Ratio of females to males	3:5
Smoking history	
Duration, y	40 (40-48)
Pack-years	85 (30-113)
Ratio of former to current smokers	1:7
Previous lung cancer	1
Family history of lung cancer	
Yes	3
No	5
Age at diagnosis, y	66 (60-73)
Screen detection	
Yes	6
No	2
Screening round, y	6.5 (3-10)
Previous screen recall for CT findings other than tumor	
Yes	4
No	4
SUV at ^{18}FDG-PET	10 (5.5-14.4)
Stage:	
Limited	5
Extensive	3

[a]Subjects' demographic characteristics, screen detection, diagnostic work-up, clinical staging, and survival are reported for SCLC detected in the LDCT arms. Continuous variables are reported in terms of median and range.
SCLC, small cell lung cancer; LDCT, low-dose computed tomography; SUV, standard uptake value; ^{18}FDG-PET, ^{18}F-fluorodeoxyglucose-positron emission tomography.

the LDCT group that were not detected by screening (two cases).

LS-SCLC accounted for 62.5% of cases (five of eight) in LDCT arms, with 66.7% (four of six) among the screen-detected neoplasms and 50% (one of two) among those not detected by screening. In the control group, 100% of subjects had symptomatic ES-SCLC (e.g., they were referred for medical investigation because of unresolving pneumonia or persistent dyspnea).

The rate of non-screen-detected SCLC was two of eight (25%) in the whole series. In the sole MILD trial, non-screen-detected cancer occurred more frequently among cases of SCLC (two of five, 40%) than among cases of NSCLC (19 of 84, 22.6%), with SCLC representing 9.5% of all non-screen-detected tumors and 8.6% of all interval cancer cases.

Only two subjects underwent surgical resection by lobectomy: one subject with stage Ia disease underwent lobectomy for curative purposes (tumor diameter 10 mm, none of 14 lymph nodes examined showed metastatic involvement), but mediastinal lymph node relapse occurred in that subject after 8 months. Therefore, she was given chemotherapy and radiation therapy; however, she died of disseminated metastases after 19 months. One subject with stage IIIa disease underwent lobectomy by thoracotomy but died of systemic metastases 18 months after initial diagnosis. The remaining subjects were treated as follows: three subjects were given chemotherapy only and four received combined chemotherapy and radiation therapy. First-line chemotherapy with cisplatin and etoposide was the only pharmacological treatment administered to five subjects, whereas two were also treated with second-line chemotherapy based on a topoisomerase inhibitor. Radiotherapy was focused on the mediastinum and brain in all three subjects who received it for curative purposes, and one subject underwent palliative radiation therapy to the left humerus and thoracic spine for pain control.

Three subjects were still alive at the time of the final clinical follow-up (three subjects had stage IV disease with survival times after diagnosis of 9, 22, and 33 months). The median overall survival time for the whole series was 20.0 months (95% confidence interval [CI]: 11.5 to not calculable months) (Fig. 3). The subjects from LDCT arms had a median overall survival time of 20.6 months (95% CI: 13.6 to nc months), with a survival time of 22.7 months for those with screen-detected SCLC (95% CI: 15.4 to nc months), 9 months and 22 months for the two with non-screen-detected SCLC (both were alive and in stage IV at the time of this study), 26.9 months for those with LS-SCLC (95% CI: 18.9 to nc months), and 14.8 months for those with ES-SCLC (95% CI: 6.6 to nc months). The overall survival times of the two subjects with SCLC in the control group were 7.6 and 21.6 months. There were no survivors at the 3-year follow-up (Fig. 3).

Discussion

A total of 10 cases of SCLC were diagnosed in 45,141 person-years (22 in 100,000 person-years), with SCLC accounting for 6% of all tumors in the two screening trials. In LDCT arms, two of eight SCLC cases (25%) were non-screen-detected interval cancers. The tumors in LDCT arms were LS-SCLC in 62.5% of cases and ES-SCLC in 37.5%, whereas all the tumors in the control group were ES-SCLC. The outcome of SCLC remained unsatisfactory, with a median survival time of 26.9 months for LS-SCLC and no survivors at 3-year follow-up despite the one case of stage Ia SCLC that had been treated with radical surgery.

