Articles

Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results

Ugo Pastorino, Massimo Bellomi, Claudio Landoni, Elvio De Fiori, Patrizia Arnaldi, Maria Picchio, Giuseppe Pelosi, Peter Boyle, Ferruccio Fazio

Summary

Background Low-dose spiral CT of the chest effectively detects early-stage lung cancer in high-risk individuals. The high rate of benign nodules and issues of making a differential diagnosis are critical factors that currently hamper introduction of large-scale screening programmes. We investigated the efficacy of repeated yearly spiral CT and selective use of positron emission tomography (PET) in a large cohort of high-risk volunteers.

Methods We enrolled 1035 individuals aged 50 years or older who had smoked for 20 pack-years or more. All patients underwent annual low-dose CT, with or without PET, for 5 years. Lesions up to 5 mm were deemed non-suspicious and low-dose CT was repeated after 12 months (year 2).

Findings By year 2, 22 cases of lung cancer had been diagnosed (11 at baseline, 11 at year 2). 440 lung lesions were identified in 298 (29%) participants, and 95 were recalled for high-resolution contrast CT. PET scans were positive in 18 of 20 of the indentified cancer cases. Six patients underwent surgical biopsy for benign disease because of false-positive results (6% of recalls, 22% of invasive procedures). Complete resection was achieved in 21 (95%) lung cancers, 17 (77%) were pathological stage I (100% at year 2), and the mean tumour size was 18 mm. There were no interval lung cancers in the 2·5 years of follow-up (average time on study from randomisation to last contact), although 19 individuals were diagnosed with another form of cancer (two deaths and 17 non-fatal admissions).

Interpretation Combined use of low-dose spiral CT and selective PET effectively detects early lung cancer. Lesions up to 5 mm can be checked again at 12 months without major risks of progression.

Lancet 2003; **362:** 593–97
See Commentary page 588

Division of Thoracic Surgery, Istituto Nazionale Tumori, Milan, Italy (U Pastorino MD)**; Division of Radiology, University of Milano** (M Bellomi MD, E De Fiori MD, P Arnaldi MD)**, and Divisions of Pathology** (G Pelosi MD) **and Epidemiology** (Prof P Boyle PhD)**, European Institute of Oncology, Milan; and Division of Nuclear Medicine, IBFM-CNR University of Milano Bicocca, Institute H S Raffaele, Milan, Italy** (C Landoni MD, M Picchio MD, Prof F Fazio MD)

Correspondence to: Dr Ugo Pastorini, Istituto Nazionale Per lo Studio e la Cura Dei Tumori, Via G Venezian 1, 20133 Milan, Italy (e-mail: Ugo.Pastorino@istitutotumori.mi.it)

Introduction

The overall 5-year survival of lung cancer in Europe is only 10%.[1] Late diagnosis of extensive disease is the main reason for treatment failure, since long-term survival of resected tumours in early stage is higher than 80%.[2]

Early-detection trials funded by the US National Cancer Institute in the 1970s did not reduce lung-cancer mortality or prevent advanced disease because of the poor sensitivity of chest radiography and sputum cytology.[3–5] Subsequent Japanese experience with CT has, however, been more promising.[6,7]

The results of the Early Lung Cancer Action Project[8] showed that spiral CT can identify very small lung cancers in high-risk individuals, with a resectability rate of 96% and a proportion of stage I tumours greater than 80%. However, to achieve such an excellent performance, high-resolution CT had to be applied intensively in a high proportion of participants, with a complex algorithm of three-dimensional reconstruction for minimum-growth assessment and a long diagnostic period (up to 2 years). Swenson and colleagues' later experience[9] with multislice CT showed a higher cumulative frequency of non-calcified nodules, and raised new questions about the challenge of differential diagnosis, efficacy, and costs of screening.

