Four-Year Results of Low-Dose CT Screening and Nodule Management in the ITALUNG Trial

Andrea Lopes Pegna, MD Giulia Picozzi, MD,† Fabio Falaschi, MD,‡ Laura Carrozzi, MD,§ Massimo Falchini, MD, ‖ Francesca Maria Carozzi, MD,¶ Francesco Pistelli, MD, § Camilla Comin, MD,# Annalisa Deliperi, MD,‡ Michela Grazzini, MD,** Florio Innocenti, MD,** Cristina Maddau, MD,¶ Alessandra Vella, MD, PhD,†† Luca Vaggelli, MD, ‖ ‖ Eugenio Paci, MD, PhD,¶¶ and Mario Mascalchi, MD, PhD ‖ for the ITALUNG Study Research Group*

Introduction: Recruitment and nodule management are critical issues of lung cancer screening with low-dose computed tomography (LDCT). We report subjects' compliance and results of LDCT screening and management protocol in the active arm of the ITALUNG trial.

Methods: Three thousand two hundred six smokers or former smokers invited by mail were randomized to receive four annual LDCT (n = 1613) or usual care (n = 1593). Management protocol included follow-up LDCT, 2-[^{18}F]fluoro-2-deoxy-D glucose positron emission tomography (FDG-PET), and CT-guided fine-needle aspiration biopsy (FNAB).

Results: One thousand four hundred six subjects (87%) underwent baseline LDCT, and 1263 (79%) completed four screening rounds. LDCT was positive in 30.3% of the subjects at baseline and 15.8% subsequently. Twenty-one lung tumors in 20 subjects (1.5% detection) were found at baseline, and 20 lung tumors in 18 subjects (0.5% detection) in subsequent screening rounds. Ten of 18 prevalent (55%) and 13 of 17 incident (76%) non–small-cell cancers were in stage I. Interval growth enabled diagnosis of lung cancer in 16 subjects (42%), but at least one follow-up LDCT was obtained in 741 subjects (52.7%) over the screening period. FDG-PET obtained in 6.5% of subjects had 84% sensitivity and 90% specificity for malignant lesions. FNAB obtained in 2.4% of subjects showed 90% sensitivity and 88% specificity. Positivity of both FDG-PET and FNAB invariably predicted malignancy. Surgery for benign lesions was performed on four subjects (10% of procedures) but followed protocol violations on three subjects.

Conclusions: High-risk subjects recruited by mail who entered LDCT screening showed a high and stable compliance. Efficacy of screening is, however, weakened by low detection rate and specificity. Adhesion to management protocol might lessen surgery for benign lesions.

Key Words: Cancer, Computed tomography, Nuclear medicine, Pulmonary biopsy.

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*Pneumonology Department, Careggi Hospital, Florence, Italy; †Radiodiagnostic Unit, Institute for Oncological Study and Prevention, Florence, Italy; ‡2nd Radiology Department, University Hospital of Pisa, Italy; §Cardiopulmonary Department, University Hospital, Pisa, Italy; ‖Radiodiagnostic Section, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Italy; ¶Analytical Cytology and Bio-Molecular Unit, Institute for Oncological Study and Prevention, Florence, Italy; #Pathology Department, Careggi Hospital, University of Florence, Italy; **Pneumonology, Hospital of Pistoia, Italy; ††Nuclear Medicine Unit, Le Scotte University Hospital, Siena, Italy; ‖ ‖Nuclear Medicine Unit, Careggi Hospital, Florence, Italy; and ¶¶Department of Epidemiology, Institute for Oncological Study and Prevention, Florence, Italy.

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Members of the ITALUNG Study Research Group: Andrea Lopes Pegna, MD, Roberto Bianchi, MD, and Cristina Ronchi, MD: Pneumonology Department, Careggi Hospital, Florence Italy. Laura Carrozzi, MD, Ferruccio Aquilini, BSc, Stella Cini, MD, Mariella De Santis, MD, Francesco Pistelli, MD, Filomena Baliva, MD, Antonio Chella, MD, and Laura Tavanti, MD: Cardiopulmonary Department, University Hospital of Pisa, Italy. Michela Grazzini, MD, Florio Innocenti, MD, and Ilaria Natali, BSc: Pneumonology Department, Hospital of Pistoia, Italy. Mario Mascalchi, MD, PhD, Maurizio Bartolucci, MD, Elena Crisci, MD, Agostino De Francisci, MD, Massimo Falchini, MD, Silvia Gabbrielli, MD, Giulia Picozzi, MD, Giuliana Roselli, MD, and Andrea Masi, MD: Radiology Department, Careggi Hospital, University of Florence, Italy. Fabio Falaschi, MD, Luigi Battola, MD, Anna Lisa De Liperi, MD, and Cheti Spinelli, MD: Radiology Department, University Hospital of Pisa, Italy. Letizia Vannucchi, MD, Alessia Petruzzelli, MD, Davide Gadda, MD, Anna Talina Neri, MD, and Franco Niccolai, MD: Radiology Department, Hospital of Pistoia, Italy. Luca Vaggelli, MD: Nuclear Medicine Department, Careggi Hospital, Florence, Italy. Alessandra Vella, MD, PhD: Nuclear Medicine Department, Le Scotte University Hospital, Siena, Italy. Francesca Maria Carozzi, BSc and Cristina Maddau, BSc: Laboratory Unit, Institute for Oncological Study and Prevention, Florence, Italy. Alberto Janni, MD: Thoracic Surgery Department, Careggi Hospital, Florence, Italy. Alfredo Mussi, MD and Marco Lucchi, MD: Thoracic Surgery Department, University Hospital of Pisa, Italy. Camilla Comin, MD: Pathology Department, Careggi Hospital, University of Florence, Italy. Gabriella Fontanini, MD, Adele Renza Tognetti, MD, Pathology Department, University Hospital of Pisa, Italy. Eugenio Paci, MD, PhD, Giovanna Cordopatri, BSc, Francesco Giusti, BSc, PhD, and Ida Esposito, BSc: Department of Epidemiology Institute for Oncological Study and Prevention, Florence, Italy.

Address for correspondence: Mario Mascalchi, MD, PhD, Radiodiagnostic Section, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy. E-mail: m.mascalchi@dfc.unifi.it

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In Western countries, lung cancer is the most common malignant neoplasm in men, and its frequency is constantly increasing in women.[1] Non–small-cell lung cancer (NSCLC) accounts for approximately 85% of these neoplasms.[2,3] Although the age-adjusted trends of mortality are decreasing, survival rates for lung cancer are still 10% to 16%.[4,5] In particular, only 15% to 20% of symptomatic patients have lesions amenable to radical surgical resection.[6]

Randomized clinical trials (RCTs) with chest radiograph as screening test for lung cancer failed to show any benefit in smokers and former smokers because of an excess of deaths in the screened arm. This was presumably because of the high number of surgically resected cancers with associated side effects and unnecessary surgical procedures for indolent cancers in the active arm.[7–10]

After publication of the Early Lung Cancer Action Project (ELCAP) study results in 1999,[11] several observational (one-arm) studies assessed the performance of low-dose computed tomography (LDCT) as a screening tool for lung cancer in at-risk individuals.[12] The largest observational study, the International-ELCAP study,[13] confirmed the high sensitivity of LDCT as a screening test and reported a 88% 10-year survival rate after surgical resection in screen-detected stage I lung cancers. However, observational studies are insufficient to establish the efficacy of a screening test in reducing tumor-specific mortality because they suffer from lead time, length, and overdiagnosis bias.[14–16]

