

Three-year findings of an early lung cancer detection feasibility study with low-dose spiral computed tomography in heavy smokers

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Background: Low-dose spiral computed tomography (sCT) showed a four-fold increase in the detection rate in high-risk subjects and a higher percentage of stage I lung cancer in comparison with chest X-ray. However, there is a considerable discrepancy among studies in the percentage of lung nodules, overall lung cancer and stage I detection rate.

Subjects and methods: From April to December 2001, 520 asymptomatic volunteers aged ≥ 55 years with a history of cigarette smoking ≥ 20 pack-years and no previous cancer were enrolled to receive an annual sCT of the chest for five consecutive years.

Results: Seventy three per cent were male, median age was 59 years and 91% were current smokers. At baseline, nodules ≥ 5 mm were detected in 114 (22%) undergoing sCT; the size of lung nodules ranged from 5 to 9.9 mm in 81.5% of the cases. Five (1%) cases of lung cancer were detected. In two additional cases a pathological diagnosis of atypical adenomatous hyperplasia was made. Three new cases of lung cancer were detected in the second and third year of the study. One interval case was detected during the third year.

Conclusions: Despite some promising data, convincing evidence from ongoing randomized trials is needed to support the routine use of sCT as a recommended tool for screening of lung cancer.

Key words: early detection, lung cancer, spiral computed tomography scan

Introduction

Current smokers are clearly at increased risk for lung cancer, but even former smokers continue to be at increased risk for many years after quitting [1]. Smoking cessation and early detection are critical goals for lung cancer prevention and control.

In lung cancer, the cure rate is highly stage-dependent, being significantly higher in stage I, but unfortunately the proportion of patients clinically diagnosed in this stage is very limited [2] and to date no screening tool has been recognized to be definitively effective in significantly reducing lung cancer mortality. The negative view about lung cancer screening came from disappointing results of large randomized, controlled trials conducted in the 1970s that failed to show any mortality reduction when chest X-rays or sputum cytology were used as potential screening tools in high-risk populations [3–6].

Low-dose spiral computed tomography (sCT) can detect lung nodules of only 2 mm and it is four times more sensitive than standard chest X-ray, but, especially in the central lung areas, nodular lesion can be missed by the radiologist because of misinterpretation of cross-sectioned small blood vessel imaging. When compared with the standard CT technique, low-dose sCT is less costly, faster and entails lower radiation exposure (0.5 versus 5.0 mSv) [7].

Interest in lung cancer screening was primarily revamped by the ELCAP study results, in which baseline screening detected 27 cases of malignant lung disease, of which 23 (85%) were found at stage I and 26 underwent curative surgical resection [8]. Subsequently, several non-randomized studies concluded that the resection of CT screening-detected early-stage lung cancer results in a higher cure rate (for review see Bepler et al. [9]).

This feasibility study was performed to verify the applicability of low-dose sCT as a diagnostic tool for early lung cancer detection in the setting of a university hospital (University of Turin, San Luigi Hospital) and it was planned and initiated at approximately the same time as a similar study was being performed at the European Institute of Oncology in Milan [10].

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The primary end points of this study were to determine the prevalence of malignant pulmonary disease at the baseline sCT examination and to assess the radiological detection of disease during the 5-year follow-up. Secondary objectives included the determination of the overall resectability of detected malignant tumors, the assessment of the proportion of cases resected for pathological stage pIA (survival 70–80%) and the evaluation of the costs by estimated years of life saved.

This preliminary report is focused on the prevalence of lung cancer at the baseline examination as well as in the subsequent 2 years, the assessment of overall resectability, and the morbidity and mortality associated with surgical resection.

Subjects and methods

Up to 500 subjects considered to be at high risk for lung cancer were asked to volunteer for annual low-dose sCT examination for five consecutive years. The study population was defined by inclusion criteria as follows: age ≥ 55 years, current daily smokers or former smokers (up to 10 years before), ≥ 20 pack-years (calculated by multiplying the number of packs per day by the total number of years smoked) and with no personal history of malignancy.

Those subjects who were willing to participate were assessed for their eligibility to enter in the early detection study by means of a phone questionnaire.

The study was conducted under the approval of the ethical review board of the Piedmont region, and followed the guidelines for good clinical practice. The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were also followed. The study did not receive any private or public funding and the personnel volunteered to take part in the project.

Each subject first signed an informed consent form for his/her participation in the study and if he/she agreed, on the same day blood, urine and sputum samples were collected.