Smoking history can easily identify individuals at high risk of lung cancer, and we restricted this study to smokers. We did a prospective demonstration study, in which we adopted a diagnostic work-up that included selective use of PET scan to improve the accuracy of spiral CT in indeterminate pulmonary nodules.[10] The protocol stipulated that low-dose spiral CT of the chest had to be repeated yearly for 5 years, and further investigation with high-resolution CT was scheduled only for lesions larger than 5 mm. PET scan was used to further investigate non-calcified lesions of larger size (⩾7 mm) after high-resolution CT assessment. We report the findings for lung cancer detected at the baseline (year 1) screen and at the first follow-up screening round (year 2). This study is not a randomised trial but a demonstration project aimed to assess several key features relevant to the establishment of randomised screening trials.

Patients and methods

High-risk population

We recruited volunteers through a newspaper and television campaign in the Lombardy region, Italy, that provided information on the study design and eligibility criteria: current or former smokers, age 50 years or older with a minimum of 20 pack-years smoking history, no history of malignant disease, and adequate performance status (assessed on the basis of the patient's eligibility to undergo thoracic surgery). We asked participants to sign written informed consent to repeat low-dose spiral chest CT annually for 5 years, and provide blood, sputum, and urine samples, complete an epidemiological questionnaire,

and undergo basic spirometry (forced expiratory volume in 1 s) on each occasion. We scheduled clinics for Saturdays between 0830 h and 1430 h, to do 25–30 examinations each week. Participants were enrolled between June, 2000, and June, 2001.

Methods

Baseline and annual single-slice spiral CT was done without contrast material, with a low-dose protocol: 140 kilo Volt peak (kVp), 40 mA; pitch 2; 10 mm collimation; one breath; and reconstruction with lung algorithm at every 5 mm. The CT scanner was a GE-CT Hispeed (General Electric, Milwaukee, WI, USA). Effective radiation dose was equivalent to 0·7 mSv (0·014 mSv mGy^{-1} $cm^{-1} \times 50$ mGy/cm), a value lower than the 1 mSv maximum recommended annual radiation dose to an individual for diagnostic purposes.

Examinations were independently reported by two radiologists within 6 days, on a workstation (Advantage 3·1 GE Medical systems) and standard lung and mediastinum windows and maximum projection visual resolution reconstruction, for between-observer variability testing. In the event of a disagreement, a third radiologist was consulted. The site, dimension, and radiological features of each nodule were defined and recorded at baseline and repeat CT.

We deemed calcified nodules or lesions with a maximum diameter of 5 mm (measured on lung window) non-suspicious and scheduled repeat low-dose CT at year 2, as per the protocol. Spiral thin-section CT limited to the area of interest (140 kVp, 220 mA; pitch 1; 1 mm collimation) and three-dimensional analysis was done within 1 month in every case of non-calcified lesion larger than 5 mm, with assessment of contrast enhancement in nodular lesions that had density more than 0 Hounsfield Units (HU).

Swenson and colleagues[11] showed that, to keep to a minimum the likelihood that a malignant lesion will be classified as benign, 10 HU should be used as the threshold for a positive diagnosis. We thought the false-positive rate was too high at enhancement between 10 and 30 HU. Lesions showing positive enhancement (>30 HU) or positive PET scan were candidates for biopsy, as well as non-calcified lesions of 20 mm or larger, unless unequivocally benign at high-resolution CT. Further examinations for growth assessment were completed within 6 months of baseline CT.

If the nodule seen on CT was more than 5 mm and had a mean density less than 0, we deemed it strongly suggestive of a benign lesion and enhancement was not feasible. If the nodule was more than 7 mm with contrast enhancement CT but was negative on PET, or if the nodule was larger than 7 mm with no enhancement but positive on PET, the protocol specified a biopsy.

Non-calcified lesions of 7 mm or larger, were tested with flourine-18-labelled fluorodeoxyglucose PET and calculation of standardised uptake value, with last-generation equipment (GE Advance, General Electric Medical System). For each patient, the metabolic activity of the lung nodule was assessed by standardised uptake values, measured with regions of interest manually drawn around the nodule on transaxial images. We deemed lung nodules with maximum standardised uptake values greater than 2·0 to be malignant.