Clinical reports show extremely short survival of SCLC[2] and minor improvement in therapy during the past 25 years, with a median overall survival time of 15 to 20 months for LS-SCLC alone.[14] In lung cancer screening trials, SCLC is still being diagnosed in TNM

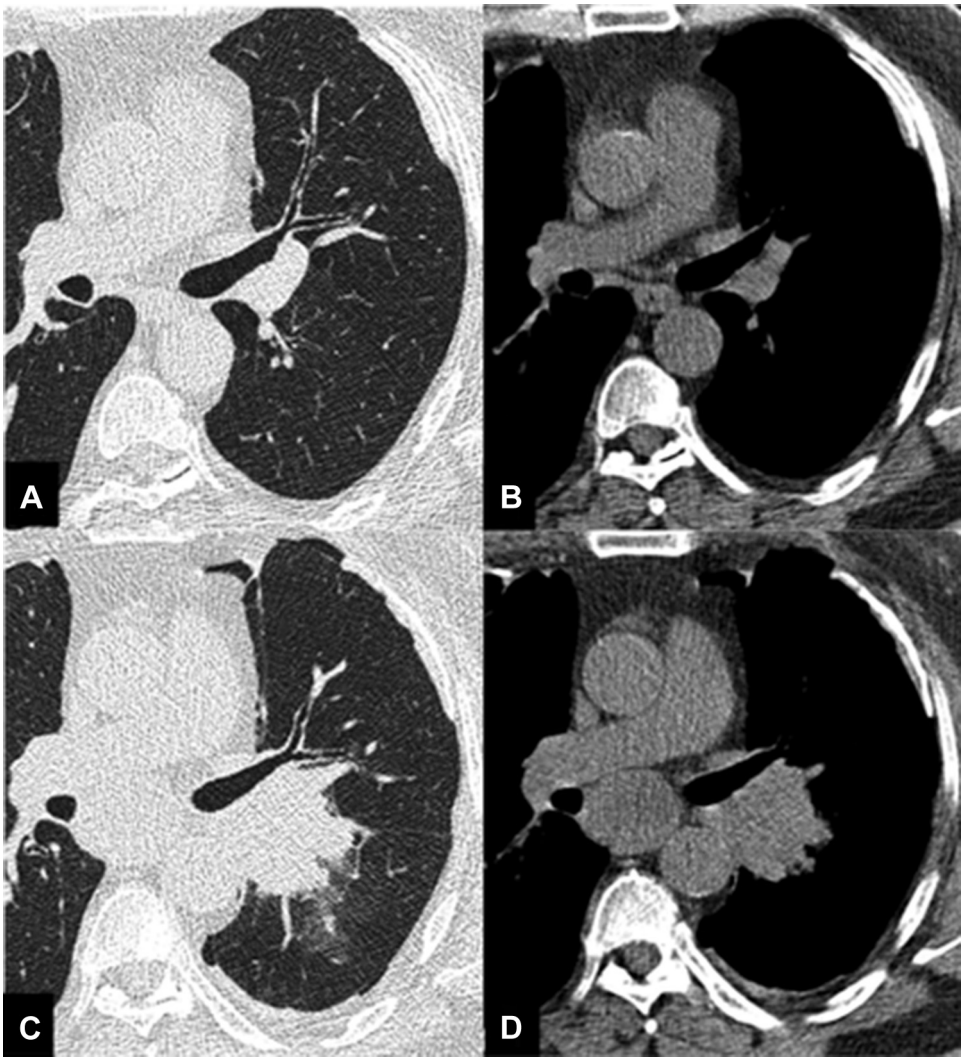

Figure 1. Screen-detected extensive-stage single cell lung cancer (SCLC) in a participant undergoing biennial low-dose computed tomography scan. SCLC is an extremely aggressive histotype of lung cancer that can hamper interval between screening rounds, as seen in this case with no parenchymal or mediastinal abnormalities at year 2 (*A* and *B*), but evidence at year 3 of untreatable neoplasm in an asymptomatic subject with a left parahilar solid mass (*C*) and subcarinal lymph node enlargement with central necrosis (*D*). This case was confirmed as extensive-stage SCLC by mediastinoscopy.

