A Randomized Study of Lung Cancer Screening with Spiral Computed Tomography

Three-year Results from the DANTE Trial

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***Rationale*: Screening for lung cancer with modern imaging technology may decrease lung cancer mortality, but encouraging results have only been obtained in uncontrolled studies.**

***Objectives*: To explore the effect of screening with low-dose spiral computed tomography (LDCT) on lung cancer mortality. Secondary endpoints are incidence, stage at diagnosis, and resectability.**

***Methods*: Male subjects, aged 60 to 75 years, smokers of 20 or more pack-years, were randomized to screening with LDCT or control groups. All participants underwent a baseline, once-only chest X-ray and sputum cytology examination. Screening-arm subjects had LDCT upon accrual to be repeated every year for 4 years, whereas controls had a yearly medical examination only.**

***Measurements and Main Results*: A total of 2,811 subjects were randomized and 2,472 were enrolled (LDCT, 1,276; control, 1,196). After a median follow-up of 33 months, lung cancer was detected in 60 (4.7%) patients receiving LDCT and 34 (2.8%) control subjects ($P = 0.016$). Resectability rates were similar in both groups. More patients with stage I disease were detected by LDCT (54 vs. 34%; $P = 0.06$) and fewer cases were detected in the screening arm due to intercurrent symptoms. However, the number of advanced lung cancer cases was the same as in the control arm. Twenty patients in the LDCT group (1.6%) and 20 controls (1.7%) died of lung cancer, whereas 26 and 25 died of other causes, respectively.**

***Conclusions*: The mortality benefit from lung cancer screening by LDCT might be far smaller than anticipated.**

Keywords: lung neoplasms; early diagnosis; screening; spiral computed tomography; randomized controlled trial

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Screening for lung cancer with low-dose spiral computed tomography (LDCT) may decrease lung cancer mortality, but hazards of downstream investigation procedures, cost issues, and possible overdiagnosis make the results of randomized studies critically important for establishing a proper health policy.

What This Study Adds to the Field

In this randomized trial, more lung cancers and three times as many stage I patients were found using LDCT. However, three-year follow-up data suggest that the effect of screening with LDCT on lung cancer mortality might be smaller than anticipated.

As the most frequent neoplasm and the most common cause of cancer death in the world, lung cancer (LC) constitutes a major public health problem. Although the great majority of the cases observed in routine clinical practice are detected in an advanced stage with poor resectability and 5-year survival rates (1–4), incidental and screening-detected cases are instead characterized by high rates of stage 1 disease with an excellent 5-year survival rate after surgery (5–8). Observational and population studies consistently support early diagnosis (9), and the existence of an easily identifiable high-risk population makes lung cancer, at least in theory, an ideal candidate for early detection programs. However, although research on this subject started long ago, evidence of the efficacy of lung cancer screening to reduce mortality is still lacking. In the last few decades, the randomized Mayo Lung Project (10, 11) and the Czech Trial (12, 13), which used chest radiographs and sputum examination for early detection, failed to observe the expected stage-shift and mortality reduction with screening.

Lead time bias (the early detection through screening of slow-growing tumors with a consequent apparent increase in the observation time from diagnosis to the symptomatic phase and death even if these are not delayed), length bias (the detection of slow-growing tumors only, whereas aggressive disease is not intercepted by screening) and overdiagnosis bias (the detection of an extra quota of indolent tumors that would have had no impact on the patients' life expectancy even if undiagnosed), were proposed to explain the increased detection of early stage tumors, increased survival time from diagnosis, and unreduced lung cancer mortality with screening (14). However, lung cancer has always been considered invariably progressive and uniformly fatal if left untreated, and debate within the scientific community is still open.

It is now hoped that LC screening with low-dose spiral computed tomography (LDCT) scanners may ultimately prove to be effective, but because encouraging results with modern, highly sensitive imaging technology have only been obtained in uncontrolled studies, rigorous investigation in randomized trials is mandatory in view of the negative results in the past, albeit with an outdated technology. Several randomized studies have been launched recently in Europe (15–19) and in the United States

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(20, 21), but so far only the Lung Screening Study (LSS) research group has published short-term follow-up results (22), and no mortality data are available yet.

We herewith present the 3-year results of the DANTE (Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays) Trial, a prospective randomized study that was started in March of 2001, comparing clinical review versus LDCT at annual intervals.

METHODS

The research was conducted by the Istituto Clinico Humanitas Hospital, Milan, Italy. Accrual started in March 2001 and ended in February 2006. Two centers of the same hospital network, the Humanitas Gavazzeni Hospital in Bergamo and the Humanitas Oncology Center in Catania, only enrolled subjects for the trial during the last year of accrual.

The trial methodology, interpretation of imaging tests, and workup of suspicious pulmonary abnormalities, have been illustrated in previous publications (23, 24) and are detailed in the APPENDIX.

In brief, male smokers or former smokers of at least 20 pack-years and aged 60 to 74 years were considered potentially eligible. For practical reasons, prospective participants were preassessed for eligibility and randomized during a telephone interview with the project assistant, whereas clinical assessment and formal enrollment sessions took place once a week. At that time, subjects were briefed on the study purpose and procedures and had to sign an informed consent form before proceeding. Participants were then requested to fill out a questionnaire on their occupational history, smoking habits, past and present health conditions, and they eventually underwent a structured medical interview and complete physical examination.