Accordingly, several RCTs for lung cancer screening with LDCT have been implemented in United States and Europe.[17–25] In 2011, the largest RCT in United States, namely the National Lung Screening Trial (NLST),[26] was halted because an interim analysis after 8 years of follow-up showed a 20% mortality reduction in the screened arm receiving annual LDCT for three rounds as compared with control arm receiving annual chest radiograph for three rounds.[27] The result of the NLST is the first one supporting the efficacy of LDCT as a screening test in reducing mortality from lung cancer in high-risk individuals, and has considerably renewed interest and enthusiasm, as also criticisms[28–30] about the possibility of offering LDCT on a large scale to smokers and former smokers. The latter has been recently recommended[31,32] despite the negative short-term results concerning decrease of mortality of three small RCTs in Europe.[18,33,34]

Variable approaches concerning subjects recruitment, timing and reading of the LDCT screening test, and the protocol for management of screen-detected suspicious nodules were proposed.[18,21,25,27,35–37] Comparative analyses of the different studies are fundamental for a thorough evaluation of efficacy of the screening procedure. To date, the complete, namely during the entire screening period, performance of both LDCT as a screening test and the management strategy for suspicious nodules was reported in five RCTs, namely the Lung Screening Study,[38] the NLST,[27] the DANTE and MILD trials in Italy,[18,33] and the Danish Lung Cancer Screening trial.[34,37]

The Italian Lung (ITALUNG) study is an RCT part of an international cooperation, aimed at the pooled evaluation of the results of the RCTs of lung cancer screening with LDCT in Europe and possibly United States.[39] The ITALUNG study design, enrolment procedure, and the results of the baseline screening round were previously reported.[20] Herein, we present the final data concerning the compliance of the subjects recruited in the active arm of the trial, who were invited to undergo four annual LDCT, the results of the LDCT screening test in the four screening rounds, and the results of management protocol for screen-detected suspicious nodules.

MATERIALS AND METHODS

ITALUNG is an RCT aimed to evaluate the efficacy of chest LDCT as a screening test in reducing lung cancer mortality, which is carried out in the Tuscany region of Italy.

The study was conducted in accordance with the amended Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/) and approved by the Local Ethic Committees of the participating institution (approval number 29–30 of September 30, 2003; number 23 of October 27, 2003; and number 00028543 of May 13, 2004).

Selection and Randomization of Study Participants

Strategy and results of the exclusive mail recruitment of trail participants were previously reported.[20] Those eligible for the trial were asymptomatic smokers and formers smokers aged 55 to 69 years, with a smoking history of at least 20 pack-years, and no history of cancer, other than nonmelanoma skin cancer, or general conditions precluding thoracic surgery.

Subjects randomized to the control arm received a letter communicating their allocation in the *usual care* arm of the study, in which no LDCT or chest radiograph is scheduled. Subjects randomized into the active arm were contacted by phone to fix an appointment for counseling, during which a pneumonologist, after providing further information about the screening LDCT examination and management of positive screening tests, collected the consent for LDCT examination, and scheduled the LDCT screening test. An additional written consent for enrolment in a biomarkers-collateral study was requested during the interview.[40] A free-access invitation for a smoking cessation program was provided to smokers enrolled both in the active and in the control arms.

All randomized subjects are planned for follow-up by cancer registry of the Tuscany region (http://www.ispo.toscana.it) for 7 years from randomization, to assess incidence of lung cancer and mortality from lung cancer or other causes. Although no specific instruction about the workup of cases of lung cancer in the control arm was provided to general practitioner or the enrolled subject, the low rate of migration of patients, who receive a diagnosis of primary lung cancer in the Tuscany region (< 3%, personal unpublished observation, 2011), makes it probable that they will be referred in the same structures participating in the ITALUNG trial. Because the management of the suspicious nodules in the ITALUNG trial is derived by the clinical practice (see below), it is expected that no major discrepancies will be active in the workup, diagnosis, and staging of such cases, and that the related information will be available and gathered from hospital chart recordings at the end of the study. The first mortality data concerning the subjects enrolled in the ITALUNG are expected for 2014.

The present report is based on the data of the subjects randomized to the active arm of the trial, who underwent baseline LDCT and were invited again for the next three annual repeat LDCT examinations. Individuals in whom lung cancer was diagnosed were not offered subsequent screening rounds.

Procedure and Instrument of Screening

The LDCT examinations were obtained in the three screening centers on eight different spiral scanners, which included one with a single row of detectors, and seven with multiple rows of detectors (3 with 4, 2 with 16, and 2 with 64 rows). The following technical parameter ranges were selected to contain the radiation dose: 120 to 140 kV, 20 to 43 mAs, pitch 1 to 2. The section collimations ranged between 3 mm in the single-detector scanner, and 0.75 mm in the 64-row detector scanner.

Because double reading increases the sensitivity of LDCT screening,[41] each LDCT examination was assessed on a workstation independently by two of 17 certified radiologists having at least 5 years of experience in chest computed tomography (CT). A consensus between the two radiologists was reached in case of disagreement. All previous LDCT examinations of the subject obtained in the context of the trial were available for comparison. Management of positive screening tests was carried out at each screening center according to a shared protocol,[20] which is fundamentally derived from that of the International-ELCAP Study.[35] This includes follow-up LDCT with or without 1 month of antibiotic therapy, chest 2-[^{18}F]fluoro-2-deoxy-D glucose positron emission tomography (FDG-PET), and CT-guided fine-needle aspiration biopsy (FNAB). Optical fibrobronchoscopy (FBS) was also performed on selected cases.

The FDG-PET examinations were performed in three centers using four scanners, two of which were dedicated positron emission tomographs (one GE Advance positron emission tomography [PET] scanner; General Electric, Milwaukee, WI; one ECAT Exact HR+ scanner; Siemens, Erlangen, Germany), and two dual-modality PET-CT scanners (1 Discovery LS; General Electric, Milwaukee, WI; 1 Gemini; Philips, Eindhoven, The Netherlands). Three trained nuclear medicine physicians visually evaluated the tracer uptake of the suspicious lesion and classified the result of the FDG-PET as positive, indeterminate (mild or faint FDG uptake, typically similar to that of mediastinum), or negative. Because most of the nodules to be investigated were of small size, we did not use the standardized uptake value because it can be unreliable in characterizing nodule uptake.[37,42] Moreover, taking into consideration that tumors identified at lung cancer screening with LDCT can show low FDG uptake,[42,43] for the purpose of computation of performance of FDG-PET, we assimilated indeterminate to positive FDG-PET results.

The majority (35 of 38) of the CT-guided FNAB was performed by two experienced interventional radiologists on a single-detector spiral CT scanner (Somatom plus 4; Siemens, Erlangen, Germany) used for the LDCT examination in one screening center, where aspiration material was evaluated by one trained cytopathologist, with rapid onsite examination (ROSE) technique.[44,45] Three CT-guided FNAB without ROSE were performed by a chest radiologist on a four-detector spiral CT scanner (Somatom Volume Zoom; Siemens, Erlangen, Germany) used for LDCT examination in another screening center. For the purpose of computation of performance of CT-guided FNAB, we assimilated inconclusive results because of inadequate or insufficient material to negative FNAB.

