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Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT

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ABSTRACT

Background: Results of randomized clinical trials (RCTs) are needed to assess the efficacy of lung cancer screening with low-dose chest computed tomography (CT) in reducing lung cancer mortality. We report design and results of enrolment and baseline screening test in the ITALUNG trial, a RCT.
Methods: Invitation letters were sent to subjects of 55–69 years of age clients of 269 general practitioners. Smokers or former smokers of at least 20 pack/years were eligible and after written consent were randomized in an active arm undergoing a low-dose CT annually for 4 years and in a control arm receiving no screening. Management of positive screening test was carried out using follow-up low-dose CT, fluorodeoxyglucose positron emission tomography, fine needle aspiration cytology and fiber optic bronchoscopy.
Results: A sample of 3206 eligible subjects was achieved by sending 71,232 letters (enrolment efficacy = 4.5%). Subjects in control (n = 1593) and active (n = 1613) arm were balanced for age, gender and smoking history. Two-hundred and seven (12.8%) subjects did not undergo CT after randomization. The baseline screening test was positive in 426 (30.3%) of 1406 subjects.

Abbreviations: CT, computed tomography; FBS, FibroBronchoScopy; FDG-PET, FluoroDeoxyGlucose positron emission tomography; FNA, fine needle aspiration; GP, general practitioner; MD, multi-detector; NCN, non-calcified nodule; NSCLC, non-small cell lung cancer; RCT, randomized clinical trial; SCLC, small cell lung cancer; SD, single detector.

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Twenty-one lung cancers (prevalence = 1.5%) were found in 20 subjects: 18 non-small cell lung cancer (NSCLC), 2 small cell lung cancer (SCLC) and a case of typical carcinoid. Ten NSCLC (47.6%) were in Stage I. Sixteen fine needle aspirations were performed in 15 lung cancers, with a positive result in 12 (75%) cases. One biopsy only (6.3%) was performed on a benign lesion. Seventeen lung cancers (81%) were treated with surgical resection in 16 subjects. One subject underwent surgery for a benign lesion (5.5% of all surgical resections).

Conclusions: Recruitment by mail of high risk subjects for a lung cancer screening RCT is feasible but not efficient. Results of the baseline screening test in the active arm of the ITALUNG trial are substantially in line with those of RCT and observational studies.

1. Introduction

Many observational (one arm) studies demonstrated that low-dose computed tomography (CT) is a sensitive tool for the identification of early lung cancer [1–5] and a 10-years survival rate of 88% was estimated for Stage I screen detected cases [6]. However results from randomized clinical trials (RCTs) are needed to assess the efficacy of lung cancer screening with low-dose CT in reducing mortality from lung cancer [7].

Two large RCTs are currently under way, namely the National Lung Screening Trial (NLST) in the United States [8] and the NELSON study in The Netherlands [9], with results expected in the forthcoming years, whereas the baseline results of three small RCTs are already available named Lung Screening Study (LSS), DEPISCAN and DANTE [10–12]. Our study, ITALUNG trial, is a relatively small-size multicentric RCT [13] ongoing in Tuscany, Italy, and is part of the EU-US Collaborative Spiral CT working group [14]. This is an international collaboration whose project is the pooling of data from trials sharing a similar standardized protocol and the creation of a powerful dataset on subjects undergoing lung cancer screening with low-dose CT [14]. Herein we present the study design and the results of enrolment procedure and baseline screening test in subjects of the active arm of the ITALUNG trial.

1.1. Methods and materials

ITALUNG is a RCT for lung cancer screening with low-dose CT carried out in three screening centers in Florence, Pisa and Pistoia districts of the Tuscany region of Italy. The study was completely funded by the Regional Health Public Authority and approved by the Local Ethic Committee of each participating institution.

The study involves 269 general practitioners (GPs) operating in the 3 districts, one screening centre for each district, where CT scans and clinical management are performed, and the Institute for Cancer Prevention Research (CSPO) of Florence as a coordinating centre.

The base for subject recruitment was the list of subjects in the 55–69 years range resident in one of the 3 districts where the screening centres are located and registered with one of the GPs who has accepted to participate in the study. These subjects received a letter signed by their GP and by the local screening centre in which the aims and characteristics of the study were explained and a standardized multiple choices questionnaire about age, gender, smoking history, and general health information were enclosed. The candidates were asked to sign their consent of being randomized and to send the letter back to the coordinating centre by mail, free of charge, or to give the questionnaire back to his/her GP. Only subjects registered with participating GPs who gave the letter back with the consent to the randomization were enrolled in the trial.

The consent to be enrolled and randomized was contained in the initial mailing as the consent to be followed up by the GP. All respondents signed the consent before knowing their eligibility and randomization status.

Eligible for the study were subjects aged between 55 and 69 years at the time of enrolment with a smoking history of at least 20 packs–year since the last 10 years (former smokers who quitted since more than 10 years were excluded). Other exclusion criteria were a history of previous cancer other than non-melanoma skin cancer and general conditions precluding thoracic surgery. Eligible subjects only were centrally randomised by a software procedure in an active arm receiving annual low-dose CT for 4 years and a control arm receiving usual care but no screening. Subjects randomized in the control arm then received a letter communicating their allocation in the no screening arm of the study and an invitation for a free access to a smoking cessation program.

Subjects randomized into the active arm were contacted by phone call to have an appointment for an interview in which a pneumologist after providing further information about CT scan and positive findings management collected the consent for CT examination and scheduled the CT screening test. An additional written consent for enrolment in a biomarkers collateral research project was also requested. A free-access invitation to a smoking cessation program was provided to all the subjects enrolled in the study.

All randomised subjects will be followed up by cancer registry of the Tuscany Region (http://www.cspo.it/) for incidence and mortality. Furthermore each enrolled subject or his/her GP will be interviewed by telephone after 4 years since randomisation to assess health conditions and smoking habits.

We considered subjects who withdrew from the screening process at whatever time after randomisation as drop-outs.

The CT screening tests were performed using five spiral CT scanners including one with single row of detectors (SD) and four with multi-rows of detectors (MD). Low-dose acquisition techniques followed the international recommendations [15] including 120–140 kVp, 20–43 mA and bone reconstruction filter. Slice collimation was 3 mm with 1.5 mm reconstruction interval with the SD scanner and 1–1.25 with 1–1.25 mm reconstruction interval with the MD scanners. Each CT scan was read independently by two radiologists on a work-station with a consensus reached in case of disagreement. Three radiologists performed all the first reading, while 15 additional radiologists performed the second reading. All 18 radiologists had a minimum of 4 years experience in chest CT.

Within the next 3 weeks the result of the baseline screening test was mailed home if negative, whereas subjects with positive test received a phone call by the local screening centre and were invited to meet the pneumologist for further assessment.

The main criterion for test evaluation was the nodule size, measured manually with electronic callipers on the workstation. CT scans was considered as negative when no focal abnormalities were found and also when solid non-calcified nodules (NCN) < 5 mm in mean diameter or pure non-solid nodules with a mean diameters < 10 mm were observed. In case of negative baseline screening test the subject was scheduled for the annual repeat screening test.

The test was considered as positive when it demonstrated at least one NCN $\geq$ 5 mm or a non-solid nodule $\geq$ 10 mm or the presence of a part-solid nodule. Management of positive screening test