Baseline and annual low-dose sCT scans of the thorax (without contrast) were performed on a double slice sCT scanner (Elscent Twin; Elscint, Haifa, Israel) at 120 kV peak, 33 mA and pitch 1.5, with a collimation of 8.8 mm and 5 mm reconstruction interval. The images, encompassing the entire lung region, were acquired in a single breath-hold at end-inspiration after hyperventilation and were reconstructed with overlapping at 4 mm intervals. All investigations were sent to a workstation and immediately archived on CD-rom in dicom format (one CD for each session). In this study, chest radiographs and lung function tests were not prospectively studied.

Two board-certified chest radiologists independently evaluated the scans for inter-observer variability. In the case of disagreement, a senior radiologist acted as arbiter to reach an agreement.

Every subject was to be followed up for 5 years with annual scans, and monitored for smoking habit.

Diagnostic algorithm

Baseline examinations without non-calcified pulmonary nodules were regarded as negative and subjects were invited to undergo repeated low-dose sCT one year later. Homogeneously calcified nodules were considered as benign and subjects were invited to repeat low-dose sCT one year later, as were non-calcified nodule(s) with a maximum transverse diameter < 5 mm.

If solitary or multiple nodules ≥ 5 mm were detected, further diagnostic procedures were determined by size of the nodule(s) and attenuation coefficient. The protocol called for inclusive reading, so that ground-glass opacities were counted as nodules.

Nodule attenuation was recorded as non-calcified or as partially or homogeneously calcified by using an arbitrary threshold of 200 Hounsfield units (HU) to differentiate between calcification and soft-tissue attenuation. Within 1 month all subjects with one or more nodule(s) with a diameter ≥ 5 mm were referred to a contrast medium chest CT scan with enhancement assessment. All the images were viewed at both lung and mediastinal windows. Based on a previous experience on the likelihood of malignancy at sCT [11] and, at the same time, to limit the possibility of false-positive rate, the contrast enhancement was considered as follows: < 20 HU, negative; 20 HU, suspicious; and > 20 HU, positive. If the probability of malignancy was considered low (size < 10 mm and enhancement < 20 HU), follow-up with repeat at 3, 6 and 12 months after baseline examination was considered case by case, using 1-mm collimation with overlapping 0.5-mm reconstructions. For nodules > 11 mm and with an HU value ≥ 20 , surgical intervention was always considered. From the second year only, standard-dose CT with thin sections (1–3 mm) was used to further analyze and follow-up new nodules or any increase in size of any previously detected nodule.

At the subsequent annual sCT, the absence of growth of the nodule(s) in the 12-month period was considered as evidence of a benign lesion. Growth was defined as an increase of the nodule's diameter in at least one dimension.

In our study PET scan was not routinely performed; however, subjects with positive enhancement were occasionally considered for this diagnostic procedure.

Radically resected subjects were assessed for post-surgical morbidity and mortality and followed up according to standard criteria (every 3 months for the first 2 years and then twice yearly). Resected specimens were classified according to WHO classification for lung tumors [12].

Results

Enrolment in the feasibility project was limited to a cohort of 520 high-risk individuals; one subject was found ineligible at the time of baseline questionnaire. The median age was 59 years (range 54–79), 91% were current smokers and 26.5% were females (Table 1).

Baseline low-dose CT identified 114 subjects as having one to six non-calcified nodule(s) with a largest diameter ≥ 5 mm, and 127 subjects having one to six non-calcified nodule(s) with a largest diameter < 5 mm. The nodule size was distributed as follows: 5–9.9 mm, 98; 10–19.9 mm, 11; > 20 mm, five. Among 278 subjects with a nodule(s), the distribution in number

Table 1. Demographic data ($n = 520$)

Characteristics	Number of subjects	%
Male	382	73.5
Female	138	26.5
Age at screening (median 59 years)		
55–59 years	278	53.4
60–64 years	168	32.3
65–69 years	51	9.8
70–74 years	19	3.6
> 75 years	4	0.7
Smoking status		
Former	46	8.9
Current	474	91.1

was as follows: one nodule, 116; two to six nodules, 118; more than six nodules, seven (Table 2).

Within 1 month, 114 subjects with a nodule(s) >5 mm received a contrast-enhanced ($n = 49$) or standard-dose ($n = 65$) CT scan. In 28 cases the nodular lesions were judged as false positive owing to blood vessel crossing, inflammatory lesions or the stigma of a previous tuberculosis. The reason for the deviation from the planned diagnostic algorithm was related to the disappointing results after performing a contrast CT scan in the first 49 subjects with nodules >5 mm, in which contrast-enhancement was sufficiently reliable only in 24 out of 49 subjects.

Within the first year, 71 subjects were submitted to at least one additional standard-dose CT scan of the nodule without contrast enhancement.

Owing to restriction facilities, PET scan was not systematically performed in subjects with positive contrast media enhancement; it was performed occasionally in six cases, and in five it was completely negative. One patient with negative PET scan was subsequently resected and a pathological diagnosis of bronchiolo-alveolar carcinoma was made.