stage III–IV in 80% to 90% of cases,[15] whereas the percentage of NSCLC cases being diagnosed at an early stage is increasing. In particular, because of its extremely aggressive behavior, SCLC frequently occurs as interval cancer despite annual LDCT screening. The NELSON group observed an incidence of SCLC of approximately 26 cases in 100,000 person-years, with SCLC accounting for 7% of all tumors and representing 20% of all interval cancers. In particular, SCLC was detected during screening in only 53% of cases.[7] These results are similar to those from our study, which reported an incidence of SCLC of 22 cases in 100,000 person-years, with SCLC accounting for 6% of all lung tumors and 8.6% of all interval cancers and being detected by screening in 75% of cases. The NLST group reported an incidence of SCLC of 83 cases in 100,000 person-years and a frequency of 13% among all lung tumors, with SCLC representing 34% of all interval cancer cases and having a rate of detection during screening of 66%.[15] The higher incidence of SCLC in the NLST than in our results and those of the NELSON group likely reflects the higher median tobacco consumption in the NLST (approximately 56 pack-years)[16,17] than in European trials (39 and 38 pack-years, respectively [Table 2]) and perhaps a slightly higher median age (61 years versus 57 and 58 years, respectively).[17] Of note, the association between cigarette smoking and SCLC was also observed within our cohort, in which median number of pack-years in the SCLC group was more than twice that in the overall population (82 and 39 pack-years) and also much higher than in the NSCLC group (46 pack-years).

