Lung cancer detection with digital chest tomosynthesis: first round results from the SOS observational study

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Objective: Baseline results of the Studio OSservazionale (SOS), observational study, a single-arm observational study of digital chest tomosynthesis for lung cancer detection in an at-risk population demonstrated a detection rate of lung cancer comparable to that of studies that used low dose CT scan (LDCT). We present the results of the first round.

Methods: Totally 1,703 out of 1,843 (92%) subjects who had a baseline digital chest tomosynthesis underwent a first round reevaluation after 1 year.

Results: At first round chest digital tomosynthesis, 13 (0.7%) subjects had an indeterminate nodule larger than 5 mm and underwent low-dose CT scan for nodule confirmation. PET/CT study was obtained in 10 (0.5%) subjects and 2 subjects had a low-dose CT follow up. Surgery, either video-assisted thoracoscopic or open surgery for indeterminate pulmonary nodules was performed in 10 (0.2%) subjects. A lung cancer was diagnosed and resected in five patients. The lung cancer detection rate at first round was 0.3% (5/1,703).

Conclusions: The detection rate of lung cancer at first round for tomosynthesis is comparable to rates reported for CT. In addition, results of first round digital chest tomosynthesis confirm chest tomosynthesis as a possible first-line lung cancer-screening tool.

Keywords: Lung cancer; lung cancer screening; digital chest tomosynthesis; early stage lung cancer

Introduction

Lung cancer is the leading cause of cancer related deaths in most of western and developing countries. Most lung cancers are detected when they are in an advanced stage. Recently, the National Lung Screening Trial (NLST) showed a screening benefit with low dose CT scan (LDCT) in people with a history of heavy smoking, at least for 30 pack years, who are age 55 to 74, current smokers or who have quit smoking within the past 15 years (1). The American Cancer Society, the American Association of Thoracic Surgeons, and the American Society of Clinical Oncology (ASCO) now recommend LDCT screening with a grade of recommendation 2B (2-4). However,

according to ASCO, the optimum screening schedule is to be determined (2). NLST demonstrated a reduction in lung cancer mortality of 20% in the LDCT arm compared to the Chest X-ray arm. Screening for lung cancer with LDCT has the potential to detect indolent tumors, resulting in overdiagnosis. The number of cases of overdiagnosis found among the 320 participants who would need to be screened in the NLST to prevent 1 death from lung cancer was 1.38. Whereas the NLST demonstrated a relative mortality reduction with LDCT, the limitations of the screening process, including the magnitude of overdiagnosis, should be considered when guidelines for mass screening programs are constructed (5). However, radiation exposure and cost of LDCT are still a problem. In a previous paper (6), we

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have shown that chest digital tomosynthesis (DT), may offer an alternative to CT-screening with a detection rate of lung nodules comparable to that reported with LDCT and a lung cancer detection rate of 0.98%, low effective radiation dose to patients (approximately 0.13 mSv) (7) and a cost of approximately 1/6 of that of CT (8). DT uses a conventional radiograph tube, a flat-panel detector, a computer-controlled tube mover, and special reconstruction algorithms to produce section images. Compared with conventional chest radiography, chest tomosynthesis improved sensitivity in the detection of CT-proven lung nodules. DT is able to detect most lung nodules larger than 5 mm, in particular 91% of nodules, whose sizes were between 4 and 6 mm, and 100% of nodules larger than 6 mm, detected in a CT scan. In addition, the effective radiation dosage to patients from chest examination with DT is low (approximately 0.13 mSv compared with 0.1 mSv for a postero-anterior and lateral chest radiograph). Although it lacks the depth resolution of CT, tomosynthesis provides some of the benefits of CT at lower costs and radiation dosages (9). We report the results of the first round results from the Studio OSservazionale (SOS), observational study.