Criteria for Positive Test and Further Diagnostic Investigations

Positivity of the LDCT screening test was fundamentally based on the nodule size or growth measured in terms of mean diameter, which was manually computed by the radiologist with electronic callipers on workstations.[20] In particular, significant growth was defined as an increase of at least 1 mm in mean diameter of a solid or nonsolid nodule, taking into account the intra- and interoperator variability in measuring mean diameter of solid nodules,[46] or the appearance or increase of a solid component in a nonsolid or part-solid nodule in two successive LDCT examinations.[35] The criteria for positive tests and further diagnostic investigations concerning baseline screening round were previously detailed.[20] At annual repeat screening rounds, the LDCT examination was considered positive if either a new solid, part-solid or nonsolid nodule was identified, or at least one solid, part-solid or nonsolid nodule already present in the last LDCT showed interim growth. If the new nodule had a mean diameter 3 mm or less, the subject received a 6-month follow-up LDCT, whereas a 3-month follow-up LDCT was obtained in case of a new nodule with mean diameter between 3mm and 5mm. In case of a nodule that was 5 mm or more in size, or if the screening test revealed multiple focal solid or nonsolid abnormalities consistent with inflammatory disease, a follow-up LDCT after 1 month of antibiotic therapy was recommended. In case of complete resolution of the abnormalities, the subject was sent for annual repeat screening, whereas, a further follow-up LDCT after 2 months was performed in case of partial or lack of resolution after antibiotic therapy.

When a solid nodule observed at baseline or repeat screening round attained a mean diameter 8 mm or more, and persisted after antibiotic therapy, chest FDG-PET examination was recommended. However, in some cases of large lesions, strongly suggestive for malignancy, CT-guided FNAB or FBS were directly performed. For FDG-PET–positive nodules, a CT-guided FNAB with ROSE was recommended, whereas, a further 3-month follow-up LDCT was obtained in FDG-PET–indeterminate or –negative nodules. A 3-month follow-up LDCT was also scheduled for nodules with positive or indeterminate FDG-PET and negative or inconclusive CT-guided FNAB. All subjects showing no nodule growth at this latter follow-up LDCT were invited to the subsequent annual repeat LDCT scan. For pure nonsolid noncalcified nodules of at least 10 mm diameter at baseline, and for new or growing nonsolid or part-solid nodule of at least 8 mm diameter at annual repeat screening, which persisted after antibiotic therapy, CT-guided FNAB was scheduled because FDG-PET is not indicated.[47]

All subjects with FNAB evidence of malignancy underwent a staging full-dose chest CT examination, with intravenous iodinated contrast administration extended to upper abdomen and head. Surgery was recommended for nodules with findings consistent with malignancy at FNAB and also in subjects with an FDG-PET–positive solid nodule, which was inconclusively evaluated at FNAB. All the surgically removed lesions were evaluated according to the World Health Organization criteria.[48] Staging of screen-detected lung cancer was based on the pathology report when available, or on

clinical and contrast-enhanced CT findings in the cases not amenable to surgical resection.

Sputum and blood samples were obtained from each participant at baseline LDCT screening test and again in case of positive LDCT examination; all the samples were stored for subsequent biomarker evaluation.[40] The global and individual radiation dose to subjects recruited in the active arm of the ITALUNG trial has been previously reported.[49]

RESULTS

One thousand six hundred thirteen subjects (1035 men and 578 women; mean age = 60.7 years; mean pack-years = 42.9; 553 former smokers) were randomized to the active arm, and 1593 (1039 men and 554 women; mean age = 61.0 years; mean pack-years = 41.6; 575 former smokers) to the control arm. The first baseline LDCT was obtained in March 2004 and the last annual LDCT examination in February 2010. Table 1 summarizes the compliance of the subjects randomized to the active arm, the results of the screening LDCT, the nodule management, and the screen-detected NSCLC in the four screening rounds of the ITALUNG trial.

One thousand four hundred six (910 men with a mean age of 61.1 years and 496 women with a mean age of 60.6 years) of the subjects (87.1%) randomized to the active arm underwent the baseline LDCT. After exclusion from the next round of invitation of subjects in whom the screening procedure revealed lung cancer, 1356 (85.1%) executed the second, 1308 (82.3%) the third, and 1263 (79.8%) the fourth annual screening round with LDCT.

LDCT was positive in 30.3% at baseline and 15.7% (range, 13.7–17.3%) at the three annual repeat screening rounds (Table 1). Twenty-one cancers (18 NSCLC, 1 carcinoid, 2 small-cell lung cancers [SCLCs]) were found in 20 subjects at baseline screening round (prevalent cancers detection rate 1.5%), and 20 (17 NSCLC, 2 carcinoid, 1 SCLC) cancers in 18 subjects at the third annual repeat screening rounds (mean incident cancers detection rate 0.5%). Adenocarcinoma (AC) accounted for nine of 18 (50%) of the NSCLCs at baseline and for 15 of 17 (88%) at subsequent annual repeat screening rounds. Three subjects of 38 (7.8%) in whom lung cancers were screen detected had two malignant lung tumors. One had AC in right lung and SCLC (limited disease) in the left lung, one had AC in the right lung and a carcinoid in the left lung, and one had AC in the right lung and AC with bronchiole-alveolar features in the left lung. Isolated lung metastases (from gastrointestinal and renal cancer, 2 each) were detected by LDCT in four subjects during the entire screening cycle. Two interval cancers, namely lesions that were diagnosed outside the screening frame, were observed in the active arm during the screening period: one SCLC with extensive disease diagnosed between the second and third screening rounds, and one stage IV NSCLC diagnosed between the third and fourth screening rounds.

The characteristics of the screen-detected primary lung cancers found at baseline and annual repeat LDCT screening rounds are reported in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/JTO/A409). Excluding two SCLCs and one large hilar mass, the average mean diameter of the screen-detected tumors was 24.2 mm at baseline,

TABLE 1. Compliance of Subjects Randomized to the Active Arm, Results of the Four Screening Rounds with LDCT, Nodule Management, and Lung Cancers in the ITALUNG Trial

	T0	T1	T2	T3	T1–T3	T0–T3
Subjects invited	1613	1593	1589	1581		
LDCT executed	1406 −87.10%	1356 −85.10%	1308 −82.30%	1263 −79.80%	3927	5333
Positive LDCT test	426 −30.30%	234 −17.30%	211 −16.10%	173 −13.70%	618 −15.80%	
Follow-up LDCT	366	225	202	173	600	966
1 month	31	27	30	32	89	120
3 months	335	163	132	115	410	745
6 months	0	35	40	26	101	101
FDG-PET[a]	60	15	15	12	42	102
Positive	14	7	7	4	18	32
Indeterminate	2	1	2	2	5	7
Negative	44	7	6	6	19	63
CT-guided FNAB[b]	18	6	5	9	20	38
Positive	12	5	4	7	16	28
Negative	3	1	0	2	3	6
Inadequate	3	0	1	0	1	4
Lung cancers[c]	18	2	9	6	17	35
Stage I	10	2	6	5	13	23
Stage II–IV	8	0	3	1	4	12

[a]Ninety-seven FDG-PET examinations were obtained in 92 subjects for 102 target lesions.
[b]Thirty-eight CT-guided FNAB were obtained in 34 subjects for 38 lesions.
[c]Three carcinoids and three small-cell lung cancers excluded—pathological or clinical stage.
CT, computed tomography; FDG-PET, 2-[18F]fluoro-2-deoxy-D glucose positron emission tomography; FNAB, fine-needle aspiration biopsy; LDCT, low-dose computed tomography.

and 17.3 mm at subsequent annual screening rounds (p = not significant). Ten (56%) of the 18 prevalent NSCLCs were in stage I (8 in stage IA and 2 in stage IB) as compared with 13 of the 17 incident NSCLCs (76%) (11 in stage IA and 2 stage IB) (p = not significant) (Table 1).

