Selected Summary (I)

Screening for Lung Cancer Coming of Age !

PASTORINO U, BELLOMI M, LANDONI C, (DE FIORI E, ARNALDIP, PICCHIO M. PELOSI G, BOYLE P, FAZIO F) EXPAND EARLY LUNG CANCER DETECTION WITH SPIRAL CT AND POSITRON EMISSION TOMOGRAPHY: 2-YEAR RESULTS. LANCET; 2003: 362: 593-97.

SUMMARY

The authors carried out a prospective non-randomized study for screening of lung cancer. The eligibility criteria included: current or former smokers, age 50 years or older with a minimum of 20 pack years of smoking history.

The screening protocol consisted of low dose spiral CT (single slice scanner) scan of thorax annually. The scan was carried out at 10 mm collimation with 5 mm reconstruction (140 kilo Volt peak, 40 mA, pitch 2). The effective radiation dose was equivalent to 0.7 mSv (maximum annual radiation recommended for diagnostic purposes is 1.0 mSv). The scans were reported by two radiologists independently. In the event of disagreement, a third radiologist was consulted. The site, dimensions and radiological features of each nodule were recorded on baseline and repeat CT.

Nodules with a maximal diameter of 5 mms (measured on lung window) and calcified nodules were taken as non-suspicious and schedules for a repeat low dose CT one year later. For suspicious nodules (nodules more than 5 mm in size with attenuation value more than 0 HU), high resolution spiral CT (1 mm collimation, 140 kVp, 220 mA, pitch 1) and 3 dimensional analysis were done within one month (with contrast enhancement for lesions with attenuation value of more than 0 HU). Enhancement of 30 HU was taken as a threshold for positive diagnosis. PET scanning was carried out for non-calcified nodules 7 mm or larger in size. Lung nodules with standardized uptake values of 2.0 or greater were deemed malignant. Patients showing positive enhancement on CECT or positive PET scan underwent biopsy. Patients with noncalcified nodules larger than 20 mm routinely underwent biopsy unless unequivocally benign on high resolution CT. Patients with non calcified nodules larger than 5 mms those who were not that were not candidates for biopsy underwent growth assessment by CT scan within 6 months of baseline study.

A total of 1035 patients were enrolled (median age 58 years, range 50 to 84) and 71% were men. Average tobacco consumption was 26 cigarettes daily for 36 years with median pack year of 40. Of the subjects, 14% had stopped smoking before accrual. In the baseline CT, 19% (199 patients) had nodules (single 145, two 32, 3 or more in 22). Out of a total of 284 nodules, 238 were 5 mm or less in size and 46 were more than 5 mm. In addition, 15 non-nodular lesions were also detected. Thin section CT was carried out in 61 (46+15, 5.9% of study population) of which 29 had CECT scan. Lung cancer was detected in 11 patients (1.1%). In addition, one case of carcinoid and one case of B-cell lymphoma were also diagnosed.

In the second year, 996 patients underwent low dose spiral CT and new or additional nodules were detected in 99 patients (10%). Total number of new or additional was 127. Twenty nodules were larger than 5 mm and 14 non nodular lesions were present. Thin section CT was done in 34 patients and CECT was done in 7 patients. Eleven cases of lung cancer (1.1%) were detected. Six of these 11 lesions had been identified on the baseline low dose CT. The lesions had grown from median size of 5.5 mm to 11.6 mm in 1 year. At baseline the lesions were either too small or identified as inflammatory or scar like lesions.

PET scanning was carried out in 29 individuals in first year. It was positive in 11 and was positive in 8 of 9 participants diagnosed with lung cancer. PET contributed to a positive diagnosis in 6 of 14 patients considered indeterminate on high

resolution CT. Three patients had false positive PET scan and these had the biopsy diagnosis of bronchiectasis, pulmonary sclerosis and inflammatory pseudotumor. At year 2, PET scan was done in 13 individuals and was positive in 11. Ten of the 11 lung cancers were positive on PET scan and one false positive PET scan was seen in a patient with inflammatory pseudotumor.