Patients and methods

The study design is reported elsewhere (6), briefly a sample size of 2,000 subjects was planned. Current or former smoker with a smoking history of at least 20 pack years; age 45-75 years; no previous history of cancer in the 5 years before the start of the study; and no chest CT scan study in the 12 months up to enrolment. The mean age was 61 years (95% CI: 48-73); on average, they smoked 580 cigarettes yearly during their life (95% CI: 420-1,400); 29% of the subjects were smokers at the time of accrual. For former smokers, the maximum time since quitting smoking was 10 years. All participants were requested to sign an informed consent form, according to the requirements of the local Internal Review Boards and Health Authorities. Under the study protocol, a chest DT (Volume RAD, GE Healthcare, Chalfont St Giles, England) exam was performed at baseline in all subjects and another 1-year later in those with a negative baseline scan. The images were reconstructed in 3 mm plane spacing in the coronal plane. Image reconstruction was done using the matrix inversion tomosynthesis algorithm (simultaneous algebraic reconstruction technique) and a sliding average of seven adjacent planes was selected to reduce noise and low-contrast tomosynthesis artifacts. The mAs in X-ray

were set with an automated control of the exposure to be ten times lower than the ones used for the chest radiograph. A scout image (chest radiograph) was obtained to check patient position; if satisfactory, the system then calculated the appropriate low-dose exposure (mAs) for the tomosynthesis scan. The images fully covered the field from the anterior skin to the back of the chest. As already reported (6), two radiologists independently viewed the tomosynthesis images. One had more than 20 years of experience with chest imaging and 2 years of clinical experience with DT. The other radiologist has 5 years of experience with chest imaging and 1 year of clinical experience with DT. Each nodule was marked on only one image per imaging technique and in the most prominent location. Both observers were instructed to mark the lung nodules on the tomosynthesis images. The observers were allowed to change window width and window level and image contrast and use the pan and zoom functions. All readings were performed on a picture archiving and communications system integrated workstation. The largest diameter in the transverse plane was measured. Subjects with a nodule >5 mm or with multiple nodules followed the same flow chart reported in the previous paper (6). If nodule <5 mm was detected by the DT a 1 year follow-up DT was warranted. An interdisciplinary team including thoracic surgeons, radiologists, and pneumologists reviewed all uncertain cases. All subjects were also followed for any interim diagnosed cancer. Mc Nemar's test was applied to assess improved observer performance in correctly diagnosed pulmonary nodules. The weighted k statistic was calculated to assess interobserver agreement. Significant differences were defined as P value less than 0.05. Statistical analysis was carried out using Mathematica 8.0 (Wolfram Research).

Results

Totally 1,703 candidates underwent first round DT (92% of baseline), the drop out was around 0.4% (68 subjects, most from geographical areas distant from our Center). The mean age was 60 years (95% CI: 49-73). Overall, subjects who had a normal finding at the baseline tomosynthesis examination and those who did not underwent a LDCT follow up underwent a first round DT. Lung nodules >5 mm were detected in 13 (0.7%). The mean diameter of the nodules detected at first round DT were 0.8 mm; the mean diameter was smaller than in the baseline DT (1.7 mm). There were no interobserver differences regarding the sensitivity to detect nodules (P>0.13; Mc Nemar's test). Only one sub-
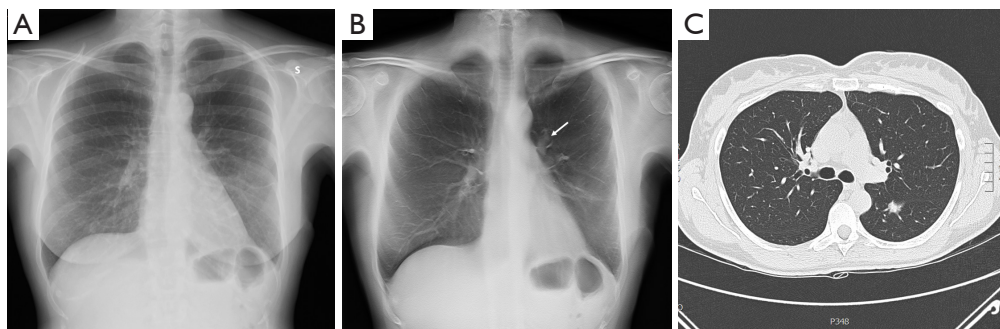
Figure 1 Digital chest tomosynthesis image showing a solid pulmonary nodule in a 57-year-old woman. (A) The pulmonary nodule is not visible on the postero-anterior chest radiograph; (B) digital chest tomosynthesis showing a left nodule (white arrow), confirmed in the CT scan; (C) the pathological examination, after the VATS lobectomy, showed the presence of an adenocarcinoma.
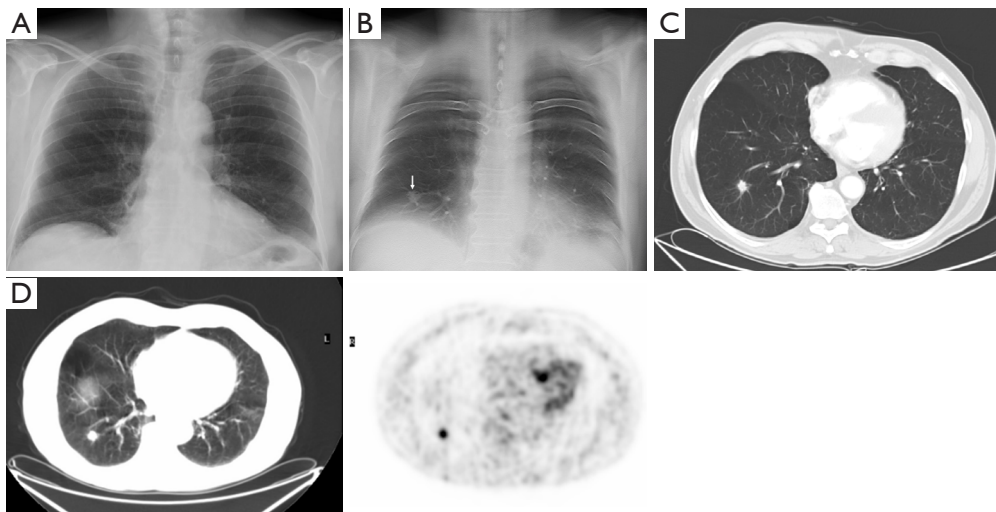