Among 114 subjects as having one to six non-calcified nodule(s) with a largest diameter ≥ 5 mm, five (4.3%) had a nodule-associated malignancy: the size was 9 mm in one case, 10–15 mm in two and >20 mm in two lesions. Prevalence of lung cancer in the study population was 1%.

Histologically, one lung cancer was an adenocarcinoma, one a squamous cell carcinoma and three were bronchiolo-alveolar carcinomas. The adenocarcinoma occurred in a 79-year-old subject; it was stage IV disease (for adrenal metastases) and the subject subsequently received single-agent chemotherapy.

The four lung cancers were completely resected and pathological staging was pIA in two cases, pIB in one case and pIIIB in another case who, after surgical resection, received adjuvant chemo-radiotherapy.

In two additional nodules (size 6 and 20 mm), contrast enhancement was increased between two subsequent CT investigations and, after a case discussion in a multidisciplinary thoracic oncology clinic, submitted to radical surgery. Both cases (one lobectomy and one atypical resection) were defined at post-surgical pathological examination as atypical adenomatous hyperplasia, which the current classification of lung tumors identifies as a pre-neoplastic lesion [13]. Two years later, the patient who underwent atypical resection developed an adenocarcinoma in the same lobe with chest wall involvement.

Table 2. Detection rate and amount of non-calcified nodules in each subject at the baseline spiral computed tomography

Non-calcified nodules	Subjects ($n = 519$) [n (%)]
Absence	278 (53.5)
Presence	241 (46.5)
1 nodule	116
2–6 nodules	118
>6 nodules	7

Subjects with newly detected or increased in size non-calcified nodules ≥ 5 mm were 5.2% and 3.3% at year 2 and 3, respectively (Table 3).

During the second and the third year, three cases of lung cancer for each year were detected (Table 4). As done at the baseline year, all the new nodules ≥ 5 mm or those that had increased in size had at least one standard-dose chest CT scan. At year 2, in five subjects non-nodular abnormalities were detected at the annual sCT and during the subsequent diagnostic work-up an endobronchial squamous cell carcinoma was diagnosed.

At the end of the first year the drop-off rate was 5% (25 subjects) (five cases of lung cancer, two of atypical adenomatous hyperplasia, five other malignancies and 13 because of subject's decision), 4.5% (22 subjects) at the end of the second year (three cases of lung cancers, two cancer-unrelated deaths, 10 other malignancies and seven because of subject's decision), and 2.3% in the third year (three cases of lung cancers, two cancer-unrelated deaths and six other malignancies).

Table 3. Summary of the new nodules and those increased in size from the previous year during the second and the third year of the early detection study

Year	New nodules	Nodules increased in size	Nodules >5 mm
Second	25	4	26
Third	18	7	16

Table 4. Pathological findings of clearly contrast-enhanced nodules

Histologic typing	Stage	Diameter (mm)	Age of patients (years)
Year 1 (baseline)			
Bronchiolo-alveolar carcinoma ^a	IA	13	57
Bronchiolo-alveolar carcinoma ^b	IIIB	24	73
Bronchiolo-alveolar carcinoma ^a	IB	12	63
Adenocarcinoma ^c	IV	>20	79
Squamous cell carcinoma	IA	9	62
Atypical adenomatous hyperplasia ^a	–	20	62
Atypical adenomatous hyperplasia ^a	–	6	62
Year 2			
Bronchiolo-alveolar carcinoma ^a	IB	12	61
Squamous cell carcinoma ^a	IA	12	77
Squamous cell carcinoma ^a	IB	^d	58
Year 3			
Squamous cell carcinoma ^a	IB	7	59
Bronchiolo-alveolar carcinoma ^a	IA	11	60
Carcinosarcoma ^c	IIIB	5	68

^aComplete resection.

^bResected and treated with adjuvant chemo-radiotherapy.

^cTreated with chemotherapy.

^dCT nodular lesion was diagnosed as tuberculosis but a pure endobronchial lesion was found during the diagnostic work up.

One interval case was observed during the third year: 6 months later the annual sCT gave a completely negative evaluation for nodules and the subject received a chest X-ray for other reasons that detected a non-calcified nodule of 20 mm in the right lobe. The subject was subsequently resected and a pathological diagnosis of adenocarcinoma was made.

At the time of this report all of the 11 surgically resected patients with the exception of one (the case of IIIB disease detected at baseline) are alive and nine are currently disease-free. Among the 11 cases of lung cancer, the proportion of patients with stage I is 72%. No morbidity or mortality associated with surgical resection was reported.