Subjects were considered ineligible if they had comorbid conditions carrying a life expectancy of less than 5 years, a history of previous malignancy treated within 10 years before accrual (exceptions were allowed for early laryngeal cancer and for nonmelanoma skin cancer, for which a 5-year disease-free interval was considered sufficient), or if they were unable to comply with the follow-up protocol for any reason.

All subjects who were actually enrolled into either arm of the study had a baseline chest radiograph and 3-day sputum cytology testing. Subjects enrolled in the LDCT arm also had a baseline CT scan of the chest on the same day. In total, five yearly LDCT screening rounds were planned: one at baseline and four yearly repeats together with a more concise version of the medical interview and physical examination that focused on reassessing smoking habits, recent medical history, and new signs and symptoms of possible neoplasia since the last assessment.

Controls had the same yearly medical interview and physical examination as the screening-arm subjects, but if no abnormalities were detected clinically, they did not undergo further evaluation. The first-line test in the case of respiratory symptoms or signs is normally a chest radiograph.

All participants were invited to attend their annual clinical review (with or without LDCT) by phone calls. In the case of an inability to reach a participant, or a participant's refusal or inability to attend follow-up visits, vital status information and details about their recent medical history was collected through telephone interviews, either with the participant or from spouses, close relatives, or family physicians, in the search for newly diagnosed cancer. If the participant was found to have been treated for malignancy or died, the final diagnosis, stage, and/or cause of death was then routinely investigated through hospital records or the family physician's records if the patient did not die in a hospital. Linkage to local health registries will be completed after the end of the last follow-up round.

Patients were considered lost to follow-up if reassessment was permanently declined (spiral CT arm), and/or if information about their present condition and life status became unobtainable by any means or was permanently refused.

Crossover contamination was assessed each time the subject was interviewed by a questionnaire inquiring about any chest radiographs and/or CT scans outside the follow-up protocol, and the reason for which they were performed.

Statistical Methods

A sample size of 2,400 subjects was planned, with a 1:1 randomization scheme. Subjects were randomized in blocks of four and stratified by center according to computer-generated lists supplied by the data center before the examinations.

The sample size was calculated on the basis of incidence and mortality data reported in the Lombardy Cancer Registry (25) for the 60 to 74-year-old male population on the Mayo Lung Project reports (26) and on the Early Lung Cancer Action Project (ELCAP) data (27) (*see* APPENDIX).

On the basis of trial monitoring data at the end of the recruitment phase, the trial has 80% power to detect a 35% reduction of lung cancer mortality and 90% power for a 41% reduction in the LDCT arm in a one-sided likelihood ratio test. Deaths due to treatment complications were considered as deaths from lung cancer. Raw data and proportions were compared by the chi-square test or the Fisher's exact test; means were compared by the *t* test using Satterthwaite approximation in case of heteroskedasticity (28). A significance level of 5% was adopted for all tests.

RESULTS

Between March 2001 and February 2006, a total of 2,811 subjects were preassessed and randomized (LDCT arm, 1,403; control arm, 1,408). Overall, 257 subjects (LDCT, 91; control, 166) declined consent to join the study, whereas 92 (46 in each arm) were found to be ineligible after formal assessment due to a history of previous cancer (n = 57), severe comorbidity (n = 11), or other reasons (n = 24). Therefore, 1,276 subjects were finally enrolled in the LDCT arm and 1,196 in the control arm. The two study groups were comparable for age, smoking exposure, and comorbid conditions, except there was a slightly higher prevalence of subjects with chronic respiratory symptoms in the LDCT arm at baseline (Table 1).

As of January 25, 2008, the median follow-up was 33.7 months (range, 1.8–79.2) for the entire study population, with 161 subjects or 6.5% having 5 years or more follow-up, whereas updated information regarding their vital status, causes of death

TABLE 1. MAIN CHARACTERISTICS, FOLLOW-UP, AND CROSS-CONTAMINATION DATA

	LDCT Arm	Control Arm	*P* Value
Enrolled, n (%)*	1,276 (51.6)	1,196 (48.4)	
Active smokers, n (%)	714 (56.0)	681 (56.9)	
Mean age (95% CI)	64.3 (64.0–64.7)	64.6 (64.3–64.9)	
Mean pack-years (95% CI)	47.3 (45.7–49.0)	47.2 (45.5–49.0)	
Comorbidities, n (%)			
Respiratory†	446 (35.0)	370 (30.99)	0.04
Hypertension	456 (35.7)	447 (37.4)	
Cardiac	159 (12.5)	165 (13.8)	
Peripheral Vascular	130 (10.2)	107 (9.0)	
Diabetes	105 (8.2)	99 (8.3)	
Other	452 (35.4)	426 (35.6)	
Previous cancer‡	13 (1.0)	7 (0.6)	
Follow-up			
Annual Reviews			
1+	1,114 (87)	1,069 (89)	
2+	842 (66)	742 (62)	
3+	562 (44)	442 (37)	
4+	251 (20)	174 (15)	
Median (range)§	35.7 (1.8–79.2)	31.5 (5.5–73.0)	0.02
Contamination, n (%)			
Extra CT	74 (6.0)	68 (6.1)	
Extra CXR	233 (18.7)	209 (18.7)	

Definition of abbreviations: CI = confidence interval; CXR = chest radiograph; LDCT = low-dose spiral computed tomography.

