Early Detection of lung cancer

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INTRODUCTION

- Lung cancer - most common cause of cancer death worldwide
- Fifty per cent of newly diagnosed lung cancer patients are former smokers
- Lung cancer - major health issue for decades to come
- The overall 5-year survival of lung cancer is only 10% in Europe and 15% in the United States

INTRODUCTION

- Progress in curative treatments during the last 20 years has been modest
- Late diagnosis of extensive disease is the main reason of failure
- Screening -effective in reducing the incidence and mortality of cancer of the cervix, breast and colon
- Similar results not reported in lung cancer

INTRODUCTION

- Screening for lung cancer has unique challenges compared with other organs
- Lung cancer consists of different cell types with different molecular profiles and growth characteristics
- Pre-invasive cancer in the entire bronchial epithelium – difficult to identify
- Tissue sampling for pathological or cytological diagnosis – difficult to obtain
- Different paradigm compared with cervical or breast cancer screening is needed

INTRODUCTION

- Modalities used for early diagnosis
  - Chest X-ray
  - CT scan
  - Newer bronchoscopic methods
  - Molecular markers

Screening has been the essence of early detection

Definition

Systematic testing of individuals who are asymptomatic with respect to some target disease.

Purpose – to prevent, interrupt, or delay the development of

advanced disease

Hillman et al. JACR 2004;1(11):861-864

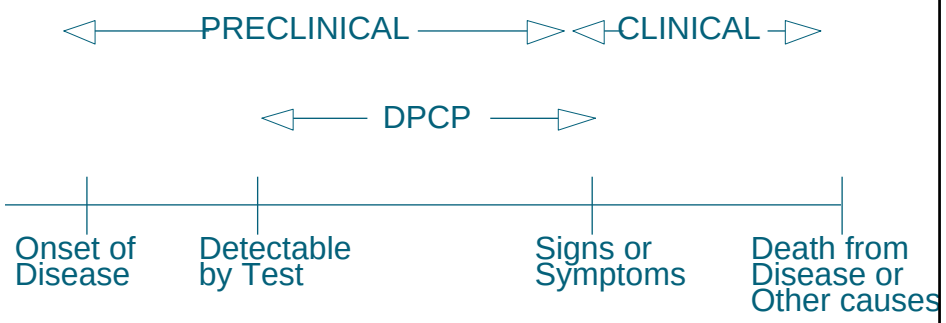
Screening vs Diagnosis

Non-patients	Patients
Asymptomatic	Symptomatic
Test non-diagnostic	Test diagnostic
Low prevalence	High prevalence

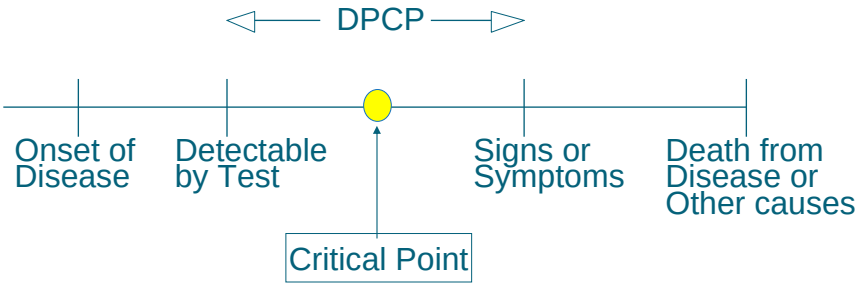
Principles of screening

- Screening should detect a cancer in its preclinical stage
- An effective treatment should be available in the preclinical stage
- Early intervention in the preclinical stage should change the course of the disease and decrease mortality
- Accessibility, cost and morbidity associated with a screening test should be reasonable