As part of management of positive screening tests, 966 (120 after 1 month of antibiotic therapy, 745 after 3 months, and 101 after 6 months) follow-up LDCT examinations were obtained. They accounted for 15% (966 of 6299) of the total number of LDCT examinations performed in the active arm of the ITALUNG trial. Seven hundred forty-one of the 1406 subjects (52.7%) who underwent the baseline LDCT had at least one positive LDCT examination for noncalcified nodule over the entire screening cycle. Lung cancer was diagnosed in 16 of 38 subjects (42%) after evidence of lesion growth at follow-up LDCT examinations. Nodule disappearance or size reduction at LDCT after 1 month of antibiotic therapy was observed in 80 of 120 subjects (67%) (in 11 of 31 subjects [35%] at baseline and 69 of 89 subjects [77%] at annual repeat screening rounds).

Ninety-seven chest FDG-PET examinations were obtained in 92 subjects, namely 6.5% of the subjects randomized to the active arm who underwent baseline LDCT. Five subjects had two FDG-PET each. Fifty-seven PET-FDG examinations were performed at baseline, and 40 at subsequent annual screening rounds. Thirty-eight primary (n = 35) or secondary (n = 3) lung cancers were ultimately diagnosed in 35 subjects (3 subjects had 2 lesions, 1 a mixed cancer and SCLC, 1 a carcinoid and AC, and 1 subject had an AC and a controlateral early AC). On a total of 102 target lesions in 92 subjects (84 subjects had a single lesion and were examined once, 5 subjects had a single lesion and were examined twice, 2 subjects had 2 lesions and were examined once, and 1 subject had 2 lesions and was examined twice) and assimilating to positive the seven indeterminate FDG-PET results, which corresponded to lung cancer in six, the overall sensitivity of FDG-PET was 84% and specificity 89% (Table 2). Overall sensitivity and specificity assimilating indeterminate FDG-PET to negative results were 68% and 90%, respectively.

Thirty-eight CT-guided FNAB (with ROSE in 34) were obtained in 38 lesions in 34 subjects, that is, 2.4% of subjects randomized to the active arm who underwent baseline LDCT. In four subjects, two CT-guided FNAB were performed on two distinct lesions. Eighteen FNAB were performed on lesions detected at baseline screening round and 20 on lesions detected at subsequent annual screening rounds. The mean diameter of the nodules referred to FNAB was 18.2 mm (range, 5–48). Overall, 34 of 38 (89%) procedures yielded adequate material for the cytological examination (Table 2). CT-guided FNAB was positive and histological examination of the surgical specimen revealed lung cancer (n = 25) or metastasis (n = 2) in 27 of 38 (71%) lesions and atypical adenomatous hyperplasia (AAH) in one lesion. CT-guided FNAB was negative in six subjects (with lung cancer in 1 subject) and inconclusive in four subjects (with lung cancer and renal metastasis in 1 subject each). By assimilating the inconclusive to the negative FNAB results, the overall sensitivity of FNAB was 90% and specificity 88%. Sensitivity was 96% and specificity 83% after exclusion of the inconclusive FNAB for insufficient material. Pneumothorax occurred in 11 of 38 (29%) of the procedures, but only two subjects (5%) needed thoracic drainage.

FBS was obtained in 30 subjects, that is, 2.1% of the subjects who underwent baseline LDCT screening. Twenty were performed at baseline and 10 at the subsequent screening rounds. FBS was positive in eight subjects (all with lung cancer) and negative in 22 subjects. In six subjects with negative FBS, a diagnosis of lung cancer was finally reached. Overall sensitivity of FBS was 57% and specificity 100%.

Twenty-eight subjects received both FDG-PET and CT-guided FNAB as part of management of suspicious nodules. Positivity of both FDG-PET and CT-guided FNAB enabled prediction of lung malignancy in all 18 subjects with such a combination of results. In particular, primary lung cancer was found in 16 cases and solitary metastases (from gastrointestinal cancers) in two cases. FDG-PET and CT-guided FNAB were both negative in four subjects without lung cancer. Discrepancies between the results of FDG-PET and CT-guided FNAB were observed in six cases. In three subjects with final diagnosis of lung cancer, FDG-PET was positive and CT-guided FNAB was negative. However in one of the three subjects, because of the deep location of the nodule, the negative FNAB was performed under transoesophegeal ultrasound guidance rather than under CT guidance. In one additional subject with a final diagnosis of lung cancer FDG-PET was negative and CT-guided FNAB was positive. In the two final subjects in whom no lung cancer was ultimately diagnosed during the screening period, the FDG-PET was positive and the CT-guided FNAB was negative in one case, and the FDG-PET was negative and the CT-guided FNAB was inconclusive in the other.

Six subjects with final diagnosis of lung cancer did not undergo FDG-PET. Three of them had large cancers (diameter range, 35–48 mm) detected at baseline screening round, for which the protocol enabled direct CT-guided FNAB. Two subjects had cancers appearing as a part-solid nodule with a very small solid component at annual repeat screening rounds, which directly underwent CT-guided FNAB. One final subject had a small peripheral solid nodule at baseline screening, which exhibited significant growth at follow-up, and also directly underwent CT-guided FNAB.

Eight subjects with final diagnosis of lung cancer did not undergo CT-guided FNAB. Five subjects with histological lung malignancy (4 NSCLC and 1 metastasis from renal cancer) had a positive FDG-PET and were directly sent to surgery as well as two subjects with carcinoid who had an indeterminate or negative FDG-PET, and one final subject with metastasis from renal cancer and negative FDG-PET.

Therapy of screen-detected primary lung cancers included surgery (lobectomy n = 29; sublobar resection n = 6; pneumonectomy n = 1) in 34 subjects with lung cancer (30 with NSCLC, 3 with carcinoids, and 1 with both NSCLC and SCLC) alone (n = 29), or in combination with both chemo and radiation therapy (n = 3) or just chemotherapy (n = 2). Six subjects with primary lung cancers did not receive surgery. Two subjects were treated with combined chemo and radiation therapy and four with chemotherapy alone.

Surgical resection for benign lung pathology was carried out in four subjects, corresponding to 10% (4 of 38) of the

TABLE 2. Results of FDG-PET and CT-Guided FNAB in the ITALUNG Trial[a]

	Screening Round	True-Positive	True-Negative	False-Positive	False-Negative	Total
FDG-PET	Baseline	16	40	0	4	60
	Repeat	16	17	7	2	42
	Total	32	57	7	6	102
CT-guided FNAB	Baseline	10	3	0	1	14
	Repeat	17	4	1	2	24
	Total	27	7	1	3	38

[a]The seven nodules showing faint FDG uptake qualifying for indeterminate PET result were considered as positive, and the four nodules whose FNAB was not diagnostic were considered as negative.