We collected blood, urine, and sputum samples and froze them in a dedicated tissue bank at –140°C. Biomarker analysis, which is not reported here, will assess whether biological markers can identify individuals at higher risk of cancer, improve the sensitivity and specificity of imaging techniques, such as low-dose CT scan and PET scan, or both.

	Baseline (n=1035)	Year 2 (n=996)	Total
Patients with nodules	199 (19%)*	99 (10%)†	298
1 nodule only	145	80	225
2 nodules	32	14	46
⩾3 nodules	22	5	27
Total number of nodules	284	127‡	411
Nodules <6 mm	238	197	345
Nodules >5 mm	46 (4·4%)	20 (2·0%)	66
Non-nodular lesions	15 (1·4%)	14 (1·4%)	29
Thin-section CT	61 (5·9%)	34 (3·4%)	95
Contrast-enhanced CT	29 (2·8%)	7 (7·0%)	36
Median (IQR) time to diagnosis (days)§	121 (52–156)	45 (34–80)	..
Lung cancers	11 (1·1%)	11 (1·1%)	22

*Proportion of low-dose CT (column %). †Patients with newly appeared or additional nodules. ‡Total number of new or additional nodules. §Period elapsed from initial low-dose CT and final diagnosis.

Table 1: **Results of low-dose spiral CT**

A team of research nurses, a data manager, and the study coordinator have maintained continuous contact with the enrolled volunteers to guarantee an appropriate follow-up. Each participant has been contacted at least twice yearly to collect relevant data on health status, hospital admission, and diagnosis or treatment of any concurrent disease, with particular emphasis on respiratory disorders and interval cancers. The study database was updated in real time with all such information.

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the paper.

Results

1035 patients were enrolled. Median age was 58 years (range 50–84), 739 (71%) were men, average tobacco consumption was 26 cigarettes daily for 37 years (median pack-years 40), and 14% had stopped smoking before accrual.

Table 1 shows the results of baseline low-dose spiral CT (prevalence) and repeat CT in year 2 (incidence). At baseline examination, we detected 284 non-calcified pulmonary nodules in 199 (19%) participants, and non-nodular lesions in 15 (1·4%). Calcified nodules of benign appearance were detected in an additional 44 participants. 61 individuals had lesions larger than 5 mm and underwent high-resolution CT (recall rate 5·9%). In five of these people, benign calcifications were revealed, leaving 56 cases for further assessment (46 nodules and 15 non-nodular lesions). On the basis of morphology and enhancement, 31 cases were considered benign, 11 suspicious for malignant disease, and 14 were of indeterminate behaviour. Lung cancer was ultimately diagnosed in 11 individuals, corresponding to 1·1% of enrolled and 18% of recalled participants. In addition, one typical carcinoid and one pulmonary marginal zone B-cell lymphoma were diagnosed.

By the end of June, 2002, 996 (96%) participants had undergone first repeat (year 2) low-dose CT. 127 new pulmonary nodules were detected in 99 (10%) individuals, and non-nodular lesions (ground-glass opacity) in 14 (1·4%). 34 of these lesions were further investigated with high-resolution CT (recall rate 3·4%) and lung cancer was diagnosed in 11 (1·1% of enrolled, 33% of recalled) cases. Six of these cases had been

	Baseline (n=29)	Year 2 (n=13)	Total (n=42)
Results (standardised uptake value)			
True positive	8 (10·3)*	10 (4·9)	18
True negative	17	1	18
False positive	3 (3·9)	1 (4·9)	4
False negative	1†	1‡	2
Accuracy	86%	85%	..
Positive stage I (<2 cm)	3 of 4 (2·0)	9 of 10 (4·0)	12
Positive stage II–III	5 of 5 (13·4)	0	5

*Average standardised uptake value. †8 mm well-differentiated adenocarcinoma. ‡11 mm adenocarcinoma with bronchoalveolar component.