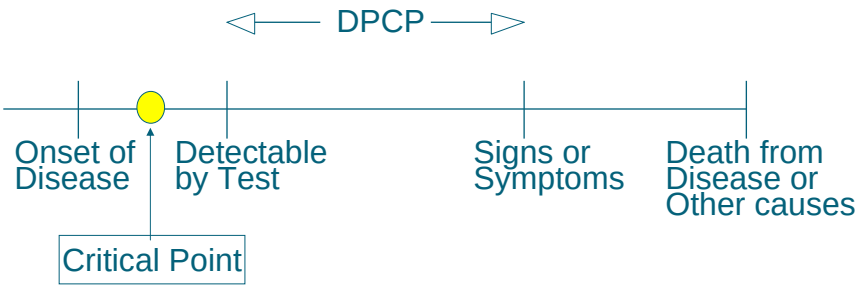
Timeline of disease



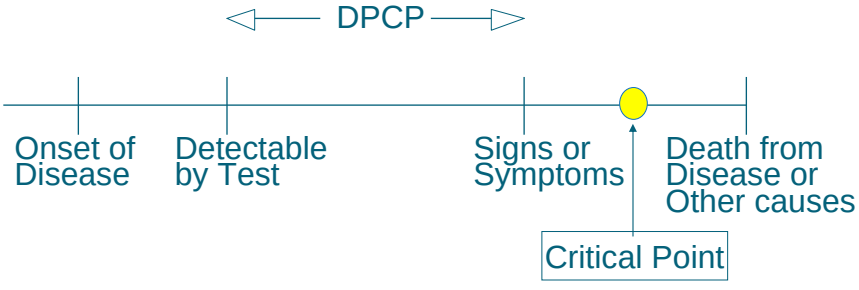
Screening Effective



Screening Ineffective



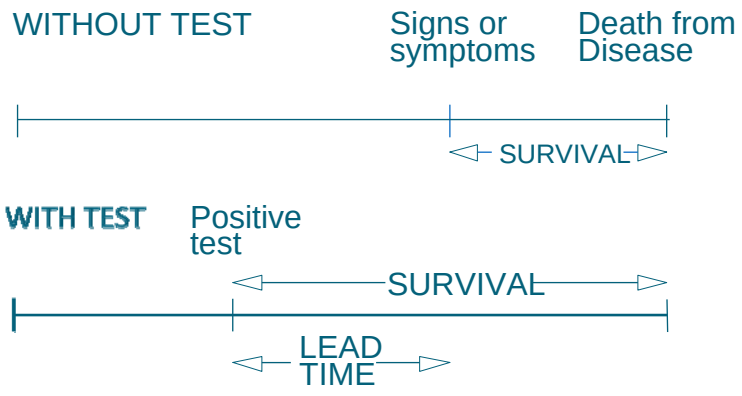
Screening Unnecessary



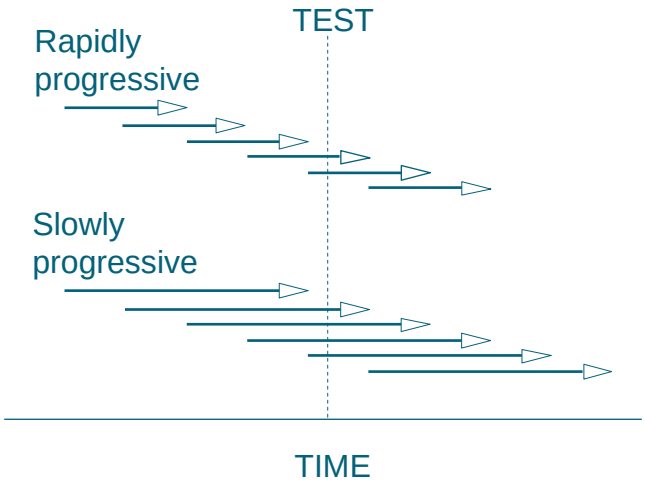
Biases of Early Detection

- Lead time bias
- Length bias
- Over diagnosis bias

Lead Time Bias



Length Bias



RADIOLOGIC AND CYTOLOGIC SCREENING

Results and criticisms

- JHLP and MSKLP studied the beneficial effects of sputum cytology screening and demonstrated no additional benefit from the addition of sputum cytology to an annual CXR screen
- Furthermore, screening in the JHLP failed to identify a substantial number of developing lung cancers
- Early detection efforts using CXR may not be successful, since certain tumors could be biologically aggressive and have the potential for rapid growth and metastasis