Figure 2 Digital chest tomosynthesis image showing a solid pulmonary nodule in a 63-year-old man. (A) The pulmonary nodule is not visible on the postero-anterior chest radiograph; (B) digital chest tomosynthesis showing a right basal nodule (white arrow), confirmed by CT scan (C) and PET (D). After the VATS lobectomy, the pathological examination showed the presence of a squamous cell carcinoma.

solid type nodules was detected and was followed with yearly DT. In the baseline round, 14.8% had abnormal findings at DT; the number of nodules found in each patient varied from 1 to 12. In the first round DT, the abnormal findings were 0.7% with number of nodules varied from 1 to 3. None of these 13 subjects had any nodules at baseline DT. At CT scan, one case resulted as false positive (pleural plaque). Twelve subjects underwent further evaluation and a PET/CT study was obtained in 10 subjects (0.6%) while 2 subjects had a follow up schedule (*Figure 1*). PET scan was positive in all subjects (*Figure 2*). Surgery, either minimally invasive or thoracotomy for non-diagnosed pulmonary nodules was performed in these 10 subjects. Histological examination of the removed specimen revealed 1 tuberculous

nodule, 2 organizing pneumonia, 1 intrapulmonary lymph node increased in size at follow-up CT and 1 lung metastasis from an adenocarcinoma of biliary tree operated more than 10 years before. A lung cancer was diagnosed and resected by VATS lobectomy in 5 subjects (*Table 1*). There was not any interim diagnosed cancer. The lung cancer detection rate at first round was 0.29% (5/1,703). At the first screen, the prevalence of lung cancer in the SOS study subjects was 23/1,919 (1.20%).

Discussion

Following the release of the NLST results (1), LDCT has been strongly recommended for the target group of heavy

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Table 1 Tumor stage and histology in subjects with lung cancer diagnosed by tomosynthesis at baseline and first round

Pathological characteristics	No. of subjects	
	Baseline	First round
Tumor stage		
IA	6	4
IB	2	
IIA	2	1
IIB	1	
IIIA	1	
IIIB	1	
IV	5	
Histology		
Adenocarcinoma	10	1
Squamous cell carcinoma	7	4
Carcinoid	1	