* Percentages were calculated on group totals.

† Symptoms consistent with chronic bronchitis per WHO criteria.

‡ One subject in each arm had a previous head and neck malignancy.

§ Follow-up expressed in months.

and occurrence of any newly diagnosed malignancy was available for 96.6% of LDCT patients and 94.7% of controls.

Compliance assessment was performed on 1,244 LDCT subjects and 1,118 control subjects, and it showed that 6.1% obtained a CT scan of the chest after detection of an abnormality in their baseline chest radiograph (2.3%), for other medical reasons (1.5%), or due to protocol violations (1.7%), whereas 18.7% obtained at least one chest radiograph for any reason.

In the same time frame, 5.9% of LDCT arm subjects obtained at least one extra CT scan of the chest outside the follow-up protocol, and 18.7% of them had one or more chest radiographs for other medical reasons (Table 1).

The number of patients diagnosed with lung cancer in both study arms following investigation for any reason and their outcomes are shown in Figure 1.

As of January 2008, 3,612 CT scans were administered for screening purposes in the LDCT screening arm, and at least one pulmonary abnormality was detected in 351 of 1,276 subjects (27.5% of the LDCT arm; 15.6% observed in the baseline CT scan). In addition, extrapulmonary abnormalities were detected by LDCT in 37 patients: effusions (n=4), pleural lesions (n=1), mediastinal masses (n=12), mediastinal lymph node enlargement (n=6), and other lesions such as hiatal hernias, aortic aneurysms, intrathoracic goiters, renal masses, adrenal masses, and diaphragmatic paralysis (n=14).

Only 226 LDCT patients (18%) underwent further evaluation following a planned screening test (sputum, 4; baseline CT, 153; follow-up CT, 100), whereas during the same period 21 patients with unremarkable CT scans underwent medical testing for intercurrent symptoms, 70 patients for unrelated medical conditions, and 12 for other reasons. Two LDCT subjects with normal CT scans were found to have extrapulmonry malignancy during the clinical review: one had axillary adenopathy on physical examination and was eventually diagnosed with lymphoma, and one reported blood in the stool and was eventually diagnosed with colon cancer. By comparison, 153 control subjects (13%) overall underwent further evaluation after a planned test (sputum, 8; chest radiograph, 38; annual review, 107), 32 for intercurrent symptoms, 79 for unrelated medical conditions, and 25 for other reasons (Figure 1).

After a median follow-up of almost 3 years, 60 patients were diagnosed with lung cancer in the LDCT group. Two patients had synchronous lung cancers at baseline according to the criteria of Martini and Melamed (29), and 1 developed a metachronous tumor 37 months after successful resection of the first one; therefore, a total of 63 lung cancers were observed in this group. By comparison, 34 patients were diagnosed with lung cancer in the control group, including one patient with a radiologically occult synchronous squamous cancer and one with a second metachronous cancer diagnosed 29 months after successful surgical treatment of the first one; therefore 36 tumors were observed in this latter group. The lung cancer detection rate in the LDCT arm was 2.19% at the prevalence screen and 4.70% at 3 years, whereas it was 0.67 and 2.84% in the control group ($P = 0.016$).

In the LDCT arm, the majority of patients (78%) were diagnosed with lung cancer by a screening procedure, i.e., 28 (46%) at the baseline screen (13 of these had a visible shadow in their chest radiograph, and there was 1 false-negative case