Table 2: **Results of PET**

	Baseline (n=60)	Year 2 (n=33)	Total
Surgical procedures	15 (25%)*	12 (36%)	27
Thoracoscopic biopsy	11 (18%)	11 (33%)	22
Benign disease excision	5 (8%)	1 (3%)	6
Lung cancers	11 (18%)	11 (33%)	22
Complete resections	10 (91%)†	11 (100%)	21 (95)
Mean (SD) resected lymph nodes	25 (8)	17 (4)	21 (6)†
Stage I	6 (55%)	11 (100%)	17 (77)
<2 cm	8 (72%)	10 (91%)	18 (82)
Mean (SD) tumour size (mm)	21 (15)	15 (7)	18
Adeno	10 (91%)	7 (64%)	17 (77)
Squamous	1 (1·7%)	3 (9%)	4 (18)
Large-cell neuroendocrine	1 (1·7%)	1 (5%)	..

*Proportion of patients who underwent high-resolution CT (recalls). †Proportion of detected lung cancers. †Weighted mean of first two columns.

Table 3: **Results of surgery**

identified at baseline low-dose CT: the lesions grew from a median size of 5·5 mm to 11·6 mm in 1 year. At baseline, the lesion had either been too small (<5 mm) to proceed to high-resolution CT or the lesion could have been larger than 5 mm but was identified as an inflammatory or a scar-like lesion. Thus, at the baseline screening the lesions were classified as benign.

Overall, 440 non-calcified lesions were detected in 298 individuals (29% of enrolled). Average time to diagnosis—the period elapsed from initial low-dose CT and final diagnosis of cancer or benign lesion—was 115 days at baseline (range 5–314 days) and 64 days at the year 2 repeat scan (range 21–215 days). The average age of the 22 lung cancer cases was 59·8 years (SD 5·9).

At baseline, PET scan was done in 29 individuals (2·8% of enrolled, 48% of recalled), and was positive in 11 (38%, table 2). PET was positive in eight of nine participants diagnosed with lung cancer, and contributed to establish proper diagnosis in six (43%) of 14 cases that were indeterminate at high-resolution CT. On the other hand, PET was the main reason for biopsy in three of five benign lesions. Tissue diagnosis of false-positive cases was: bronchiectasis, pulmonary sclerosis with lymphocytic infiltrates, and inflammatory pseudotumour. Mean standardised uptake value was 10·3 for malignant and 3·9 for benign lesions. We noted a much larger difference between stage II–III and small (<2 cm) stage IA lung cancers (standardised uptake value 13·4 *vs* 2·0). The false-negative cases were two well-differentiated adenocarcimomas of 8 mm and 11 mm size, one of which showed a substantial broncholoalveolar component.

At year 2, PET scan was done in 13 individuals (1·3% of enrolled, 38% of recalled), and was positive in 11 (85%). Despite the smaller size of lesions, all but one case of lung cancer was PET positive, and the average standardised uptake value in limited stage IA (<2 cm) was higher than at baseline (4·0 *vs* 2·0). The only false-positive case was a 10 mm inflammatory pseudotumour with organised bronchiolitis obliterans. If contrast-enhanced CT was positive and PET negative, individuals had malignant disease, and the same for lung cancer; all false positives were negative on contrast-enhanced CT (or this procedure was not done) and positive on PET. Negative contrast-enhanced CT and negative PET lesions were benign.