CT, computed tomography; FDG-PET, 2-[18F]fluoro-2-deoxy-D glucose positron emission tomography; FNAB, fine-needle aspiration biopsy.

subjects undergoing surgical resections of lung lesions detected by LDCT screening. Three of them followed violations of the management protocol. In particular, the first subject was referred to surgery without undergoing FDG-PET or CT-guided FNAB because a comparison between the baseline LDCT and a prior chest CT performed for other reasons 2 years before enrolment in the trial showed increase of the mean diameter of a solid nodule from 5 mm to 8 mm. Histological examination revealed hamartocondroma. The second subject showed a new part-solid nodule of 10-mm mean diameter at the last annual repeat screening round, which doubled its diameter at 3-month follow-up LDCT. The lesion was positive to FDG-PET and was surgically removed without preliminary CT-guided FNAB. Surgical pathology failed to identify malignant cells. The third subject underwent surgery for a solid lesion positive to FDG-PET and CT-guided FNAB in the right upper lung, which increased in mean diameter from 6 mm to 9 mm in the last annual repeat screening round, and which on pathological examination was found to be an AC. However, during the same surgical session the thoracic surgeon also decided to resect a purely nonsolid nodule of 10 mm in diameter in the right inferior lobe, which was not previously evaluated with FNAB, and whose pathology showed it to be AAH. The fourth subject underwent surgical removal of a nonsolid nodule that showed an increased diameter from 8 mm to 12 mm mean diameter from baseline to second annual repeat screening round with indeterminate FDG-PET and positive CT-guided FNAB, but the histological diagnosis also in this case was AAH.

Five extrapulmonary malignancies (2 cases of malignant mesothelioma, 1 of primary breast cancer, 1 of primary kidney cancer, and 1 thymoma) were detected in the subjects of the arm undergoing LDCT screening.

DISCUSSION

Comparative analyses of the recruitment strategies, subjects' compliance, performance of LDCT as screening test, and management protocols for suspicious nodules are fundamental for a thorough evaluation of efficacy and cost effectiveness of the screening procedure of lung cancer with LDCT in at-risk populations and for its standardization. Moreover, they are mandatory before data pooling of RCTs.

Different from all other observational studies[12] and several RCTs[17,18,21,27] that recruited volunteers in response to advertisements in the media implying a selection bias, we recruited participants to the ITALUNG trial by direct mailing to subjects potentially at high risk of lung cancer because of age and smoking history.[20] A similar recruitment procedure was adopted in the Dutch-Belgian Lung Cancer Screening Trial (NELSON) and German trials.[19,24] In general, this procedure follows the one used in the Tuscany region of Italy for population screening of breast cancer with mammography, and of colorectal cancer with fecal occult blood test; both involved direct mailing to registered residents. Admittedly, the overall 23.9% adhesion in terms of replies to mail invitation in the ITALUNG trial is lower than the 32% to 33% reported in the NELSON and German trial,[19,24] and much lower than that of breast (60–70%)[50] and colorectal screening (56%) in Tuscany.[51] In our opinion, besides general reasons for nonattendance to cancer screening procedures, including distrust in medicine and screening and a sense of fatality about diseases, two additional reasons for the lower adhesion to the mail invitation in the ITALUNG trial are the unproven efficacy of the LDCT screening at the time of enrollment (2004–2006), and the possibility of being randomized in the control arm receiving usual care. Further information about the experience of the participants to the ITALUNG trial is being collected with follow-up questionnaires.

We observed a high and sustained compliance of the subjects randomized to the active arm, with a 79% proportion of the subjects that completed four annual LDCT rounds. Notably, the greatest drop out (12.8%) in the active arm of our study occurred between the consensus to be randomized and execution of the baseline LDCT, which is similar to what was observed in the Depiscan (12.7%)[52] and in the Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE) (19%)[33] RCTs, but remarkably higher than in the NLST (2.6%)[27] and Danish (0.2%)[34] RCTs. In our opinion, this phenomenon is presumably because of our study design, in which we first obtained the participant's consent to the randomization and then invited the eligible subjects allocated to the active arm to LDCT testing. In the period between compilation of the questionnaire for eligibility and the date of the LDCT, these subjects might have elaborated their fear and anxiety about the screening procedure, especially after explanation during the preliminary counseling of the screening procedure with LDCT and of the probability of obtaining a false-positive test, which would require further possibly invasive investigations in absence of a lung cancer.[12] This detailed information could have the effect of discouraging subjects passively recruited by mail,[23] and ultimately determine decline in the test appointment. This mechanism is unlikely to occur in studies recruiting volunteers, and indicates that further investigation is worthwhile to improve the communication with high-risk subjects.

In our study, 90% of the subjects who executed baseline LDCT completed the four screening rounds. The final

79% compliance was higher than those in several observational studies and RCTs,[12] but lower than those in the Lung Screening Study (LSS) (84% at the second year),[38] NLST (90% at the third year),[27] Multicentric Italian Lung Detection (MILD) (95% and 96%),[18] and Danish trial (90% at the fifth year),[34] which, however, recruited volunteers. The adhesion and compliance rates in the ITALUNG trial might constitute valuable reference terms for future screening programs of lung cancer with LDCT involving population-based invitation (by mail or counseling) of subjects at high risk of lung cancer. In the active arm of the ITALUNG trial we observed a low rate of screen-detected lung cancers, which were mostly represented by ACs in early stages and were surgically resectable. The 1.5% prevalence of screen-detected lung cancers in ITALUNG is substantially in line with those reported in observational studies (range, 0.2%–2.7%)[12] and RCTs (range, 0.8%–2.4%)[17,18,21,22,24,27,52,53] that recruited elderly heavy smokers and former smokers. Also, the 0.5 mean annual incidence rate of screen-detected lung cancers in ITALUNG is comprised within the range of previous observational studies and RCTs, in which it was consistently lower than 1%.[12,13,18,27,33,34,38,53]

In ITALUNG AC accounted for 56% of NSCLC at baseline and for 88% of NSCLC at subsequent annual repeat screening rounds. This predominance of AC in screen-detected lung cancers is well established[13,18,24,27,34] and presumably reflects the capability of LDCT to show small ACs appearing as peripheral nodules, whereas, detection with LDCT of central tumors developing in the large and medium-size airways, which more frequently correspond to squamous carcinomas, is suboptimal.[54]

The majority of the screen-detected NSCLC (23 of 35, 66%) in the ITALUNG was in stages IA or IB and with a small and not statistically significant increase of such low-stage cancers from baseline (56%) to subsequent annual repeat (76%) screening rounds. Increase of low-stage cancers in LDCT screening rounds after baseline (stage shift) is considered an indirect element militating in favor of the capability of LDCT screening to efficiently impact on lung cancer mortality, but available data on stage shift in lung cancer screening with LDCT are inconsistent.[55,56] The predominance of low-stage NSLCL was observed in all prior observational studies[12] and RCTs.[18,21,24,38,53] As expected, screen-detected lung cancers in low stages are amenable to surgical resection, and this occurred in 35 of 41 of cancers (85%) in the ITALUNG trial, which again is in line with other observational studies and RCTs.

