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Screening and diagnosis of NSCLC

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Introduction

Lung cancer is the biggest cancer killer in Europe. Non-small-cell lung cancer (NSCLC) accounts for the vast majority of cases. The annual number of newly diagnosed patients in Europe exceeds 200 000, accounting for ~20% of all cancer deaths, and on average 28% of male cancer deaths across the continent [1, 2]. In females, lung cancer accounts for 10% of deaths. Five-year survival is 9.6%, ranging from 5.9% in Denmark to 16.2% in Switzerland [3].

Despite these figures and the fact that screening is an accepted strategy in invasive cancers with similar incidence but lesser mortality and better survival than lung cancer, e.g. breast, colorectal and prostate cancer, screening in lung cancer is not routinely advocated. The introduction of low-dose spiral computed tomography (LD-SCT) has reopened the debate. The present status of lung cancer screening will be reviewed here.

For cancer registration and treatment reasons, a lung cancer diagnosis should be confirmed whenever possible. The various methods of obtaining a tissue diagnosis and their accuracy will be reviewed.

Screening

The primary aim of cancer screening is to decrease its mortality at a population level. This implies that the tumor is detected when a therapeutic intervention is likely to influence the clinical evolution, provided such an effective treatment is available. This interaction between screening and treatment is the source of biased expectations with regard of the true screening effect. The ratio of lung cancer deaths to population screened is the only reliable and unbiased estimator of the effect of screening. Survival after diagnosis is a biased estimator of the screening effect, as screening is associated with the diagnosis.

A screening tool should preferably not harm, neither itself, nor by the occurrence of false positives generating extra costs, anxiety and stress. In addition, screening should be cost-effective in a society perspective, and avoid burdening the already strained public health expenditures.

Up to now, two screening methods have been studied in randomized controlled trials: chest X-ray and sputum cytological examination (Table 1) [4–9].One non-randomized controlled trial and six randomized controlled trials, including a total of 245 610 persons, were reported and included in a recent meta-analysis [10]. Another is still ongoing [11]. In all studies, the control group received at least some type of screening at baseline and/or at the end of the study. Randomization is hence to be considered between more or less frequent screening. More frequent screening with chest radiography was associated with an 11% relative increase in mortality from lung cancer compared with less frequent screening [risk ratio (RR) 1.11; 95% confidence interval (CI) 1.00–1.23], suggesting that frequent chest radiography might even be harmful. A non-statistically significant trend towards reduced mortality from lung cancer was observed when screening with chest radiography and sputum cytological examination was compared with chest radiography alone (RR 0.88; 95% CI 0.74–1.03). The 5-year survival rate of patients diagnosed with lung cancer was better in the more often screened group, with a combined RR of death from lung cancer of 0.91 (95% CI 0.84–0.99; $P = 0.02$). Several of the studies included had potential methodological weaknesses and were powered to detect an unrealistic 50% decrease in lung cancer mortality. The study population consisted furthermore of male smokers only. With females becoming an increasing fraction of lung cancer patients with an independent prognostic importance, results of studies in males might not be necessarily extrapolated to the female population. Although survival is improved, the current evidence does not support screening for lung cancer with chest radiography or sputum cytological examination. However, recent narrative reviews have drawn conflicting conclusions [12–14]. Furthermore, newer screening methods have now been proposed, such as LD-SCT.

Low-dose spiral computed tomography scanning

The development of CT scanning technology reopens the lung cancer screening debate [15]. The introduction of spiral scanning techniques with helical reconstruction algorithm has further improved the spatial resolution over conventional CT scans. The latter were hampered by single slice techniques and breathing artifacts [16, 17]. Present day fourth-generation multislice (up to 64 detectors) spiral CT scan apparatus delivers a radiation dose approaching that of a chest radiograph and inferior to mammography (50 mAs). No intravenous contrast material is administered. Images covering the entire lung region can be acquired in a single breath-hold at end-inspiration (12 s), following hyperventilation, and are reconstructed at overlapping 3-mm intervals. Images are viewed at so-called lung and mediastinal windows [width 1600 Hounsfield units (HU), level −650 HU; width 325 HU, level 25 HU,

Table 1. Randomized trials evaluating screening in lung cancer

Study (study population) [Ref.]	Intervention and control	No. of participants	Number of cancers at prevalence screen		Number of cancers at incidence screen		Lung cancer mortality	
			Absolute	Per 1000 persons	Absolute	Per 1000 persons	Absolute	Per 1000 persons
London (males >40 years) [4]	Chest X-ray every 6 months for 3 years	29 723	31	1.0	101	NA	62	2.1
	Chest X-ray after 3 years	25 311	20	0.8	76	NA	59	2.4
	Total	55 034	51	0.9	177	NA	121	2.2
MSKC-LCSP (smoking males >45 years) [5]	Chest X-ray and sputum every 4 months; follow-up for 5–8 years	4968	30	6.0	114	3.7	74	2.7
	Yearly chest X-ray and sputum; follow-up for 5–8 years	5072	23	4.5	121	3.8	82	2.7
	Total	10 040	53	5.3	235	3.75	156	2.7
JHLP (smoking males >45 years) [6]	Chest X-ray and sputum every 4 months for 4.5 years	5226	39	7.5	194	NA	NA	3.4
	Yearly chest X-ray and sputum for 4.5 years	5161	40	7.8	202	NA	NA	3.8
	Total	10 386	79	7.6	396	NA	NA	2.7
MLP (smoking males >45 years) [7]	Chest X-ray and sputum every 4 months for 6 years	4618	NA	NA	206	5.5	122	3.2
	Advice: yearly chest X-ray and sputum	4593	NA	NA	160	4.3	115	3.0
	Total	10 933	91	8.3	366	NA	237	NA
Czech study (smoking males >40–64 years) [8, 9]	Chest X-ray and sputum every 6 months for 3 years	3172	NA	NA	39	NA	19	3.6
	Chest X-ray and sputum after 3 years	3174	NA	NA	27	NA	13	2.6
	Total	6364	18	2.8	66	NA	.32	NA