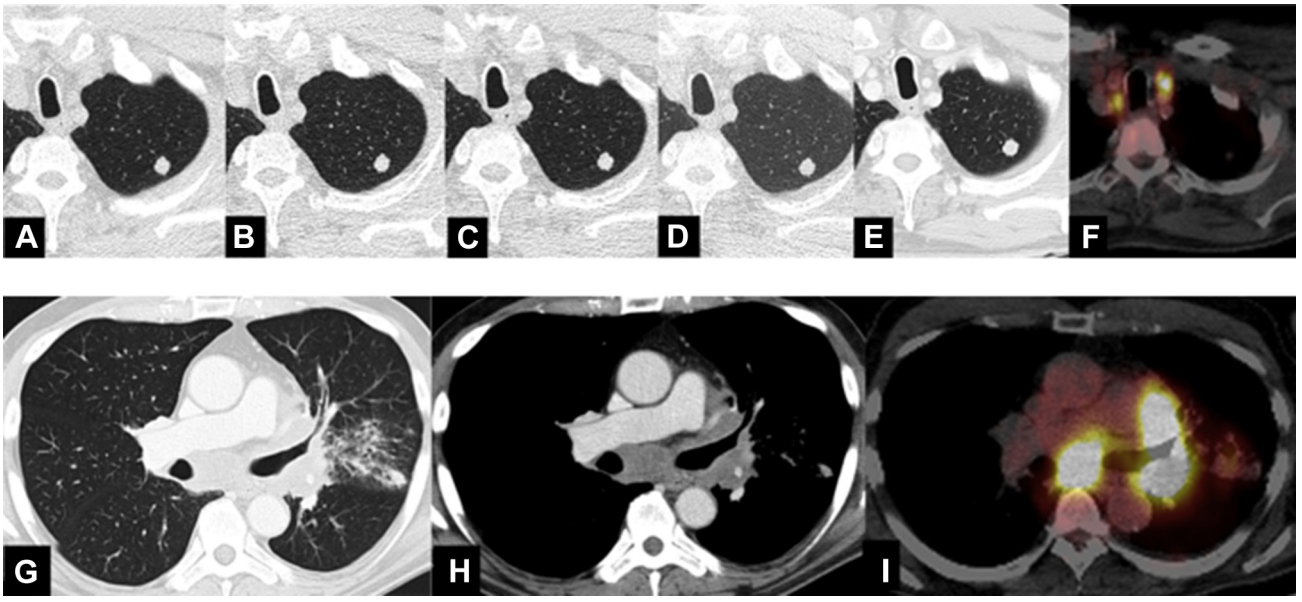

Figure 2. A false-positive finding requiring further investigation and non-screen-detected extensive-stage single cell lung cancer in a participant undergoing biennial low-dose computed tomography (LDCT) scan. The specificity of LDCT for solid noncalcified nodules detected at baseline is low, which can necessitate further investigation (e.g., additional LDCT control and positron emission tomography (PET)-CT characterization (*A*-*F*); this limitation is reflected in overdiagnosis of slow-growing neoplasms or benign findings. On the other hand, screening with LDCT does not provide clinical improvement of aggressive thoracic tumor (*G*-*I*). A noncalcified solid pulmonary nodule of the left upper lobe was detected at T0 (*A*) and remained stable over three biennial LDCT controls (*B*, *C*, and *D*), as well as on a CT scan with contrast agent that was performed almost 2 years after the previous LDCT control (*E*). Thereafter, the nodule was confirmed as benign by ^{18}F-fluorodeoxyglucose-PET-CT (*F*). The subject underwent CT with a contrast agent for work-up of a cough with persistent hemoptysis. The CT scan showed a left hilar mass with irregular reticulation of the adjacent lung parenchyma, suggesting lymphangitis carcinomatosa (*G*) and diffuse mediastinal lymphadenomegaly with compression of the airways (*H*), which showed high uptake of ^{18}F-fluorodeoxyglucose during PET-CT (*I*).

To our knowledge, this is the first report about outcome of SCLC in the setting of a lung cancer screening trial. Median survival time in our study was slightly longer than those reported in the clinical literature.[14] We think that this limited improvement should be attributed to the anticipation of diagnosis rather than to actual improvement of outcome. In this study, we report a higher rate of ES-SCLC in the control group than in the LDCT arm; however, the large number of LS-SCLC cases in LDCT arms did not warrant significant clinical improvement. From our experience, the lack of real advantage from early diagnosis was related to the poor efficacy of current treatment options for progression of the disease.[25,26] Surgery is usually not an option in such subjects because systemic spread and paraneoplastic syndrome typically impede the therapeutic potential of resection. In particular, we reported an anecdotal case of stage Ia SCLC in which radical surgery did not prevent mediastinal relapse, systemic spread of the disease, and cancer-related death within 3 years from diagnosis. Dedicated research on novel medical therapy is being fostered in an attempt to provide systemic treatment of SCLC.[27] Recently, the comprehensive genomic profile of 110 patients with SCLC was investigated; the investigation found evidence of biallelic inactivation of the tumor protein p53 gene (*TP53*) and the retinoblastoma 1 gene (*RB1*) in more than 90% of the cases and inactivating mutations in NOTCH family genes in 25% of them.[28] Overall, the study identified several novel candidate genes, some of which appear to be possible targets for more efficacious therapy for SCLC.[28]

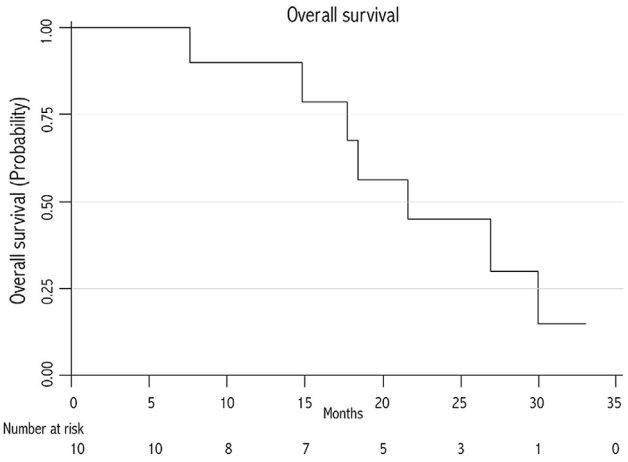

Figure 3. Overall survival curve shows no survivors at 3 years after diagnosis of SCLC.