smokers (30 pack-years; 55 to 74 years of age) by a few medical and surgical associations (2-4). However, according to ASCO the optimum screening schedule is to be determined. As previously reported the adsorbed radiation doses and costs associated with LDCT screening encourage the search for other strategies for the early detection of lung cancer or to select among individuals at high risk those who should be referred for LDCT. DT, a computerized evolution of the traditional tomography, or stratigraphy developed by the Italian radiologist Alessandro Vallebona, demonstrated in our previous observational study to be able to detect lung nodules and lung cancer in a risk population in a percentage comparable to the rates reported for LDCT at baseline (0.9%) (6). In the first round, the lung cancer detection rate (0.29%) was lower than other screening trial may be due to the limited number of participants. In our experience, DT allowed to select a subgroup (from 7% at baseline to 0.7% at first round) of patient with lung nodules to undergo CT scan either low dose or contrast enhanced depending from the size of the nodule. DT has been shown to be superior to chest radiography in the detection of pulmonary nodules (7,8). DT was also compared with CT in its ability to detect artificial pulmonary nodules 5 and 8 mm in diameter and Ground Glass Opacities (GGO) in a phantom (10). The detectability indices for tomosynthesis and CT were similar. Although, according to Zhao et al. (11), the GGO 5-8 mm with a density of –800 HU has a detection rate higher with LDCT than with DT. This is, however, a minor issue because

GGO <10 mm in diameter have a very long grow rate (12). According to Nakata et al. (13), GGO <10 mm in diameter were in most cases atypical adenomatoid hyperplasia. It has been reported that DT is significantly better than chest radiography at visualizing small nodules in the peripheral lung. In the paper of Izumo et al. (14), DT was conducted in advance and used for mapping the location of the GGO lesion in the coronal plane before bronchoscopy. Real time DT cannot be used for guided bronchoscopy because of the time necessary for image reconstruction. For the improvement of the diagnostic accuracy of DT for GGO, it is useful to develop real-time DT. The reduction of lung cancer specific mortality in a prospective randomized clinical trial was necessary to insure that lung cancer deaths were being prevented by screening (15). In the first round, there was a high rate of surgery for benign lesion. All lesion were PET positive and not existent in the baseline round DT. The slow growing lung cancers detected by screening are almost exclusively non-solid or partial solid nodules that typically correspond pathologically with in situ non-invasive and microinvasive adenocarcinoma with broncho-alveolar features. Detection of new nodules during subsequent annual repeat screens after a baseline screening study is common, in confirmation of the fact that nodules typically grow in the interim between annual screens. Application of well-designed and validated diagnostic algorithms can aid in prevention of overaggressive diagnostic management and overtreatment. Overtesting and overtreatment might also be prevented by modification of the definition of what represents a positive screening result. A comparable increase in size criterion for a cut-point for nodules has been discussed, but is unsupported by published data (16). A further step to ameliorate the DT detection rate of lung nodules and to reduce false positive result will be the Computed Aided Detection (CAD) of lung nodules (15). CAD systems improve the performance of radiologists in the detection process of pulmonary nodules. However, to be used routinely in the radiology department these systems must meet the following requirements: improve the performance of radiologists (high sensitivity in the diagnosis, low number of false positives), have high processing speed, present high level of automation, low cost, and the ability to detect different types and shapes of nodules. Further researches are needed to improve existing systems and propose new solutions. Future CAD systems should improve the level of automation, through integration with picture archiving and communication systems and the electronic record of the patient, decrease the number of

false positives, measure the evolution of tumors, evaluate the evolution of the oncological treatment, and its possible prognosis (17). Accurate lung segmentation is important for improving the performance of CAD in chest DT. Wang *et al.* (16) developed an automated lung segmentation method with good performance that could be useful for the development of CAD schemes.

SOS trial, being an observational study, has no comparison arm. The specificity of DT was very high since 2% were false positive at baseline and only one lesion (0.06%) detected by DT was not confirmed at CT scan in first round. DT examinations led to the discovery other pathological finding in 17/1,919 (0.69%) of subjects: extra-pulmonary tumor, interstitial lung disease, bullous emphysema, pleural effusion, pleural lesion, and mediastinal enlargement due to various reasons (e.g., thoracic aorta aneurism, non-Hodgkin lymphoma). DT could keep a screening program more cost-effective avoiding futile LDCT along with its cost and radiation burden.

Conclusions

The first round results on the use of chest DT in the early detection of lung cancer are as good as for the baseline; the detection rate is comparable to the rates reported for LDCT and is attained at a far lower cost and radiation dose. The first round tomosynthesis screen has provided further data about its effectiveness in the follow-up of high-risk subjects. Large scale randomized controlled trial will be need to confirm DT benefits and identify where it is best used in the clinical setting, and how to further improve the sensitivity and specificity of chest DT. It can be easily understood that, if present data will be confirmed by other studies and clinical trials, chest DT could become the first-line lung cancer screening tool among patients at high-risk of lung cancer (who should undergo a LDCT scan if positive to DT).

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