Ten of 11 baseline lung cancers underwent complete resection (table 3); the remaining individual had adrenal-gland metastases. In every patient, tissue diagnosis was obtained before definitive treatment. Pathological stage was IA in six, IIIA in two, and II, IIIB, and IV in one each. With the exception of one squamous-cell cancer, all remaining cases were adenocarcinomas. Five participants (8% of recalls, 33% of invasive procedures) underwent surgical biopsy for benign disease because of false-positive results. In accordance with study protocol, biopsy was taken by video-assisted thoracoscopy in three patients, and by limited thoracotomy in one central lesion. A further participant refused video-assisted thoracoscopy and underwent thoracotomy and lobectomy at another Institution, against the advice of the study group (this lesion was diagnosed as a benign inflammatory lesion).

At year 2, all detected lung cancers were amenable to complete resection. Pathological stage was IA in ten and stage IB in one; histology was adenocarcinoma in seven, squamous cancer in three and large-cell neuroendocrine cancer in one. Limited excision for tissue diagnosis was done in every patient before lobectomy, and in ten of 11 cases was feasible with minimum invasive access (video-assisted thoracoscopy).

Lateral muscle-sparing-limited thoracotomy followed by radical lobectomy and lymphnode dissection was the standard procedure for the whole series. The average number of resected nodes was 25 in baseline cases (SD 8) and 17 (4) in year 2 cases; mean primary tumour size was 21 mm (15) and 15 mm (7), respectively.

Active follow-up of the cohort for the present analysis was closed at the end of February, 2003 (2631 person-years). No interval lung cancer was registered. All but one (95%) of the 22 patients with screening-detected lung cancer were alive, two with evidence of distant disease. The patient who had stage IV disease died with brain metastases 15 months after baseline CT. Two patients underwent additional pulmonary surgery (middle-lobe lobectomy, left completion pneumonectomy) for malignant lesions of uncertain nature (second primary cancer or metastasis). One patient remained free from disease, the other developed multiple distant metastases 6 months after salvage surgery.

Seven individuals died from causes other than lung cancer: two malignant disease (kidney and stomach), three cardiovascular events (two ruptured aneurisms, one myocardial infarction), one of liver cirrhosis, and one in a road accident. 173 hospital admissions were recorded, including 17 cases of malignant disease. Most common tumour sites were breast (five cases), prostate (three), and bladder (two). As expected, the main cause of admission was cardiovascular disease in 45 cases (15 coronary), followed by orthopaedic in 27, and benign tumour in 26 (seven prostate, six vocal cord, five bladder).

Discussion

Lung carcinoma is the most fatal cancer worldwide, and the estimated number of deaths will exceed 1·3 million annually early in the third millennium.[12] Worldwide initiatives aimed at prevention through smoking control have achieved important results in terms of prevalence of active smokers in some countries, and reductions in mortality are occurring in many countries in Europe

among men, but not women.[13,14] On the other hand, smoking-cessation plans have generated a large cohort of former smokers at high risk of lung cancer. Even where therapeutic resources have been applied in an optimum way, the improvement of population-based lung-cancer survival has been slight in the past decade. Currently more than 90% of all people diagnosed in Europe die within 5 years, a proportion that compares poorly with the mortality of breast or colon cancer.[1,12] However, survival is more than 80% when lung cancer is resected before it reaches a diameter of 2 cm.[2]

Early detection trials with conventional sputum cytology and chest radiography proved unable to decrease lung-cancer mortality,[3–5] and the negative outcomes of these large trials stopped any further development of early detection programmes in this disease. The advent of low-dose spiral CT has made possible thorough examination of the lungs in a few seconds without intravenous contrast,[15] with costs that are similar to screening mammography. Observational studies in smokers have achieved promising results for accuracy and sensitivity of low-dose spiral CT, compared with chest radiography, with a high proportion of complete resections and a frequency of stage I tumours between 60% and 80%.[6–8,13] Our pilot study, which used a simplified design, has confirmed these results with 95% resectability in screening-detected lung cancers, and 77% of stage I disease (100% at year 2). The lower lung-cancer detection rate at baseline, compared with the Early Lung Cancer Action Project[8] (1·1 *vs* 2·7%) can be potentially explained by the younger median age in our study (58 *vs* 67 years) and differences in smoking habits.