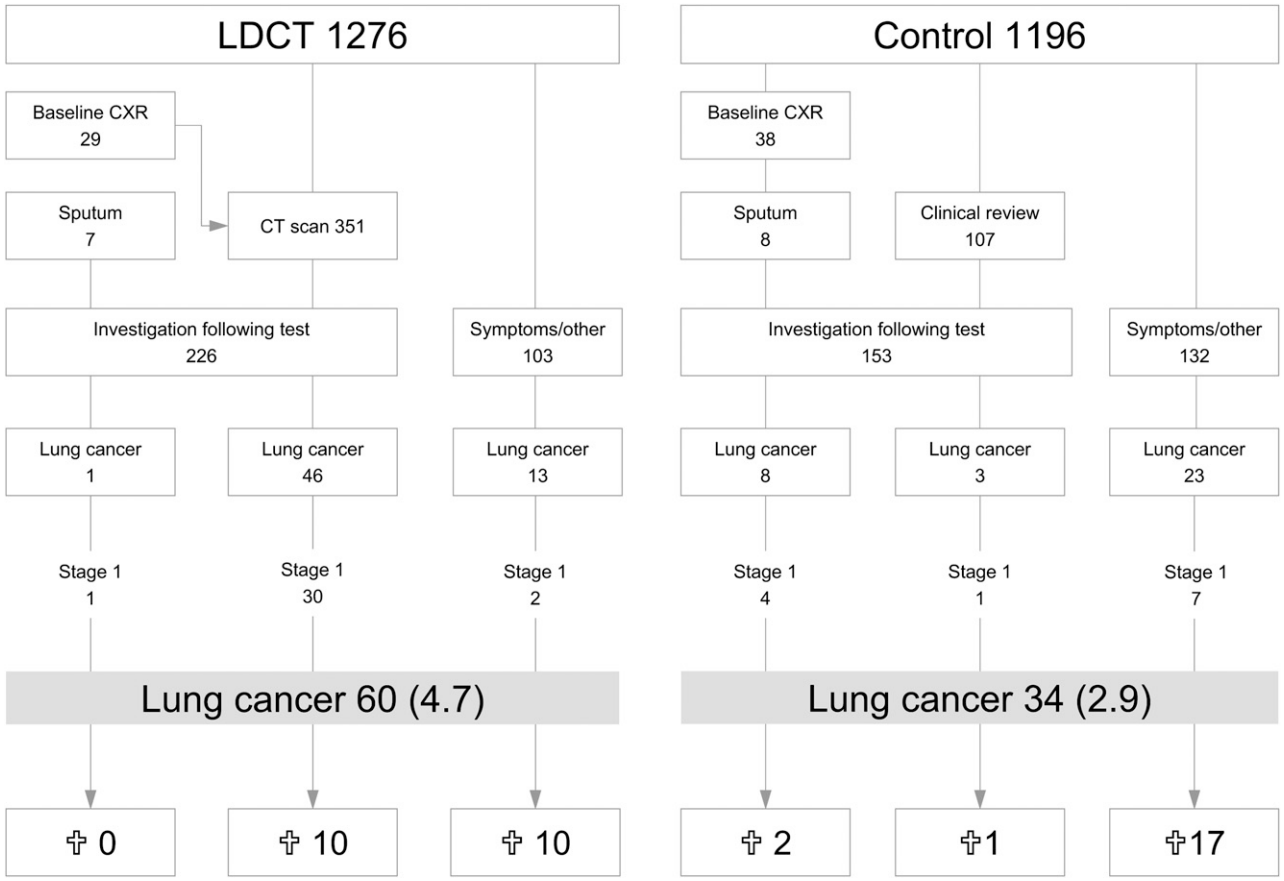

Figure 1. Number of patients diagnosed with lung cancer, with stage 1 disease, and lung cancer deaths according to detection modality. ✞ = Lung cancer deaths. Percentages are shown in parentheses.

detected by sputum cytology only), and 32% by follow-up CT, whereas 10 (16.7%) interval cases were diagnosed during the observation period due to symptoms or for other reasons, and 3 more after the planned five screening rounds.

In the control arm, 8 (23%) cases were detected at the baseline screen by a chest radiograph, 9% were suspected clinically during a scheduled annual examination, and 68% were detected due to symptoms or other reasons (Figure 1). One case in the control group was diagnosed with lung cancer due to incidental patient misallocation to LDCT after an annual clinical review, and another one due to the patient's spontaneous application to a nonrandomized study running in the same area. There was a borderline difference in the absolute numbers of nonscreening detected (e.g., interval and postscreening) cancer cases with respect to total enrolled subjects between the two study arms (13/1,276 or 1.02% vs. 23/1,196 or 1.92%; $P = 0.0607$).

Operability rates were 39/60 (65%) in the LDCT arm versus 18/34 (52%) in the control arm, and complete resectability rates were 36/60 (60%) in the LDCT arm versus 17/34 (50%) in the control arm. The differences were not significant ($P = 0.250$ and $P = 0.347$, respectively).

One patient in each group had a contralateral synchronous radiologically occult tumor that could not be resected because the patient died of postoperative complications in one case, and because radiotherapy was chosen in the other case. These were counted as incomplete resections.

As of January 2008, a total of 20/60 patients (33%) died of lung cancer in the LDCT arm (two of postoperative complications): 10/28 (36%) of those detected at baseline, 0/19 of those detected by a follow-up LDCT, and 10/13 (77%) interval or post-screening cases. Only 1 of 33 stage I patients died of lung cancer, whereas the remaining 19 patients who died had stage II, III, or IV disease. In the control arm, a total of 20/34 patients (59%) died of lung cancer (one of postoperative complications): 2 patients were detected at baseline by a chest radiograph, and 18 were detected during follow-up for various reasons. Two cases in the LDCT arm died in distant hospitals from a widespread malignancy of uncertain origin (insofar as no biopsy had been obtained). In one case, lung cancer was the likely cause of death based on CT reports, whereas the other was classified as a death from other causes. Crude mortality data do not show any significant differences as to lung cancer-specific mortality, mortality for competing causes, and overall mortality (Table 2).

The distribution of all histological types was similar in the two study arms, with adenocarcinoma being most frequent in both groups. Bronchioloalveolar carcinoma associated with focal ground-glass opacity, ordinarily not visible on chest radiographs, was incidentally detected only once in the control group in a patient who received a LDCT for other reasons. In six patients the diagnosis of lung cancer was established clinically, but no pathological diagnosis could be obtained (Table 3).

A total of 30/46 patients (65%) diagnosed by LDCT in the screening arm were in stage I as opposed to only 2/13 interval cases (15%). In the control arm, 4/8 lung cancers were detected at baseline by a chest radiograph, and 8 subsequently observed, were in stage I as opposed to 19/26 (70%) patients diagnosed with stage II, III, or IV disease during follow-up.

A higher number and proportion of patients with stage I disease were observed the LDCT arm, reaching statistical significance. However, the absolute number of patients with advanced lung cancer (stage IIIB–IV) that was detected during the study period was identical in both arms (Table 3).