Of the 11 patients diagnosed on baseline, only six patients had stage I disease while 1 patient had stage IV disease (adrenal gland metastases). Ten of the 11 patients had adenocarcinomas. Ten patients underwent complete surgery. In year 2, all detected lung cancers underwent complete resection. Histology was adenocarcinoma in 7, squamous cell carcinoma in 3, and large cell neuroendocrine in one. Lateral muscle sparing limited thoracotomy and radical lobectomy with lymphadenectomy was the standard procedure.

No interval lung cancers were detected. At last follow up, one patient with lung cancer and stage IV disease had died, two were alive with distant disease and others are alive with out disease. Seven of the study subject died from causes other than lung cancer (two had malignancy: kidney & stomach, three had cardiac disease, one had cirrhosis of liver and one died of road traffic accident). A total of 173 hospital admissions were recorded including 17 for malignant disease (breast cancer 5, prostate cancer 3, bladder tumor 2, etc.).

Based on these results, the authors conclude that their protocol of low dose spiral CT followed by high resolution CT with contrast enhancement and selective PET scan is successful in early detection of lung cancer while minimizing over-investigations and over-diagnosis. Majority of these cancers were early and 95% could undergo curative resection.

They also suggest that the policy of observing nodules up to 5 mms and rescanning after 1 year does not lead to significant tumor progression. The patients who had progression of small lesions observed at baseline were still in stage I at second evaluation. They highlight that interval cancers were not observed in their study.

Overall, the follow up is short and the study is only a pilot study. This study can form a basis for a large randomized trial to evaluate the survival advantage for the screened population with this protocol. They point out that large trials may be required to demonstrate a survival advantage as competing causes of death would also operate in the study because heavy smokers have a high risk of many other disorders.

COMMENT

There is no doubt or question about the fact that effective screening strategies for lung cancer are badly needed. Lung cancer is one of the leading cancers worldwide in terms of incidence and a leading killer due to high case fatality ratio. Clinically apparent lung cancer often presents with advanced disease (nearly 50% have distant metastases)[1]. Radical surgery for early stage lung cancer leads to much better survival. For tumors less than 2 cms in diameter, 5 year survival is approximately 80%[2]. This mandates us to pick up more lung cancers in an early stage.

The whole issue has been hanging fire due to the failure of previous studies using sputum cytology and chest x-rays to demonstrate any benefit of screening[3-7]. However, interest has been reactivated with advances in CT scanning technology. Modern spiral CT scanners can do fast scans of the whole thorax with low doses of radiation, making them suitable for screening applications.

One of the first studies using low dose spiral CT has been carried out in Japan (Anti Lung Cancer Association)[8]. In this study, 1669 patients were evaluated and 9993 CT scans were carried out from 1993 to 1998. Twenty four lung cancers were detected on CT scanning that were missed by chest x-ray. Twenty two of these were stage I (T1N0M0).

The ELCAP study (Early Lung Cancer Action Project) screened 1000 individuals with moderate to high risk by performing a baseline chest x-ray and CT followed by annual CT scan. Twenty seven cancers were detected among 233 nodules identified on CT scan and 85% of these were early[9]. There are two large scale lung cancer screening studies ongoing in the USA at present.

The current study from Milan, Italy also shows that low dose spiral CT is effective at detecting early lung cancers in a high risk population. Only one out of the 22 cases detected in the study had distant metastases. One interesting fact is the high

percentage of adenocarcinomas in the diagnosed cancers. This is in contrast to the conventional distribution. We need to wait for the later year's data to see if more squamous carcinomas are diagnosed later on. Is this screening protocol missing out on squamous carcinomas? There have been no interval cancers in the initial two years but longer observation periods are required.