A major concern in systematic use of spiral CT is the high frequency of false-positive findings for benign nodules. In the 2-year report of Mayo Clinic, based on multi-slice CT, 69% of 1520 screened patients had uncalcified pulmonary nodules, and only 3% of them proved to have malignant disease.[9] In our experience, use of single-slice CT showed uncalcified lesions in only 29% of participants, and in 7% of these we diagnosed lung cancer. However, most of these benign lesions are very small and may not require immediate investigation. With our selective protocol, in which uncalcified lesions up to 5 mm were sent to 12 months follow-up, only 9% of participants (4·6% of low-dose CT) underwent further investigation of suspicious lesions with high-resolution CT, with or without PET, and in 23% of them the lesion was malignant.

Differential diagnosis of lesions smaller than 6 mm can be very difficult, and expands greatly the probability of unnecessary investigations and the total costs of screening, as in the Early Lung Cancer Action Project. In addition, the expertise needed for fine-needle aspiration biopsy of small and deeply-located pulmonary lesions is not reproducible in most centres that are ready to start early detection programmes. We found selective use of PET scan to be helpful in replacing fine-needle aspiration biopsy for differential diagnosis. Combined with a simplified algorithm for CT assessment, PET enabled us to complete the diagnostic work up within an average time of 3·8 months at baseline and 2·1 months at year 2, thereby reducing the anxiety related to the diagnostic phase. On the other hand, delayed diagnosis of very small tumours does not seem to have affected their curability. Six lesions deemed non-suspicious at baseline CT and proven malignant at year 2 showed a median change in maximum diameter from 5·5 mm to 11·6 mm in 1 year, and were all managed by standard lobectomy, with a final pathological report of T1N0 disease.

Six cases were offered surgical biopsy for benign lesions because of false-positive results, representing 6% of recalls and 22% of invasive procedures. In three of these cases, PET was the main reason to recommend biopsy, all at baseline, since the only false-positive PET at year 2 was a case of inflammatory pseudotumour, for which resection was recommended on the basis of radiologically malignant features and a negative baseline CT. This proportion of benign biopsies (22%) falls in the range of 17–22% reported in large trials,[7,16,17] with the favourable exception of 6% in the Early Lung Cancer Action Project. The absence of death in 27 cases of screening-determined surgery, for benign or malignant disease, confirm the observation of the Early Lung Cancer Action Project[8] and Bernard's study[17] of a more favourable morbidity profile of early lung cancer resection, compared to symptomatic cases. Overall, these data show that whenever early detection programmes are done in centres of excellence, the risk of unnecessary resections is much lower than the 50% value feared by some researchers,[18] on the basis of early video-assisted thoracoscopic experience[19,20] and the risk of postoperative mortality is not comparable with the 4% observed in community hospitals.[21,22]

A different biological reason for criticism against lung-cancer screening lies in the risk of overdiagnosis (also called pseudo-disease), that is detection of indolent and slowly progressing cancer,[23,24] as well as in the possibility that very small cancers have already generated distant metastases.[18] In a pathological review of a Mayo Clinic project, Stanley[25] found that between 7% and 15% of original screening-detected lung cancers could represent only in-situ carcinoma. Although these data cannot explain the excess of cancers reported in the screened group through misdiagnosis, in-situ carcinoma may have contributed to overdiagnosis. Among our participants we detected no case of in-situ carcinoma or pure non-invasive broncholoalveolar adenocarcinoma. The assessment of metastatic potential of small lesions requires longer follow-up than we report here, but only one (6%) of 17 pT1 tumours had metasteses

Early randomised trials are still unable to prevent advanced and incurable lung cancer because they use periodic chest radiography examination. However, data are few on the frequency and curability of interval lung cancer in spiral CT trials. In Japanese studies, with follow-up of more than 3 years, the risk of interval lung cancer ranges from 3% to 14% of incident cases, after baseline screening.[7,16] The absence of advanced disease in the average 2·5 years follow-up of our trial seems promising, but must be confirmed by long-term observation.