Invasive procedures were performed in a significantly higher proportion of LDCT patients compared with controls ($P < 0.0001$). Seven patients in the LDCT arm and one in the control arm had a diagnostic video-assisted thoracoscopic surgery (VATS) and went on to thoracotomy either due to a positive diagnosis of resectable lung cancer or because the VATS was inconclusive due to adhesions or an inability to locate the lesion, whereas one patient in each arm underwent intentional VATS surgery for removal of an anterior mediastinal mass (a stage I thymoma and a thymic cyst).

Forty-one spiral CT patients underwent thoracotomy, and 4 patients had a VATS lobectomy (all for lung cancer). Overall, 45 patients underwent a major surgical procedure for suspected lung cancer, and the diagnosis was confirmed in 39; therefore, 6/45 or 13.3% in the LDCT arm and had a major surgical procedure for benign disease compared with 3/20 or 15% in the control arm. In addition, 5 patients in the LDCT group underwent intentional thoracotomy for other conditions detected by LDCT: 1 malignant pleural mesothelioma, 1 esophageal cancer, 1 complex aspergilloma, 1 localized empyema, and 1 esophageal leiomyoma.

Investigational procedures in both groups are summarized in Table 4.

DISCUSSION

In contrast to a huge number of uncontrolled studies on early detection of lung cancer with LDCT, only a few randomized

TABLE 2. ALL-CAUSE MORTALITY

	LDCT ($n = 1,276$)(%)	Control ($n = 1,196$)(%)	Total	*P* Value
Cause of death				
Lung cancer	20 (1.6)	20 (1.7)	40	0.84
Other causes	26 (2.0)	25 (2.1)	51	0.93
Total deaths	46 (3.6)	45 (3.8)	91	0.83

Definition of abbreviation: LDCT = low-dose spiral computed tomography.
Percentages calculated on group totals.

TABLE 3. STAGE AND HISTOLOGY OF PATIENTS WITH LUNG CANCER

	LDCT ($n = 1,276$)(%)	Control ($n = 1,196$)(%)	*P* Value
Patients with lung cancer	60 (4.7)	34 (2.8)	0.02
Stage*	61 (4.8)	35 (2.9)	
IA	20 (1.6)	4 (0.3)	
IB	13 (1.0)	8 (0.7)	
All Stage I	33 (2.6)	12 (1.0)	0.004
II	4 (0.3)	2 (0.2)	
IIIA	7 (0.6)	4 (0.3)	
IIIB	6 (0.5)	3 (0.3)	
IV	11 (0.9)	14 (1.2)	
Stage IIIB-IV	17 (1.3)	17 (1.4)	0.86
Histology*	63 (4.9)	36 (3.0)	
Adenocarcinoma	19 (1.5)	12 (1.0)	
BAC	8 (0.6)	1 (0.1)	0.04
Squamous cell	19 (1.5)	11 (0.9)	
Small cell	6 (0.5)	2 (0.2)	
NSCLC, NOS	5 (0.4)	3 (0.3)	
Other†	4 (0.3)	2 (0.2)	
NA	2 (0.2)	5 (0.4)	

Definition of abbreviations: BAC = bronchioalveolar carcinoma; LDCT = low-dose spiral computed tomography; NA = not available; NOS = not otherwise specified; NSCLC = non–small cell lung cancer.
Percentages are calculated on group totals.
* For patients with synchronous tumors, only the stage of the most advanced tumor is counted. For patients with metachronous tumors, the stage and histology of each tumor is counted separately. In all patients with synchronous tumors, both lesions had the same (squamous) histology.
† LDCT arm: 2 adenosquamous carcinoma, 1 large-cell neuroendocrine carcinoma, 1 pleomorphic carcinoma. Control arm: 1 carcinosarcoma, 1 large-cell neuroendocrine carcinoma.

TABLE 4. INVESTIGATIONS FOLLOWING A POSITIVE PLANNED TEST DURING THE OBSERVATION PERIOD

	LDCT (*n = 1,276*)(%)	Control (*n = 1,196*)(%)	*P* Value
Any abnormality in CT	351 (27.5)		
2nd line LDCT/HRCT	199 (15.6)	22 (1.8)	
PET	57 (4.5)	4 (0.3)	
Any investigation	226* (17.8)	153 (12.8)	0.001
Any invasive procedure†	96 (7.5)	36 (3.0)	<0.0001
VATS procedures	20 (1.6)	6 (0.5)	0.01
Negative for lung cancer	6	2	
Positive for lung cancer	5	3	
Proceeded to open surgery	3	1	
Inconclusive	4	—	
Proceeded to open surgery	4	—	
VATS for other condition	1	1	
VATS lobectomy (lung cancer)	4	—	
Thoracotomy	46 (3.6)	20 (1.7)	0.004
Negative for lung cancer	6	3	
Positive for lung cancer	35	17	
For other condition	5	—	

Definition of abbreviations: CT = computed tomography; LDCT/HRCT = low-dose spiral CT/high-resolution CT; PET = positron emission tomography; VATS = video-assisted thoracoscopic surgery.

Percentages are calculated on group totals.

* Including one case with radiologically occult lung cancer detected by sputum examination.