Results and criticisms

- In the MLP and Czechoslovak trials no favorable effect on lung cancer stage distribution was seen
- Early stage cases was higher with screening (240 vs 212), the number of advanced cases were similar (303 vs 304)
- The anticipated ‘stage shift’ was not observed, and the additional cases of cancer detected seem to be not clinically relevant (i.e. overdiagnosis bias)

Results and criticisms

- Data against overdiagnosis bias has been documented in autopsy studies (*Henschke et al.Lung Cancer 2003*)
- MLP has also been criticized for poor compliance with the scheduled testing (compliance of 75% in the intervention group) and absence of a completely unscreened arm
- Also, the study was designed to detect a 50% reduction in lung cancer mortality and had an inadequate statistical power to identify a more modest reduction

Results and criticisms

- Follow-up time in the trial to show a screening benefit was believed to be brief
- An extended follow up analysis was done but with this also no reduction in lung cancer mortality was observed
- Rate of detection improved but no mortality benefit

The American Cancer Society and the National Institutes of Health

do not recommend routine interval chest radiograph screening for lung cancer

Future prospects

- National Cancer Institute (NCI) has sponsored the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial
- A large, multicentre, randomized controlled cancer screening trial of more than 150000 men and women between the ages 55 and 75 years

Future prospects

- The primary endpoint of this trial is cancer-specific mortality and the trial is sized to detect a 10% lung cancer mortality reduction (power of 89%)
- For lung cancer, smokers will undergo a baseline CXR and then annually for 3 years and non-smokers will undergo CXR annually for 2 years
- The control group will receive routine medical care
- A 13 years follow up has been proposed

Improvisations

- Computed radiography (CR)
- Direct digital radiography (DDR)

Digital radiography(DR)

- Image processing
- Energy subtraction (ES)
- Temporal subtraction of serial radiographs (TS)
- Computer-aided detection (CAD)

Digital radiography(DR)

- DR with image processing is FDA-approved
- Has been shown to increase radiologists' ability to detect pulmonary nodules.
- DR uses an x-ray sensing system that allows a wider range of exposures to be recorded.
- There are several types of DR that fall into two categories:
  - CR
  - DDR

Digital radiography(DR)

- There are analog and digital image processing methods
- Can be applied across the entire image (global processing) or to specific portions of an image (adaptive processing)
- Specific portions of an image can be based on anatomic regions identified by the computer or on regions of specific optical density

Digital radiography(DR)

- *Sorenson et al* (1987) used FROC analysis with Bunch transform to ROC coordinates
- FROC mean true-positives in the retrocardiac region were 0.500 for conventional and 0.700 for the unsharp mask images, a 40% increase in true-positives
- For all nodules the conventional mean was 0.625 and for unsharp mask images it was 0.677

Image processing

- *Sherrier et al* (1998) compared processed images with unprocessed images
- Az improved from 0.68 on the unprocessed images to 0.78 with adaptive filtration, a 15% improvement
- *Hoffmann et al* (1993) using synthetic nodules demonstrated Az for underexposed retrocardiac and retrodiaphragmatic regions improved from 0.708 to 0.849 ($P < 0.01$), a 20% increase in sensitivity.
- For overexposed lung periphery Az improved from 0.958 to 1.0 ($P < 0.05$)

Image processing

- Image processing changes had no effect on the detection of 10 mm nodules but improved detection of 5 mm nodules

  Schaefer-Prokop 1996, Leppert AG 1995, Li F 1997
- They recommend processing with unsharp masking with midrange frequency suppression and low frequency enhancing filters
- Enhances the detection of smaller nodules, particularly when they occurred in regions of the image that had low contrast (ie, in lightly or heavily exposed regions)

Image processing

- Various trials studied the efficacy of DR in CT proven nodules

Heesewijk et al 1996, Muller et al 1996

Woodard et al 1998, Yang et al 1999, Awai et al2001

- When digital images with appropriate image processing are used – improved performance

- Benefit - greatest with the smallest nodules and for those

Energy Subtraction(ES)