Table 2. Incidence of SCLC and Proportion of SCLC with Respect to All Lung Cancers, Median Tobacco Consumption, and Patient Age[a]

Lung Cancer Screening Trial	SCLC (n in 100,000 Person-Years)	SCLC as Percentage of Lung Cancer Cases (%)	Cumulative Tobacco Consumption (Median Pack-Years)	Age (y)
NY-ELCAP[18]	69	10	40	66
DANTE[19]	97	8	47	64
DLST[20,21]	51	11	NA	NA
NLST[16,17]	83	13	56	61
ITALUNG[22]	56	9	42	61
COSMOS[23]	81	10	NA	58
NELSON[7]	26	7	38	58
LUSI[24]	65	13	NA	NA
Current study	22	6	39	57

[a]Data are reported for major lung cancer screening trials worldwide, along with median tobacco consumption and age.
SCLC, small cell lung cancer; NY-ELAP, New York-Early Lung Cancer Action Project; DANTE, Dante Trial. A Randomized Study on Lung Cancer Screening with Low-Dose Spiral Computed Tomography; DLST, Danish Lung Screening Trial; NA, not applicable; NLST, National Lung Screening Trial; ITALUNG, Italian Lung Trial; COSMOS, Continuous Observation of Smoking Subjects; NELSON, Dutch-Belgian Lung Cancer Screening Trial; LUS1, Lung Screening and Intervention trial.

This paper highlights a limitation of lung cancer screening by LDCT that lies at the edge opposite overdiagnosis, which was reported by Patz in more than 18% of NSCLC.[29] In particular, our results show that lung cancer screening by LDCT is unable to improve the outcome of SCLC. The only two subjects amenable to surgical resection for curative purposes died within 2 years. This finding confirms in practice the theory of Baldwin et al., who postulated the insufficiency of annual LDCT-screening for detection of fast-growing tumors such as SCLC because they hamper a sustainable LDCT screening protocol.[30] Therefore, primary prevention appears to be the only currently existing option for reduction of mortality due to SCLC. Smoking cessation programs should be regarded as a mandatory strategy within screening and should be extensively implemented in countries in which screening will be applied to general population, such as the United States.[31] On the basis of our results, we suggest that a smoking cessation program could be the optimal strategy to reduce mortality due to SCLC, which is closely related to active smoking[2] and shows a progressive decrease in risk by the time of quitting smoking.[32] Therefore, a smoking intervention forearm of LDCT screening along with the use of active drugs such as varenicline should be considered.[33]

This study has one main limitation: the small number of SCLC cases, which limited the possibility of comparison between SCLC in the screening and control groups and between screen-detected and non-screen-detected SCLC. This limitation also prevented comparison of SCLC with NSCLC. Another limitation is the presence of recently diagnosed SCLC cases, for which long-term evolution could not be described. However, they are unlikely to improve the outcome of SCLC in the MILD trial because of their advanced stage (all patients in stage IV).

Conclusions

In conclusion, the subjects in whom SCLC developed were a subgroup of smokers with extremely high cumulative tobacco consumption. Accordingly, the frequency of SCLC in our population was lower than in a population with higher cumulative tobacco consumption. Screening did not provide improvement of the therapeutic outcome of SCLC compared with that in clinical reports. In our study, median overall time of survival of LS-SCLC was slightly longer than that of ES-SCLC, which is apparently related to anticipation of diagnosis. Surgery was ineffective even in stage Ia SCLC, and no patients were alive at 3 years.

Acknowledgments

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