† Including percutaneous biopsy, mediastinoscopy, bronchoscopy, VATS surgery, or thoracotomy. Invasive procedures carried out for staging purposes in patients with an established lung cancer diagnosis are not shown.

studies are currently in progress in the world. In the United States, the National Lung Screening Trial (NLST) (21) has successfully enrolled 53,461 patients from 2002 to 2004 (C. Berg, personal communication). In Europe, there are five ongoing trials: the largest one is the Dutch-Belgian-Danish NELSON Study (15, 16), which has enrolled 20,000 patients since 2004. In addition there is the LUSI trial in Germany, active since 2007 (17) and two randomized trials in Italy besides our own, the ITALUNG trial in Tuscany, which has randomized 3,206 subjects in 2003 (18), and the MILD trial in Milan (19), which started in 2005 and is still recruiting. Another study is awaiting approval in the U.K. (30).

The DANTE trial, born as a single-institution study in 2001, was the first randomized study to be launched. Despite the enthusiasm raised by the Early Lung Cancer Action Project (27) and by Japanese studies (31), we decided to run a randomized trial rather than another observational study because previous negative results with chest radiographs and sputum, with a greater number of early-stage cases detected and treated but no mortality advantage, made us fear the same could happen with CT although on a different scale. In fact, a more sensitive screening tool such as LDCT might ultimately increase the detection rate of pulmonary nodules only to increase false positive rates and overdiagnosis as hypothesized for the patients of the Mayo Lung Project (32, 33). Financial restrictions dictated a relatively small trial, but we thought that pooling our data or joining in a metanalysis would be pursued in the future.

We set the minimum enrollment age at 60 years, on the basis of incidence and mortality rates reported by the Lombardy Tumor Registry (the region where the two main hospitals are located), to increase the expected number of events or trial "efficiency." Patients with a previous cancer could be eligible if deemed cured, for example, patients with previous early-stage laryngeal cancer that was successfully treated and who remain at elevated risk of developing lung cancer (only one patient with previous laryngeal cancer was recruited in each arm). Women were excluded from the trial because the Mayo Lung Project and the Czech Study only enrolled males and our trial results would have been more comparable with those. Moreover, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) data (34), on the prevalence of LC detected by a screening chest roentgenogram in females, were not yet available when the DANTE trial was in its planning phase, which would have made it difficult to account for the effect of the baseline screening with a chest radiograph in calculating the sample size and power of the trial. Assuming that the ratio of female to male smokers enrolled in the trial in that age range was the same as the general Italian population, approximately one-third or less (35), the inclusion of women would have meant 400 female smokers or less in each arm. Although we recognized this exclusion could limit the generalizabilty of the results, extrapolations on the effect of screening according to sex would have been of limited value. Admission criteria were otherwise similar to those of the other trials.

Comparisons between the DANTE trial and the other randomized trials, both the earlier and the modern ones, are difficult, not only because of the different imaging technology used, but also because of their different study designs and populations. For example, no study ever compared screening by any modality with plain usual care, apart from the PLCO trial (34), launched in 1993, for which no data beyond baseline have been published to date.

In the Mayo Lung Project, subjects in the control arm were advised to have an annual chest radiograph, and over 50% of them did so. In the Czech study, annual screening in the control group began at the end of the third year. Control subjects in the LSS study and in the NLST had an annual chest radiograph; therefore, the control arm was also a screening arm. Only current European studies have been comparing LDCT with usual care or, as in the DANTE trial, with annual clinical review with no preplanned test.

In the DANTE trial, baseline chest radiograph and sputum examination were offered to all subjects in either arm before the actual screening phase with LDCT, which took place irrespective of their results. Rather than for methodological reasons related to our research, it was done mainly to attract participants willing to join a randomized study of CT versus no CT, by offering all of them at least a baseline screen with a different test, and the same principle applied to the annual clinical review. Screening with chest radiograph led to the detection of eight patients with LC in the control arm who were nevertheless kept in the study. However, from that moment on, control subjects had chest radiographs only for medical reasons.

One might object that an annual clinical review for controls is not exactly the same as usual care; however, we thought such a review would make it easier to monitor crossover contamination, new cancer cases, and deaths in both study arms, and we expected its impact on cancer detection and mortality to be very limited. In fact, only three cases of LC were clinically detected during a scheduled follow-up examination in the control arm (Figure 1).

As the observation time increases, subjects in western countries are more likely to undergo imaging tests, including CT scans, for various reasons.

The only randomized trial based on LDCT for which contamination data are available is the Lung Screening Study (22). In this trial, 15% of chest X-ray arm subjects were surveyed after a negative baseline evaluation and 16.4% were surveyed after negative Year 1 screening; 2.6% and 3.47% of them reported having a CT scan of the chest within 6 months. Contamination analysis in the DANTE trial was conducted on 93.4% of the subjects over the course of the entire study period; it was shown that 18% of controls had at least one chest radiograph for any reason since the start of the study, and 6% had a LDCT of the chest.

The LC detection rate in the DANTE trial was higher than those reported in all previous screening studies based on LDCT, whereas the proportion of stage 1 disease was not as high as

reported by Japanese authors (36, 37) and the I-ELCAP research group (8). Our results were nonetheless in line with most series where early-stage LC accounts for 47 to 70% of cases (38–44).

Interval cases represented 16.7% of all LCs in the screening arm, ranking high among other controlled and uncontrolled studies with LDCT where the rate varied between 5% (40) and 19% (43), perhaps because of the relatively advanced average age of our screenees.