Other detected lesions

One hundred and thirty-seven extra-pulmonary findings (26%) were discovered during the first year, among which 6% were adrenal adenomas, 3.4% hepatic and renal cysts, hepatic angiomias, renal calculosis and cholelithiasis, and in four cases an aortic aneurysm was detected. Incidentally, a stage I renal carcinoma was identified and submitted to radical nephrectomy. In all of these findings additional imaging investigations were requested to reach a definitive diagnosis in 62 subjects, while in the remaining 75 the abnormalities were already known and diagnosed.

Discussion

Currently, there is preliminary evidence from non-randomized studies that low-dose sCT is able to increase the proportion of prevalent cases of stage I non-small-cell lung cancer, but no data on reduction, more or less significant, in the disease-specific mortality rate has yet been demonstrated. This information will hopefully come from randomized clinical studies already initiated throughout the world.

To verify the feasibility of such an approach in the setting of a university hospital with a long-standing tradition in the management of respiratory diseases, in 2000 we initiated a feasibility study enrolling >500 high risk subjects as defined by chronological age and pack-years limits. The inadequacy of the unit of 'pack-years' to estimate the individual lung cancer risk is a matter of debate [14], and future initiatives to develop a more appropriate lung cancer risk model are encouraged but, at the time the study was initiated, this simple selection criterion, together with a lower age limit of 55 years, was considered a straightforward way to enrich our study population. Recently, a huge epidemiological study suggested that the incidence of lung cancer is higher among subjects with moderate to severe chronic obstructive lung disease and the use of pulmonary function tests has been suggested as a way to further select subject population to enrol in early detection programs [15], however this proposal needs to be prospectively validated.

Similar to another recently published paper [10], our study adopted a simplified study design to follow-up the non-calcified nodules detected at baseline low-dose sCT scan. For the

additional diagnostic work-up we decided to ignore nodules with a maximum diameter ≤ 5 mm as well as those that were calcified, based on the extremely low likelihood of malignancy [11]. There are some relevant differences in a comparative analysis between the Milan study and our data: at baseline examination the percentage of patients with nodules >5 mm judged to be worth further investigation was 4.4% in the Milan study and 21.9% in our study. The latter percentage is closer to that previously reported in the Mayo experience [16]. This huge difference may be partially related to the interpretation of the CT findings, which may be partially secondary to the radiologists' training in thoracic imaging, as indirectly confirmed by the observation in the Milan study that 54% of the newly detected tumors in the 2-year screening were visible at the baseline low-dose CT scan. In the perspective of huge randomized, multicenter studies, the use of a training set of radiological slides should be mandatory as a way of increasing the quality control of the study, and each participating center should include at least one radiologist with a well-recognized training in thoracic imaging. Despite these potential improvements, only the use of a computer-aided diagnosis system, as recently suggested [17, 18], will really help radiologists in the detection of pulmonary nodules.

As previously reported in similar studies, most of the lung cancers detected at the baseline were adenocarcinomas (four out of five), and in only one case was the diagnosis of squamous cell carcinoma made. Similarly, the overall findings over the 3 years of this feasibility study consistently confirm data about the higher incidence of adenocarcinomas and of stage I disease (72% in the current study). In addition, two cases of ground-glass opacity were detected that at the subsequent pathological examination both resulted in being atypical adenomatous hyperplasia. This lesion is currently considered by the WHO classification as a pre-neoplastic lesion preceding the development of an overt, solid adenocarcinomas [13], as documented in one of our cases.

Data from repeated follow-ups indicate a progressive decrease in the annual rate of newly diagnosed cancer, and this finding has been fully confirmed by our data. This issue raises another relevant question concerning the frequency of the follow-up. The choice of repeating the low-dose sCT scan annually was based on empirical observations, but no objective data are available that strongly support this decision, and a reasonable scientific question may be to determine the best frequency for follow-up. The drop-out rate was in the range of 3–5%, which indicates, at least in our cohort of subjects, a relatively good compliance over the 3-year period.

Several studies have already tried to quantify the cost-effectiveness of lung cancer early detection programs; unfortunately, the conflicting results of such studies are highly dependent on large numbers of assumptions, and are therefore only as good as those assumptions [19–21].

Even if a low-dose sCT scan in randomized clinical studies will significantly reduce the disease-specific mortality, the applicability of such an approach in general clinical practice could pose significant challenges to the health-care community in terms of technical and human resources.

In conclusion, until more data, cheaper technology and less invasive surgical procedures are available, together with convincing evidence from ongoing randomized trials supporting the routine use of sCT, a conservative attitude about accepting this new early lung cancer diagnostic tool should be encouraged. To date, the estimation of lung cancer mortality as it has been evaluated from sCT early detection trials already published indicates an outcome similar to prior chest radiography trials in high-risk subjects [22].

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