It is noteworthy that despite the different recruitment strategies mentioned above, the variable schedule of the screening LDCT rounds with a couple of studies offering biennial rather than annual LDCT screening rounds,[18,53] and some additional minor differences in the target population (sex, age, or pack-years distribution), in the LDCT acquisition technique (slice collimation ranging between 5 mm[17,21] and 0.75 mm[18], implying a possible lower sensitivity to small solid and nonsolid nodules in LDCT examinations adopting thicker collimation) and in the criteria of positivity of the screening test (mean diameter of > 4 or > 5 mm and volume > 50 or > 60 mm^3 for prevalent solid nodules)[17,18,22,36] and nodule management (see below), the yield of the LDCT in terms of rates and types of screen-detected lung cancers is remarkably similar in observational and randomized studies involving elderly heavy smokers and former smokers. The low detection rate for prevalent and especially incident lung cancers are key elements in explaining the high cost/effectiveness ratio of lung cancer screening with LDCT alone.[12,18] This clearly indicates that alternative or supplemental strategies for increasing the rates of screen-detected lung cancers with LDCT by improving the selection of the target population are needed. Inclusion of subjects with additional risk factors besides smoking history and age, such as occupational asbestos exposure,[57] chronic obstructive pulmonary disease,[58] and especially, inclusion of sputum or blood biomarkers[40,59,60] in a multidimensional integrated screening strategy should be explored in this context.

In the active arm of the ITALUNG, we observed two interval lung cancers, both in advanced stage, over a screening period of 4 years in 1406 subjects, confirming that the most virulent forms of lung cancer can rarely elude LDCT screening.[18,61] Ascertainment, using cancer registry, of interval lung cancer cases in the active arm of ITALUNG trial is still underway. However, the above mentioned low rate of interval cancers apparently seems to support efficacy of the screening procedure in identifying lung cancers.

In ITALUNG, we observed a 30.3% recall rate at baseline LDCT screening test, which almost halved (15.7%) and stabilized at subsequent annual screening rounds. The baseline figures seem higher than the average 20% reported in observational studies and RCTs[12] with the exception of three.[62–64] This high recall rate might be because of the radiologist learning curve or reflect characteristics of screened population. As a matter of fact, at the end of four annual screening rounds, 52.7% of subjects in the active arm of the ITALUNG were recalled at least once for follow-up LDCT. This high cumulative false-positivity rate is in line with the data in the Mayo Clinic study in which 69% of the participants had at least one false-positive finding over the 5-year program,[56] and both substantially match the 21% cumulative probability of one or more false-positive LDCT examinations after one screening and 33% after two, calculated using the Kaplan–Meier analysis.[23]

Reduction of the numbers of follow-up or recall LDCT would be valuable, and in our opinion, two basic strategies can be hypothesized. The first concerns recent developments in the efforts to radiologically characterize solitary lung lesions, possibly using CT texture analysis.[65,66] The second solution entails combination of LDCT with blood or sputum biomarker status, which could independently contribute in identifying subjects with lethal lung cancers appearing as small nodules.[40,59]

At variance with NLST, in which management of screen-detected suspicious nodules was left to the subject's personal health provider, the members of the ITALUNG trial adopted a shared protocol for management of positive LDCT screening test, which is simple, cheap, and clinically based. In fact, it basically relies on double reading for nodule detection on LDCT and on operator's measurement of mean diameter to assess lesion growth, on visual assessment of FDG-PET uptake of the suspicious nodule, and on CT-guided FNAB with ROSE. Other protocols are more technologically oriented

because they are based on adoption of software for nodule volumetry[18,36] and computation of the standardized uptake value of FDG-PET,[18,36,67–69] and do not include CT-guided FNAB.[18,22,67–69] One additional distinguishing feature of the ITALUNG protocol as compared with other observational studies and RCTs is the adoption of antibiotic therapy before 1-month follow-up LDCT, which is expected to decrease the rate of subsequent investigations by revealing the active inflammatory nature, especially of incident nodules.[47,70]

The main instrument used for management of suspicious nodules in the ITALUNG trial was follow-up LDCT, which accounted for the majority of further investigations, and although associated with additional exposure to low-dose radiation,[49] often completed the management. In particular, the 36% rate of total or partial regression after 1 month of antibiotic therapy of prevalent nodules as compared with the 77% rate of total or partial regression of incident nodules in the ITALUNG trial is in line with the 29% disappearance or reduction after 1 month of antibiotic therapy of nodules detected at baseline screening and with the 74% disappearance or reduction of nodules detected at annual repeat by the ELCAP group.[70] This is in line with the view that prevalent nodules are frequently scars of benign processes, whereas, incident nodules frequently correspond to active infective or inflammatory processes.

The second most frequently used investigation for nodule management in our study was FDG-PET, which overall was carried out in 6.5% of the subjects randomized to the active arm who underwent baseline LDCT. This frequency of FDG-PET is higher than in other observational studies and RCTs (range, 2%–4.5%).[18,27,33,42,68,71] The excess of FDG-PET in our study was related to the high number of FDG-PET examinations performed at baseline (59%), whereas, the mean number of FDG-PET at the subsequent annual repeat LDCT screening round was 13.6%. By assimilating the indeterminate to the positive FDG-PET results, we observed overall 84% sensitivity and 90% specificity, which are substantially in line with those previously reported.[37,42,68,69,71]

In ITALUNG, 2.4% of subjects randomized to the active arm ultimately had FNAB during the screening cycle (CT-guided in 37 lesions and ultrasound-guided in 1 lesion) as part of their diagnostic workup (38 lesions in 34 subjects). This rate is similar to another LDCT screening studies adopting FNAB as part of the protocol,[72] but higher than in the NELSON (< 1 %)[53] and German (1.5 %)[24] trials. In the majority (89%) of lesions, FNAB was carried out with ROSE, which is associated with lower rate of nondiagnostic results, in our series it was 11%, as compared with FNAB alone.[73] The large majority of the subjects (32 of 38) in whom a primary lung cancer was ultimately diagnosed at histological examination underwent preliminary FNAB. If we assimilate the inconclusive to negative FNAB results, we obtained a 90% sensitivity and 88% specificity. These figures are better than those reported both in an LDCT screening program, in which 21% FNAB yielded unsatisfactory results and 12% FNAB were false-positives leading to surgery on benign pathology,[72] and in the clinical practice in which the average sensitivity is also 90% but 21% of FNABs produce nondiagnostic results.[74] The unique false-positive result of FNAB in our study, which led to surgery for benign pathology was a case of AAH. This is considered a preneoplastic lesion and is indistinguishable on cytological examination from the former category of bronchioloalveolar carcinoma,[44,46] which corresponds to the new category of early AC, comprising AC in situ, minimally invasive AC, and lepidic predominant AC.[75]

In a study the combination of volumetry at follow-up LDCT with FDG-PET improved the sensitivity for diagnosis of lung cancer from 71% (volumetry or FDG-PET alone) to 90% with a decrease of specificity from 91% to 82%.[37] In our study the combination of positive FDG-PET and CT-guided FNAB invariably predicted primary or secondary lung malignancy, that is, a 100% sensitivity was reached, and no double false-positive (at FDG-PET and FNAB) was observed. These data, although obtained in a relatively small sample, justify the view that CT-guided FNAB with ROSE is very useful for management of suspicious nodules detected in LDCT lung cancer screening.

The rate of surgical curative therapy in the subjects with screen-detected lung cancer in the ITALUNG trial is in line with previous data,[12,18,34] and reflects the early stages of the large majority of the screen-detected lesions.