Although the higher proportion of stage I disease, of resectable LC, and a slightly lower proportion of cancers detected because of symptoms or unrelated medical causes in the screening arm could be interpreted as encouraging clues (as they would indeed be in the absence of overdiagnosis), we performed three times as many invasive procedures and found twice as many LC cases with LDCT than without it, whereas the absolute numbers of advanced and lethal LC cases were unfortunately identical in the two arms, a finding that Bach and colleagues predicted by applying a simulation model to a group of 3,246 high-risk individuals from three observational trials (45). Moreover, a significant proportion of major surgical procedures (13%) were performed for pulmonary lesions that ultimately turned out to be benign, as other groups have already reported (44, 46).

The effect of competing causes of death in an aging population heavily exposed to cigarette smoke should not be underestimated either. In our trial, 56% of the deaths in the LDCT arm were due to competing causes after approximately 3 years. Simulation studies have investigated the benefit of LC screening with LDCT on disease-specific and overall mortality (47) and the theoretical benefit was limited to a mere 2% after 15 years by the impact of other causes of death; in our opinion if screening programs for LC were to be implemented widely in the future, admission criteria should be quite selective.

Our preliminary data were presented orally in a number of international meetings, and each time considerable interest was expressed by the audience of clinicians (48, 49). However, as this was not a formal interim analysis, for which the study had not been expressly designed, we did not calculate focused effect size measures (i.e., mortality rates and confidence intervals) that will be provided at the end of the study, and limited ourselves to computing and comparing raw data and proportions to give the readers a general idea of how the study is evolving. Our findings should therefore not be regarded as evidence that screening with LDCT is ineffective; nonetheless, our results are a warning that the effect on mortality might be far smaller than anticipated.

In conclusion, possible overdiagnosis, false positives, hazards of downstream investigation procedures, and cost issues make the results of randomized studies critically important in establishing a proper public health policy, and the final results from all ongoing randomized trials are awaited. In the meantime, continued application of current policies is supported by our data, and screening for LC with LDCT should not be advertised or proposed to high-risk subjects outside research programs.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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APPENDIX: TRIAL METHODOLOGY

Baseline Assessment

1. Self-administered questionnaire. Patients were requested to fill in a detailed questionnaire formulated in layman's terms. The questionnaire inquired in detail about their occupational history, with particular attention to possible professional exposure to chemicals or radiation, smoking history (whether active or former smoker, how many cigarettes a day, year started, year quit if applicable, periods of interruption) past medical history, including medication, allergies, surgery or hospitalizations for any reason, respiratory, cardiocirculatory digestive, renal, genitourinary, and neurological disturbances.

2. Interview and physical examination. Symptoms and signs were investigated by the physician through a structured medical interview, followed by a complete physical examination. Height, weight, pulse, blood pressure, and pulse oximetry saturation levels were reported, together with any abnormal findings. Comorbidities were recorded and graded as follows:

Grade 1 (mild): absence of symptoms, no medication needed

Grade 2 (moderate): symptoms present but controlled by medication

Grade 3 (severe): unsatisfactory degree of symptom control, and/or need for supramaximal medication.

Respiratory comorbidity was defined according to the current WHO criteria for chronic bronchitis, i.e., a chronic productive cough for more than 3 months for more than 2 consecutive

years, and/or based on the medical records, and examination outcome.

Annual Clinical Review

Every year all subjects in both arms undergo clinical review.

Smoking habits, recent medical history, hospitalizations, new medication, and new symptoms and signs since last contact are assessed by the physician through a structured medical interview, followed by a complete physical examination.

Height, weight, pulse, blood pressure and pulse oximetry saturation levels are reported once again, together with any abnormal findings.

The annual interview and physical examination are more focused toward signs and symptoms of lung cancer (for example, shortness of breath, chest pain, cough, haemoptysis, club fingers, superficial enlarged lymph nodes, or signs of pleural effusion), or extrapulmonary neoplasia.

Screening arm patients undergo a new spiral CT irrespective of the interview outcome or physical findings. Supplementary diagnostic testing as appropriate is advised if suspicious extrapulmonary abnormalities are detected.

Control arm patients do not undergo any further evaluation if the interview and physical findings are normal, or consistent with their previous clinical condition. Supplementary diagnostic testing as appropriate is advised if suspicious abnormalities are detected.

The first-line test in the case of respiratory symptoms or signs is normally a chest radiograph.

Compliance and Crossover Contamination Assessment

A structured form investigating whether the patient has received any chest roentgenograms or CT scans outside the DANTE project since the last contact and for which reason, is filled in by the physician every time for all participants, or the same questionnaire may be administered by the project assistant on the telephone if the subject is unable to come at that time.

Low-Dose CT Scan Protocol

Spiral CT images of the whole lungs are obtained during maximal inspiration at the end of a single breath hold using a single-slice scanner with low-dose setting (140 kvp, 40 mA), and reconstructed in overlapping contiguous 5 mm increments, 1.25 pitch, with a high-resolution bone algorithm (width 1700, level -600).

Hard copies of lung windows only were supplied for reading at the beginning of this trial, when multislice scanners and workstations were not yet available in our facilities. This modality was employed for all baseline screens for uniformity. Multislice scanners and workstations were deployed in late 2003, and replaced the older scanners and hard-copy readings for repeat screens and second-line assessments.

Two experienced chest radiologists read the images independently and a consensus reading is obtained with the participation of the local coordinator in the case of a disagreement. Both separate readings and the final consensus are documented.