There are however many issues that need to be settled before large scale application of lung cancer screening is possible. One of the issues is the large number of nodules detected on spiral CT vis a vis the number of malignancies. The criteria for suspecting malignancy need to be defined properly to minimize the number of patients who undergo the mental agony of suspected lung cancer as well as reduce the number of unnecessary invasive investigations while at the same time avoiding a delay in diagnosis. Interval rescanning is a possible approach to look for growth in borderline lesions. PET scanning has shown good results in the current study but there were 3 false positive results on PET scanning. In addition, the availability of PET scanning is very limited while spiral CT scanners are now becoming widely available.

One thing should be clear: CT scanning technology has reached a stage where more advancement would not lead to better detection rates for peripheral lesions. In fact, nodules smaller than 5 mms detected on CT scanning were only kept under observation in the current study. However, newer multislice CT scans can be used for virtual endoscopy and may improve the detection of central lesions (which may have more squamous cancers). In addition, they can reduce scan times and radiation doses. What is also needed is a more accurate way of diagnosing malignancy among the nodules identified on CT scans and developing a clear and systematic algorithm for handling these cases. The early lung cancer action project has come out with the observation that "subsolid or part solid" nodules (that do not completely obscure the underlying lung parenchyma) are more likely to be malignant than solid nodules[10]. Further, majority of malignancies in the part solid nodules was bronchoalveolar carcinoma or adenocarcinoma with bronchoalveolar features. Assessment of growth on high resolution CT is a reasonable criterion for suspecting malignancy, to be confirmed by FNAC.

A major issue in lung cancer screening is going to be the cost issue. Compared to other screening approaches such as Pap smear for cancer cervix, fecal occult blood testing for cancer of large bowel and mammography for breast cancer, the cost of lung cancer screening with spiral CT is going to be much higher. In addition, the follow up investigations required for suspicious lesions are also invasive/costly. Who will foot the cost of such investigations? This question is more important because the major risk factor for lung cancer is smoking, a form of addiction for which the person has to take a fair share of the blame. Would the tobacco companies face another round of litigation if screening for lung cancer among smokers / former smokers becomes an accepted approach.

We have to wait for more mature data to show a survival advantage for lung cancer screening before it becomes acceptable outside trial setting. Even if it becomes accepted, large scale screening for lung cancer does not seem very feasible in India. The reason for this is not a lack of need. In fact, lung cancer is a major cancer among the urban population. However, screening for cancer of cervix and breast have not been very widely used in India in spite of the fact they have been proved effective for a long time and availability is not a problem at least in the urban areas. A government supported program on cancer screening does not exist till now and financial issues make it unlikely in the near future. In such as scenario, we can only continue to give the advice to high risk individuals to undergo screening on their own.

Other approaches to lung cancer screening under evaluation (molecular markers of cancer in sputum and bronchoscopic evaluation for transformed mucosa) are still "not here yet". What would be their place in the early diagnosis approaches remains to be seen. It is possible that combination of modalities may be used. Laser induced fluorescence has been used to identify malignant and premalignant lesions on bronchoscopy[11]. Such lesions are not likely to be picked up on CT scanning which is more effective for peripheral lesions. An important question is going to be the choice of therapeutic approach for bronchoscopically diagnosed central lesions (both malignant and premalignant).

To have the last word, we would still add that detecting lung cancer early by these approaches is still too late. This is amply shown by the fact that one patient had adrenal gland metastases at diagnosis and distant metastases developed in two more patients despite the short follow up. More patients are likely to have recurrent as well as second primary tumors. The ultimate approach should be primary prevention i.e. no tobacco. That is the only way that we can prevent one third of all the cancers in the world.

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Arun Goel[@], Malay Nandy[#], Dinesh Singh[$]
The Departments of Surgical Oncology[@], Medical Oncology[#], and Radiation Oncology[$], Dharamshila Cancer Hospital & Research Centre, Vasundhara Enclave, Delhi-96
Correspondence to Arun Goel, E-mail: arungoel@bol.net.in

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