- ES radiography (also called dual energy radiography in the literature) - research imaging technique -implemented in clinical systems over the past 7 years
- Energy subtraction - FDA-approved method for chest imaging - improve the detection of noncalcified nodules superimposed on bony structures
- *Ho et al* (1989) compared two methods for ES - Both ES methods were statistically significantly superior to the conventional SF image

Energy Subtraction(ES)

- Similar results were shown by *Ishigaki et al1988, Kelcz et al1994, Kido et al1995*
- ES imaging provides improved lung nodule detection
- Sensitivity improved for all nodules, particularly - that are obscured by ribs
- The detection of calcification in nodules is also improved
- Patients who had calcified nodules were less likely to be classified as having potentially malignant lesions

Computer aided detection(CAD)

- Effective method for increasing radiologists' detection of small lung nodules
- Computer searches the image for findings that could indicate the presence of a lung nodule
- *Krupinski et al* - placement of a solid circular boundary around a lung nodule enhanced its detection
- When no circle was provided the Az was 0.523; with a dashed circle it was 0.690 and with a solid circle it was 0.800

Temporal Subtraction(TS)

- Method for enhancing the detection of lung nodules on serial CXRs
- In this method two studies of the chest are taken at different times
- The older image is then subtracted from the newer image, resulting in increased conspicuity of any change that might have occurred over time

Combined modalities

- Evidence is presented that
  - DR CXR with appropriate image processing is superior to standard CXR for nodule detection
  - DR CXR with ES is superior to DR CXR without ES,
  - CXR and DR CXR with CAD is superior to CXR and DR CXR
- Preliminary data suggest that CAD might provide further potential improvements when added to DR CXR with ES

CT SCREENING OF LUNG CANCER

CT screening of Lung Cancer

- The ELCAP study reported a prevalence of CT detected lung cancer of 2.7%
- Subsequent studies published from the USA, Germany and Japan reported lower prevalence rates of 1.1–1.7% in high risk populations
- Only Mayo Clinic Lung study reported a high prevalence of nodules which was flawed by the presence of high rates of endemic fungal granulomatous disease in that area

CT screening of Lung Cancer

- In a recent study by Mac Redmond et al (2004) it was demonstrated that the prevalence of lung cancer detected by LDCT in a population of asymptomatic high risk smokers at baseline screening was 0.46%
- Prevalence rate of tumors suitable for curative surgical therapy was 0.23%.
- Disappointingly low yield of lung cancer using LDCT in a high risk population

CT screening of Lung Cancer

- The overall prevalence of nodules (19.3%) was also lower than in other studies (23–51%)
- The intervention rate was significantly higher in this study
- A large number of benign nodules were surgically removed
- This compares with data from Europe and the US showing that 50% of nodules removed surgically in routine clinical practice are benign
- This degree of intervention for false positive nodules may be unacceptable in the context of a mass screening

Pitfalls in CT Screening

- Radiation exposure can cause induction of malignancy,
- Exposure of 100 individuals with an effective dose equivalent of 1 Sievert (Sv) could possibly cause five additional malignancies
- Assuming a linear risk with lower doses, one lowdose CT scan with an effective dose equivalent of 1 mSv would cause five malignancies in 100,000 screened individuals

Pitfalls in CT Screening

- Annual screening between the ages of 40–60 yrs would, therefore, cause 100 malignancies per 100,000 screened subjects
- Further detailed analyses are needed regarding morbidity and mortality data
- Assumptions that tumour size correlates with biological behaviour and that small lesions are equivalent to early-stage disease have not been confirmed for lung cancer

Pitfalls in CT Screening

- Cost of LDCT is quite high and cost effectiveness of the test needs consideration
- The additional cost generated by significant incidental disease is considerable in terms of both diagnostic and therapeutic intervention

Summary

- The role of low dose spiral CT scanning in screening for lung cancer remains contentious.
- Concerns remain regarding the high false positive and benign intervention rates which may result in unacceptable morbidity and patient anxiety
- Observed prevalence rates of early stage cancers – difficult to translate into real reductions in mortality
- Additional costs, with as yet unproven additional benefit - generated by the high rates of ancillary disease