The 10% rate of surgery for benign lesions in the ITALUNG trial is lower than those reported in the majority of other screening studies, which can be as high as 33%.[76] This low rate supports the validity of our management protocol and seems noteworthy, especially if one considers that two of the four cases referred to surgery for benign lesions corresponded to AAH and that in three cases referral to surgery followed protocol violations. Strict adherence to a protocol derived by the clinical routine and including follow-up LDCT with or without 1 month of antibiotic therapy, FDG-PET, and CT-guided FNAB with ROSE is expected to further lessen the rate of surgery for benign lesions in LDCT screening of lung cancer.[29]

CONCLUSIONS

The results of the ITALUNG trial indicate that high-risk subjects recruited by mail to participate in an RCT offering LDCT or usual care for screening of lung cancer show a lower adhesion than subjects invited to undergo other consolidated population-based screening programs such as those for breast or colorectal cancer. However, the adherents randomized to receive four annual LDCTs show a high and sustained compliance throughout the screening cycle.

The low rate of screen-detected lung cancers and the high recall rate in the ITALUNG trial are in line with those of other observational and randomized studies, and confirm that improved definition of target population and maybe integration of the risk stratification with biomarkers are required to increase the cost effectiveness of lung cancer screening programs.

Adoption of a shared protocol for nodule management derived by the clinical routine, including follow-up LDCT (with 1 month after antibiotic therapy) and measurement of nodule mean diameter, visual assessment of FDG-PET, and CT-guided FNAB with ROSE yields high accuracy for preoperative detection of lung malignancies, the few surgical

interventions for benign lesions being associated with protocol violations.

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REFERENCES

1. American Cancer Society. Cancer Facts and Figures 2012. Atlanta, GA: American Cancer Society, 2012.
2. Travis WD. Pathology of lung cancer. *Clin Chest Med* 2012:32:669–692.
3. AIRTUM Working Group. Italian cancer figures, report 2009: cancer trend (1998–2005). *Epidemiol Prev*. 2009;33(XX Suppl 1):1–168.
4. Howlander N, Noone AM, Krapcho M, et al. (Eds.) SEER Cancer Statistics Review, 1975–2009. Bethesda, MD: National Cancer Institutehttp://seer.cancer.gov/csr/1975_2009_pops09/. Accessed April 2012.
5. AIRTUM Working Group. Italian cancer figures, report 2011: survival of cancer patients in Italy. *Epidemiol Prev*. 2011;35:1–200.
6. Midthun DE, Jett JR, Ross ME. Overview of the risk factors, pathology, and clinical manifestations of lung cancer. 2012. Available at: http://www.uptodate.com. Accessed on
7. Kubík AK, Parkin DM, Zatloukal P. Czech Study on Lung Cancer Screening: post-trial follow-up of lung cancer deaths up to year 15 since enrollment. *Cancer* 2000;89(11 Suppl):2363–2368.
8. Parkin DM, Moss SM. Lung cancer screening: improved survival but no reduction in deaths–the role of "overdiagnosis." *Cancer* 2000;89(11 Suppl):2369–2376.
9. Marcus PM, Bergstralh EJ, Zweig MH, Harris A, Offord KP, Fontana RS. Extended lung cancer incidence follow-up in the Mayo Lung Project and overdiagnosis. *J Natl Cancer Inst* 2006;98:748–756.
10. Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality. The Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. *JAMA* 2011;306:1865–1873.
11. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* 1999;354:99–105.
12. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA* 2012;307:2418–2429.
13. International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;355:1763–1771.
14. Patz EF Jr, Goodman PC, Bepler G. Screening for lung cancer. *N Engl J Med* 2000;343:1627–1633.
15. Bach PB, Jett JR, Pastorino U, Tockman MS, Swensen SJ, Begg CB. Computed tomography screening and lung cancer outcomes. *JAMA* 2007;297:953–961.
16. Paci E. Observational, one-arm studies and randomized population-based trials for evaluation of the efficacy of lung cancer screening. *J Thorac Oncol* 2007;2(5 Suppl):S45–S46.
17. Gohagan J, Marcus P, Fagerstrom R, Pinsky P, Kramer B, Prorok P; Writing Committee, Lung Screening Study Research Group. Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: The Lung Screening Study of the National Cancer Institute. *Chest* 2004;126:114–121.
18. Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev* 2012;21:308–315.
19. van Iersel CA, de Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). *Int J Cancer* 2007;120:868–874.
20. Lopes Pegna A, Picozzi G, Mascalchi M, et al.; ITALUNG Study Research Group. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. *Lung Cancer* 2009;64:34–40.
21. Infante M, Lutman FR, Cavuto S, et al.; DANTE Study Group. Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. *Lung Cancer* 2008;59:355–363.
22. Pedersen JH, Ashraf H, Dirksen A, et al. The Danish randomized lung cancer CT screening trial–overall design and results of the prevalence round. *J Thorac Oncol* 2009;4:608–614.
23. Croswell JM, Baker SG, Marcus PM, Clapp JD, Kramer BS. Cumulative incidence of false-positive test results in lung cancer screening: a randomized trial. *Ann Intern Med* 2010;152:505–12, W176.
24. Becker N, Motsch E, Gross ML, et al. Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. *J Cancer Res Clin Oncol* 2012;138:1475–1486.
25. Baldwin DR, Duffy SW, Wald NJ, Page R, Hansell DM, Field JK. UK Lung Screen (UKLS) nodule management protocol: modelling of a single screen randomised controlled trial of low-dose CT screening for lung cancer. *Thorax* 2011;66:308–313.
26. National Lung Screening Trial Research Team. Baseline characteristics of participants in the randomized national lung screening trial. *J Natl Cancer Inst* 2010;102(23):1771–1779
27. National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
28. Sox HC. Better evidence about screening for lung cancer. *N Engl J Med* 2011;365:455–457. Accessed December 28, 2012.
29. Wood DE. Maximizing the benefit and minimizing the risks of lung cancer screening. *J Thorac Imaging* 2012;27:211–212.
30. Zompatori M, Mascalchi M, Ciccarese F, Sverzellati N, Pastorino U. Screening for lung cancer using low-dose spiral CT: 10 years later, state of the art. *Radiol Med* 2013;118:51–61.
31. American Lung Association. Providing guidance on lung cancer screening to patients and physicians April 23, 2012. Available at: http://www.lung.org/lung-disease/lung-cancer/lung-cancer-screening-guidelines/ Accessed April 23, 2012.
32. NCCN Clinical Practice Guidelines in Oncology. Lung cancer screening. Version 1.2013. Available at: http://www.nccn.org Accessed June 15, 2012.
33. Infante M, Cavuto S, Lutman FR, et al.; DANTE Study Group. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. *Am J Respir Crit Care Med* 2009;180:445–453.
34. Saghir Z, Dirksen A, Ashraf H, et al. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. *Thorax* 2012;67:296–301.
35. Henschke CI. International Early Lung Cancer Action Program: enrolment and screening protocol. Available at: http://www.IELCAP.org. Accessed March 17, 2004.
36. Xu DM, Gietema H, de Koning H, et al. Nodule management protocol of the NELSON randomised lung cancer screening trial. *Lung Cancer* 2006;54:177–184.
37. Ashraf H, Dirksen A, Loft A, et al. Combined use of positron emission tomography and volume doubling time in lung cancer screening with low-dose CT scanning. *Thorax* 2011;66:315–319.
38. Gohagan JK, Marcus PM, Fagerstrom RM, et al.; Lung Screening Study Research Group. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. *Lung Cancer* 2005;47:9–15.
39. Field JK, Smith RA, Duffy SW, et al. The Liverpool Statement 2005: priorities for the European Union/United States spiral computed tomography collaborative group. *J Thorac Oncol* 2006;1:497–498.
40. Carozzi FM, Bisanzi S, Falini P, et al.; ITALUNG Study Research Group. Molecular profile in body fluids in subjects enrolled in a randomised trial for lung cancer screening: perspectives of integrated strategies for early diagnosis. *Lung Cancer* 2010;68:216–221.
41. Wormanns D, Ludwig K, Beyer F, Heindel W, Diederich S. Detection of pulmonary nodules at multirow-detector CT: effectiveness of double reading to improve sensitivity at standard-dose and low-dose chest CT. *Eur Radiol* 2005;15:14–22.
42. Bastarrika G, García-Velloso MJ, Lozano MD, et al. Early lung cancer detection using spiral computed tomography and positron emission tomography. *Am J Respir Crit Care Med* 2005;171:1378–1383.
43. Lindell RM, Hartman TE, Swensen SJ, et al. Lung cancer screening experience: a retrospective review of PET in 22 non-small cell lung carcinomas detected on screening chest CT in a high-risk population. *AJR Am J Roentgenol* 2005;185:126–131.