Interpretation of Chest Radiographs

CXR results are considered positive if showing a non-calcified lung shadow, a hilar mass, an enlargement of the mediastinum, pleural effusion or thickening, or lytic bone lesions.

Interpretation of LDCT Scans

LDCT results are considered positive if they show noncalcified pulmonary nodules, or nonnodular lesions suggestive of malignancy, such as hilar masses, focal ground glass opacities (GGOs), major atelectasis, endobronchial lesions, mediastinal adenopathy, pleural effusion, or pleural masses.

Significant abnormalities of the heart, aorta, or mediastinal structures, not suggestive of lung malignancy but requiring further evaluation, such as cardiomegaly, pulmonary fibrosis, bilateral effusions or aneurysms are reported as well.

Directives for Further Diagnostic Workup of Pulmonary Lesions Found on LDCT

When a suspicious pulmonary lesion is found on LDCT, further investigation is warranted. If the lesion shows benign calcifications on HRCT, or shows some regression after antibiotic trial, it is considered benign and the patient scheduled for a new CT scan after one year. In all other cases investigation normally follows based on the size and aspect of the nodule. The workup protocol is not rigid, and may be adjusted on the basis of the personal preferences, experience and availability of facilities.

In summary. *If the lesion is smooth and less than 10 mm in size*, the patient is followed by LDCT at 3, 6 and 12 months; if no change occurs, follow-up after one year. *Non-smooth lesion smaller than 6 mm*: follow-up by LDCT at 3, 6 and 12 mo, if no change occurs, follow-up after one year. *Non-smooth lesion* $\geq$ *6 mm but* $\leq$ *10 mm*: oral antibiotics and new HRCT after 6 to 8 wk. If no regression occurs, evaluation on a case-by case basis as to the opportunity to follow the lesion or to perform invasive procedures to obtain a tissue-diagnosis (bronchoscopy, percutaneous fine-needle or core biopsy, or VATS). *Lesion* $\geq$ *10 mm but* $\leq$ *20 mm*: oral antibiotics and new HRCT after 6 to 8 wk. If no regression occurs, PET-scan is recommended. If the PET is positive, a tissue diagnosis is sought. If the PET-scan is negative, close follow-up is preferentially chosen. *Lesion* $\geq$ *20 mm*: discretional oral antibiotics and new HRCT or standard contrast-enhanced CT, and PET-scan. If the PET is positive, a tissue diagnosis is sought. If the PET-scan is negative, close follow-up is preferentially chosen. *Focal ground glass opacities*: oral antibiotics and new HRCT after 6 to 8 weeks. Evaluation on a case-by case basis as to the opportunity to follow the lesion or to obtain a tissue-diagnosis based on the size, number of lesions, location and ratio of any solid versus non-solid component (24).

Statistical Methods

Subjects were randomized 1:1 by permuted block randomization in blocks of four and stratified by Center according to computer-generated lists supplied by the Data Center before the assessment session. Sample size calculations were based on the incidence and mortality data reported in the Lombardy Cancer Registry in the 60–74 year-old male population, on the Mayo Lung Project reports, and on the ELCAP data. Males only were recruited in analogy with the Mayo Lung Project and Czech study (25–27). In the planning phase the following hypotheses were taken into account:

Mortality reduction: 50% after 5 years in the screening arm

Significance level: 5% ($\alpha = 0.05$)

Power: 90% by two-tail Fisher's exact

Lost to follow-up: 5% per year

A 90% power is higher than normally required in clinical studies (80%), and the Fisher's exact test is not very powerful and requires a larger sample than the likelihood ratio test. Also, the hypothesized number of dropouts was overstated in calculating the sample size. The resulting figure of 2,285 was increased by 5% to 2,400 (1,200 in each arm).

At the end of the recruitment phase, based on the initial monitoring data, the trial had an 80% power (one-tail likelihood

ratio test) to detect a 37% mortality reduction in the screening arm after five years, assuming less than 5% annual drop-off rate.

Assuming less than 3.6% annual dropout rate, the trial would have 80% power (one-tail likelihood ratio test) to detect a 35% mortality reduction and 90% power for a 41% mortality reduction in the screening arm after five years.

Tumors are classified as prevalent if the lesion was first detected at the baseline chest radiograph or sputum examination and/or baseline spiral-CT, regardless of when the diagnosis was established, whereas tumors subsequently detected during the study are classified as incident even if retrospectively visible in earlier scans.

All proportions are compared by the chi-square test or by the Fisher's exact test; means are compared by the *t* test, using the Satterthwaite's approximation in the case of heteroskedasticity (28). A significance level of 5% was adopted for all tests.

At the end of the study, raw lung cancer mortality will be compared by the likelihood ratio test, whereas the age-adjusted mortality rates by a generalized linear model accounting for age-related effects in mortality comparisons.

Endpoint Ascertainment

A patient's death may be notified by a spouse, a relative, by any person in close relationship with the deceased participant, or by the family physician, either spontaneously or when the subject is invited for the annual review. Copies of any medical records concerning the underlying diagnosis or death cause are requested from the family if available. If not, contacts are initiated with the hospital where the patient was admitted last, or has died, to obtain a copy of the clinical charts. If the patient has died at home and no hospital record is available, written information is sought from the family doctor's records. Linkage with the electronic database of the local health registries will be completed at the end of the planned observation period for all participants. Investigators are not blinded to the cause of death nor to subjects' allocation.