Recommendations

- Recent data on LD-CT in screening of lung cancer is encouraging and needs evaluation under well designed clinical trials

  USPSTF
- Early studies of lung cancer screening with LDCT appear promising
- Individuals should only be screened with LDCT in the context of well-designed clinical trials

  ACCP

  2003

Role of CT- PET

- Value of PET - undetermined pulmonary nodules detected by spiral CT has been confirmed by several meta-analyses,
- Sensitivity of 96–97% and a specificity of 78–82%, with the accuracy reaching 92% with the CT/ PET fusion ma

Hellwig et al 2001,Gould et al JAMA 2001,Hickeson et al Eur J Nucl Med Mol Imaging

Role of CT- PET

- Addition of PET to conventional workup prevented unnecessary surgery in one out of five patients with suspected non-small-cell lung cancer

PLUS study Lancet 2002

- Selective use of PET in lung cancer screening is useful and may minimize the number of invasive procedures for benign lesion

Bastarrika et al AJRCCM 2005

- Using PET in a screening setting does amplify some of the limitations of PET since the lung cancers detected by screening more often are slow growing, well differentiated and small (higher frequency of false-negative)

Role of CT- PET

- Integrated PET–CT provided additional information in 20 of 49 patients (41 percent), as compared to each alone
- Better diagnostic accuracy
- Tumor staging was significantly more accurate with integrated PET–CT than with CT alone (P=0.001), PET alone (P<0.001), or visual correlation of PET and CT (P=0.013)
- Node staging was also significantly more accurate with integrated PET–CT than with PET alone (P=0.013).
- In metastasis staging, integrated PET–CT increased the diagnostic certainty in two of eight patients

Lardinois et al, N Engl J Med 2003

Role of CT- PET

- 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
- 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 (false positives)

Pastorino et al Lancet 2003

Role of CT- PET

- Complete resection was achieved in 21 (95%) lung cancers,
- 17 (77%) were pathological stage I (100% at year 2), and the mean tumor size was 18 mm.
- There were no interval lung cancers in the 2·5 years of follow up
- 19 individuals were diagnosed with another form of cancer (two deaths and 17 non-fatal admissions)

Pastorino et al Lancet 2003

Summary

- To what extent fusion PET/CT may improve the diagnostic accuracy in smaller solid lesions remains to be defined by future studies
- Early results obtained from retrospective and prospective studies appear promising

  Marom et al Radiology 2002, Vansteenkiste et al Lancet Oncol 2004

- No recommendations by any of authorities are available for its use in screening

Sputum analysis

- Sensitivity in screening studies is ~20–30% and thus too low to be clinically relevant.
- Cytological sputum examination demonstrated higher sensitivities for squamous cell carcinoma, centrally located lesions, lower lobe lesions and lesions that are >2 cm in size
- The Memorial Sloan-Kettering and the John Hopkins Lung Projects no benefit on lung cancer-specific mortality by the addition of sputum cytology to annual chest radiography in lung cancer screening

Improvisations

- A first sputum-based immunocytochemical trial used two monoclonal antibodies, as markers of early disease.
- Abnormal positive expression patterns - detected for these antibodies in archived sputum samples of lung cancer patients ~2 yrs before their lung cancer became clinically apparent
- Sensitivity of 91% and a specificity of 88%

Improvisations

- The role of hnRNP A2/B1 overexpression for detecting preclinical lung cancer has been described in two large studies
- In a population of 6,000 Chinese tin miners, heavy smokers and from the Lung Cancer Early Detection Working Group
- In order to further improve the sensitivity of hnRNP markers, the use of combined screening with spiral CT has been initiated

Improvisations

- Malignancy-associated changes (MACs) - nongenetic changes in normal cells induced by the presence of malignant cells in the vicinity
- In a retrospective analysis on sputum samples of patients included in the Mayo Clinic Early Lung Cancer Study, MACs could be detected in excess of 1 yr before any other clinical evidence of squamous cell carcinoma
- The technique has been improved, and recent data showed a sensitivity of 75% for detecting stage-0/I lung cancer, and of 85% for adenocarcinomas, with a specificity of 90%