Competing risks of death are another critical factor for the outcome of early detection programmes, particularly when risk is determined by smoking status, since smoking causes many fatal disorders other lung cancer.[12] Our study provides useful elements by which to assess the impact of comorbidity on the overall life expectancy of typical high-risk populations. In fact, at present follow-up, lung cancer accounted for only one (12%) of eight observed deaths, and 52% of registered malignant diseases. These proportions seem to show that randomised trials comparing spiral CT with chest radiography among patients with a lung cancer risk of 0·5–1·0% per year will not show a survival benefit because of competing risks of death, if the period of screening is too short (2–3 years).[26]

In a period of limited resources for ageing populations, lung-cancer screening may not reach a sufficient cost-benefit balance to win against competing medical priorities, even in developed countries. The vigorous

debate between supporters and opponents has properly pointed out that the real costs of early detection programmes for the entire community and national health care systems might exceed those sustained by the at-risk volunteers for a private chest CT scan.[27] Nonetheless, a cost-benefit estimate based on the assumption that spiral CT can only achieve a 13% reduction in lung-cancer mortality (ie from 85% to 74%) seems far too pessimistic, and the value of more than US$100 000 per year of life gained disproportionate.[28] The benefit of early lung-cancer resection can be further expanded, if low-dose spiral CT is applied to routine follow-up of patients, with the aim of curing second primary tumours.[29]

We have shown that low-dose spiral CT combined with selective use of PET can effectively detect early lung cancer. A more conservative approach to very small CT-detected nodules is justified, and lesions up to 5 mm can be followed up at 12 months without major risks of progression. There is much to learn about early detection of lung cancer. For example, adenocarcinoma is over-represented, which might indicate the ease with which CT can detect peripheral lesions and that a limitation of CT might be to miss some central lesions, probably squamous tumours. Although prospective randomised trials are the proper instrument with which to measure the ultimate outcome of any screening policy, pilot studies addressing specific technical issues and methods are of fundamental importance in a phase of accelerated development of imaging and molecular technology, to design the optimum protocol to be tested in large-scale trials.[30]

Contributors

U Pastorino and P Boyle developed the design and organisation of the study, participated in all stages of the study, made the initial interpretation of the study findings, and prepared the first draft of the report. M Bellomi was responsible for the spiral CT examinations, assisted by E De Fiori and P Arnaldi, and had overall responsibility for all CT features of the study. F Fazio was responsible for the PET scanning, assisted by C Landoni and M Picchio. G Pelosi was responsible for the pathological assessments. The initial draft of the report was amended after the input of M Bellomi and F Fazio, and all researchers contributed to the preparation of the final draft.

Conflict of interest statement

None declared.

Acknowledgments

UP was working at the European Institute of Oncology during the study. This study was supported by a Research Grant from the Italian Ministry of Health (Ricerca Finalizzata the Italian Association for Cancer Research (AIRC) and the European Institute of Oncology. We thank Francesca Penati for the general management of early detection clinic and Claudio Jacomelli for the design and update of the study database.