44. Vazquez MF, Flieder DB. Small peripheral glandular lesions detected by screening CT for lung cancer. A diagnostic dilemma for the pathologist. *Radiol Clin North Am* 2000;38:579–589.
45. Vazquez MF, Koizumi JH, Henschke CI, Yankelevitz DF. Reliability of cytologic diagnosis of early lung cancer. *Cancer* 2007;111:252–258.
46. Picozzi G, Diciotti S, Falchini M, et al. Operator-dependent reproducibility of size measurements of small phantoms and lung nodules examined with low-dose thin-section computed tomography. *Invest Radiol* 2006;41:831–839.
47. Libby DM, Smith JP, Altorki NK, Pasmantier MW, Yankelevitz D, Henschke CI. Managing the small pulmonary nodule discovered by CT. *Chest* 2004;125:1522–1529.
48. Travis WD, Brambilla E Müller-Hermelink HK, Harris CC (Eds). World Health Organization Classification of Tumours. Pathology and Genetics: Tumours of the lung, pleura, thymus and heart. Lyon, France: IARC Press, 2004.
49. Mascalchi M, Mazzoni LN, Falchini M, et al. Dose exposure in the ITALUNG trial of lung cancer screening with low-dose CT. *Br J Radiol* 2012;85:1134–1139.
50. Giordano L, Giorgi D, Ventura L, Castagno R, Paci E, Segnan N. Time trends of process and impact indicators in Italian breast screening programmes (1999–2009). *Epidemiol Prev* 2011;35(5–6 Suppl 5):28–38.
51. Sali L, Grazzini G, Ventura L, et al. Computed tomography colonography in subjects with positive faecal occult blood test refusing optical colonoscopy. *Digest Liver Dis* December 19, 2012 [Epub ahead of print].
52. Blanchon T, Bréchot JM, Grenier PA, et al.; Dépiscan Group. Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). *Lung Cancer* 2007;58:50–58.
53. van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. *N Engl J Med* 2009;361:2221–2229.
54. MacRedmond R, McVey G, Lee M, et al. Screening for lung cancer using low dose CT scanning: results of 2 year follow up. *Thorax* 2006;61:54–56.
55. Patz EF Jr, Swensen SJ, Herndon JE 2nd. Estimate of lung cancer mortality from low-dose spiral computed tomography screening trials: implications for current mass screening recommendations. *J Clin Oncol* 2004;22:2202–2206.
56. Swensen SJ, Jett JR, Hartman TE, et al. CT screening for lung cancer: five-year prospective experience. *Radiology* 2005;235:259–265.
57. Das M, Mühlenbruch G, Mahnken AH, et al. Asbestos Surveillance Program Aachen (ASPA): initial results from baseline screening for lung cancer in asbestos-exposed high-risk individuals using low-dose multidetector-row CT. *Eur Radiol* 2007;17:1193–1199.
58. Carrozzi L, Viegi G. Lung cancer and chronic obstructive pulmonary disease: the story goes on. *Radiology* 2011;261:688–691.
59. Sozzi G, Pastorino U, Croce CM. MicroRNAs and lung cancer: from markers to targets. *Cell Cycle* 2011;10:2045–2046.
60. Boeri M, Verri C, Conte D, et al. MicroRNA signatures in tissues and plasma predict development and prognosis of computed tomography detected lung cancer. *Proc Natl Acad Sci USA* 2011;108:3713–3718.
61. Early warnings. Screening programmes for cancer detection are not always as effective at saving lives as might be hoped. Improving the situation will require a concerted effort on a broad front (Editorial). *Nature* 2009;458:679.
62. Wilson DO, Weissfeld JL, Fuhrman CR, et al. The Pittsburgh Lung Screening Study (PLuSS): outcomes within 3 years of a first computed tomography scan. *Am J Respir Crit Care Med* 2008;178:956–961.
63. Swensen SJ, Jett JR, Sloan JA, et al. Screening for lung cancer with low-dose spiral computed tomography. *Am J Respir Crit Care Med* 2002;165:508–513.
64. Diederich S, Wormanns D, Semik M, et al. Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. *Radiology* 2002;222:773–781.
65. Kido S, Kuriyama K, Higashiyama M, Kasugai T, Kuroda C. Fractal analysis of small peripheral pulmonary nodules in thin-section CT: evaluation of the lung-nodule interfaces. *J Comput Assist Tomogr* 2002;26:573–578.
66. Wang H, Guo XH, Jia ZW, et al. Multilevel binomial logistic prediction model for malignant pulmonary nodules based on texture features of CT image. *Eur J Radiol* 2010;74:124–129.
67. Veronesi G, Bellomi M, Mulshine JL, et al. Lung cancer screening with low-dose computed tomography: a non-invasive diagnostic protocol for baseline lung nodules. *Lung Cancer* 2008;61:340–349.
68. Veronesi G, Bellomi M, Veronesi U, et al. Role of positron emission tomography scanning in the management of lung nodules detected at baseline computed tomography screening. *Ann Thorac Surg* 2007;84:959–65; discussion 965.
69. Veronesi G, Bellomi M, Scanagatta P, et al. Difficulties encountered managing nodules detected during a computed tomography lung cancer screening program. *J Thorac Cardiovasc Surg* 2008;136:611–617.
70. Libby DM, Wu N, Lee IJ, et al. CT screening for lung cancer: the value of short-term CT follow-up. *Chest* 2006;129:1039–1042.
71. Pastorino U, Bellomi M, Landoni C, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. *Lancet* 2003;362:593–597.
72. Wagnetz U, Menezes RJ, Boerner S, et al. CT screening for lung cancer: implication of lung biopsy recommendations. *AJR Am J Roentgenol* 2012;198:351–358.
73. Fassina A, Corradin M, Zardo D, Cappellesso R, Corbetti F, Fassan M. Role and accuracy of rapid on-site evaluation of CT-guided fine needle aspiration cytology of lung nodules. *Cytopathology* 2011;22:306–312.
74. Wahidi MM, Govert JA, Goudar RK, Gould MK, McCrory DC; American College of Chest Physicians. Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132(3 Suppl):94S–107S.
75. Travis WD, Brambilla E, Noguchi M, et al. American Thoracic Society. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society: international multidisciplinary classification of lung adenocarcinoma: executive summary. *Proc Am Thorac Soc* 2011;8:381–385.
76. Pastorino U. Lung cancer screening. *Br J Cancer* 2010;102:1681–1686.