Molecular markers

- Serum biomarker assays
- Sputum biomarker assays
- Exhaled breath biomarker assays

cDNA microarray analysis, comparative genomic hybridization, proteomics, tissue microarrays, RT-PCR, and assays of bioactivity

Molecular markers

- PCR assays on stored sputum samples of patients with pulmonary adenocarcinoma, containing mutations for either K-ras or p53, were screened for the presence of these oncogene mutations.
- In eight of 10 patients, the same mutation identified in the primary tumor was also detected in at least one sputum sample, sometimes >1 yr prior to the clinical diagnosis
- p16 gene methylation and microsatellite instability-nonsmall cell lung cancer, although with rather limited sensitivity

Molecular markers

- Identical microsatellite alterations have been found in lung cancers and corresponding sputum samples demonstrating minimal atypia
- p53 mutations and p16INK4a-promoter hypermethylation were detected in sputum samples of COPD pts. (in 10 of 25 investigated), with equivalent results in bronchoscopically obtained specimens
- In three of eight chronic smokers, possessing genetic alterations, a subsequent diagnosis of lung cancer could be made

Molecular markers

- Aberrant promoter methylation of multiple genes, including the retinoic acid receptor- gene has been demonstrated in nonsmall cell lung cancer
- In 21 patients (miners exposed to radon and smokers developing lung cancer), abnormal promoter methylation of p16INK4 and a DNA repair gene, 06MGMT, was detected in sputum collected 5–35 months prior to the diagnosis of their lung cancer,
- A constellation of methylation on 8 to 9, identified to be frequently hypermethylated in lung cancer - point for future research

Autofluoroscence bronchoscopy

- It utilizes differences in the biochemical, metabolic and structural composition of normal, preneoplastic and neoplastic tissues
- When the bronchial surface is illuminated by violet or blue light, normal tissues fluoresce strongly in the green
- As the bronchial epithelium changes from normal to dysplasia, and then to carcinoma *in situ (CIS) and invasive cancer,* there is a progressive decrease in the green autofluorescence but proportionately less decrease in red fluorescence intensity

Autofluoroscence bronchoscopy

- Increase in blood content results in a further decrease in the green autofluorescence in the lesion
- Preneoplastic and neoplastic lesions can appear to be brown, brownish red or red depending on the severity of the lesions, presence of endogenous porphyrins and the vascularity

Autofluoroscence bronchoscopy

- Two multicentre trials - sensitivity of detecting high-grade dysplasia, CIS or microinvasive cancer increases from 9–11% using WL examination alone to 56–66% using AFB

Lam et al Chest 1998 ,Ernst et al J. Bronchol. 2005

- Two prospective randomized trials also confirmed the improved sensitivity of AFB versus WL examination

Hirsch et al J. Natl. Cancer Inst. 2001 Häussinger et al Thorax 2005

Autofluoroscence bronchoscopy

- The sensitivity in detecting dysplasia and CIS increased from 18% to 73% [1]
- Sensitivity in detecting dysplasia and CIS increased from 58% by WL alone was 82% by WL + AFB [2]

Hirsch et al J. Natl. Cancer Inst. 2001 [1],Häussinger et al Thorax 2005[2]

Summary

- No large RCTs available but seem to be potentially useful for early detection of lung cancer
- Newer bronchoscopic technologies such as EUS or optical coherence tomography might prove in the near future to be of significant additional value for the screening of early stages of lung cancer

Take Home Messages

- No major medical professional organization currently recommends screening for lung cancer
- The U.S. Preventive Services Task Force (USPSTF) gave lung cancer screening a grade D recommendation in both 1985 and 1996
- Recent data with newer techniques seems to be encouraging and might change the outlook of screening programmes
- Identifying the at risk groups and people who would really benefit from these screening methods should be attempted upon

Take Home Messages

- Large well designed clinical trials are required to formulate an opinion about the role of screening in early diagnosis of lung cancer
- Till then CXR, LDCT, Bronchoscopy may be used under well designed trials for the early diagnosis of lung cancer