References

1 Survival of cancer patients in Europe: the EUROCARE 2 study. Lyon, France: IARC scientific publications 1999: 1–572.
2 Patz EF, Rossi S, Harpole DH, Herndon JE, Goodman PC. Correlation of tumor size and survival in patients with stage Ia non-small cell lung cancer. *Chest* 2000, **117:** 1568–71.
3 Melamed MR, Flehinger BJ, Zaman MB, Heelan RT, Parchick WA, Martini N. Screening for lung cancer: results of the Memorial Sloan-Kettering study in New York. *Chest* 1984; **86:** 44–53.
4 Tockman MS. Survival and mortality from lung cancer in a screened population: the Johns Hopkins Study. *Chest* 1986; **89:** 324–25S.
5 Fontana RS, Sanderson DR, Woolner LB, et al. Lung cancer screening: the Mayo program. *J Occup Med* 1986; **28:** 746–50.
6 Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. *Radiology* 1996; **201:** 798–802.
7 Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet* 1998; **351:** 1242–45.
8 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.
9 Swensen SJ, Jett JR, Hartman TE, et al. Lung cancer screening with CT: Mayo Clinic experience. *Radiology* 2003, **226:** 756–61
10 Gould MK, Maclean CC, Kuschner WG, Rydzac CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. *JAMA* 2001; **285:** 914–24.
11 Swensen SJ, Viggiano RW, Midthun DE, et al. Lung nodule enhancement at CT: multicentric study. *Radiology* 2000; **214:** 73–80.
12 Peto R, Lopez AD, Boreham J, Thun M, Heath CW Jr, Doll, R. Mortality from smoking worldwide. *Br Med Bull* 1996; **52:** 12–21.
13 Boyle P, d'Onofrio A, Maisonneuve P, et al. Measuring progress against cancer in Europe: has the 15% decline targeted for 2000 come about? *Ann Oncol* 2003; **14:** 1312–25.
14 Levi F, Lucchini F, Negri E, Boyle P, La Vecchia C. Mortality from major cancer sites in the European Union, 1955–1998. *Ann Oncol* 2003, **14:** 490–95.
15 Diederich S, Wormanns D, Heindel W. Lung cancer screening with low-dose CT. *Eur J Radiol* 2003; **45:** 2–7.
16 Sobue T, Moriyama N, Kaneko M, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. *J Clin Oncol* 2002; **20:** 911–20.
17 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:** 508–13.
18 Swensen SJ. Screening for cancer with computed tomography. *BMJ* 2003; **326:** 894–95.
19 Bernard A. Resection of pulmonary nodules using video-assisted thoracic surgery: the Thorax Group. *Ann Thorac Surg* 1996; **61:** 202–05.
20 Mack MJ, Hazelrigg SR, Landreneau RJ, Acuff TE. Thoracoscopy for the diagnosis of the indeterminate solitary pulmonary nodule. *Ann Thorac Surg* 1993; **56:** 825–32.
21 Romano PS, Mark DH. Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. *Chest* 1992; **101:** 1332–37.
22 Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB. The influence of hospital volume on survival after resection for lung cancer. *N Engl J Med* 2001; **345:** 181–88.
23 Watanabe S, Watanabe T, Arai K, Kasai T, Haratake J, Urayama H. Results of wedge resection for focal bronchioloalveolar carcinoma showing pure ground-glass attenuation on computed tomography. *Ann Thorac Surg* 2002; **73:** 1071–75.
24 Kodama K, Higashiyama M, Yokouchi H, et al. Natural history of pure ground-glass opacity after long-term follow-up of more than 2 years. *Ann Thorac Surg* 2002; **73:** 386–93.
25 Colby TV, Tazelaar HD, Travis WD, Bergstralh EJ, Jett JR. Pathologic review of the Mayo Lung Project: is there a case for misdiagnosis or overdiagnosis of lung carcinoma in the screened group? *Cancer* 2002; **95:** 2361–65.
26 Hillman BJ. Economic, legal, and ethical rationales for the ACRIN national lung screening trial of CT screening for lung cancer. *Acad Radiol* 2003; **10:** 349–50.
27 Stanley RJ. Inherent dangers in radiologic screening. *Am J Roentgenol* 2001; **177:** 989–92.
28 Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. *JAMA* 2003; **289:** 313–22.
29 Johnson BE. Second lung cancers in patients after treatment for an initial lung cancer. *J Natl Cancer Inst* 1998; **90:** 1335–45.
30 Mulshine JL, Smith RA. Lung cancer. 2: screening and early diagnosis of lung cancer. *Thorax* 2002; **57:** 1071–78.