MSKC-LCSP, Memorial Sloan-Ketttering Cancer Center Lung Cancer Screening Project; JHLP, Johns Hopkins Lung Project; MLP, Mayo Lung Project; NA, not available.

respectively] [15]. Computer-aided diagnosis techniques record characteristics such as size, location, texture and pattern of calcification, and allow data analysis according to a preset algorithm, minimizing inter- and intra-observer variability.

The use of multislice spiral CT has lowered the detection threshold for pulmonary nodules to 1–3 mm, without an increase in radiation dose and with less respiration artifacts [16, 17]. Sensitivity for nodules >1 cm is estimated at 95% and for nodules <1 cm 91%, but this high sensitivity comes at the cost of a decreased specificity. A non-calcified pulmonary nodule (NPN) is identified if it does not show a benign pattern of calcification. These are observed in 10% to 50% of screened subjects from the risk population [15, 18–22]. Most NPN <8 mm are benign. The likelihood of malignancy increases with size, approximating 50% in one series of NPN >20 mm [19]. Lung cancers are diagnosed in between 0.9% and 2.7% of screened subjects. LD-SCT hence detects more lung cancers in an earlier 'asymptomatic' stage than do conventional chest X-rays: 0.48% versus 0.03% to 0.05% (Table 2).

Typically, ≥70% of the tumors are in stage IA, as compared with <10% in patients with symptoms. As stage is the strongest predictor of survival, the latter has been repeatedly shown to be improved in patients detected by screening.

Multiple reasons may explain why a large number of earlier stage tumors does not necessarily result in improved lung cancer mortality. Lead-time bias is caused by the diagnosis of

Table 2. Summary of the Japanese Anti-Lung Cancer Association experience (1975–2002) [23]

Screening tool/time period	No. cases studies	Histology (%)			Stage (%)		Mean diameter peripheral-type lung cancers (cm)	Cancer detection rate (%)	5-year overall survival (%)
		AD	SQ	SC	IA	III/IV			
Chest X-ray and sputum cytology 1975–1993	26 338	49	35	12	42	33	3.0	0.16	49
LD-SCT 1993–2002	15 342	63	30	3	78	14	1.5	0.41	84

AD, adeno; SQ, squamous; SC, small cell; LD-SCT, low-dose spiral computed tomography.

cancers detected by screening in an asymptomatic patient. The increased survival reflects the interval between diagnosis by screening and first symptoms. Length-time bias occurs when slow-growing tumors are detected, which have a longer survival. To avoid this bias, observation after screening should be sufficiently long. Overdiagnosis bias implies that the individual in whom cancer is detected was destined to die of a competing cause before the cancer would have resulted in symptoms and been clinically detected [24]. This does not mean that the cancer is not a true cancer, or that its histology is not similar to other types of invasive cancers. Overdiagnosis is inevitable for lung cancer screening, as the majority of the cancers develop in current or former heavy cigarette smokers. A heavy smoker loses 10 years of life expectancy on average because of diseases caused by smoking; one-fifth of these are lung cancers, but the other four-fifths are competing causes of death (largely cardiac, some respiratory), and these are the reasons for death in overdiagnosed cases.

Controlled studies of spiral CT scanning have not been reported. Japanese data suggest the superiority of LD-SCT over chest X-ray in detecting early and potentially curative lung cancer. A number of recently published series across three continents support a benefit of LD-SCT in detecting earlier stage NSCLC (Table 3).

Although different imaging and management approaches have been used, they achieve fairly consistent results. The challenge of the most efficient diagnostic work-up has also been highlighted in a recent paper on cost-effectiveness [25]. Non-invasive case validation was associated with a lower overall cost compared with more frequent invasive case validation. Another issue is the management of spurious and incidental findings (aortic aneurysm, emphysema, other cancers) [19].

The influence of LD-SCT on lung cancer mortality is currently being studied in several large screening trials in Europe and the USA [27]. In the Dutch–Belgian NELSON trial, randomization is being carried out in 24 000 at-risk men and women between active smoking cessation with or without annual LD-SCT for 4 years. No baseline screening is performed in the control arm. The National Lung Cancer Screening Trial (NLST) in the USA is randomizing 50 000 persons at-risk between annual conventional chest X-ray and annual LD-SCT for 3 years. In an Italian study proposal, randomization will be between between yearly and every second year screening with LD-SCT for 10 years, with or without PET scan. Similar Danish and French pilot studies are planned, randomizing between LD-SCT and chest X-ray or no screening, respectively. Most of these trials aim at a lung cancer mortality reduction of 50% in the screened population. The results of these trials will not be available for 5–10 years.

New developments in screening

Sputum immunocytology promises much greater sensitivity than conventional sputum cytology: experiments with the monoclonal antibody 703D4 have shown that overexpression of hnRNP A2/B1, an RNA-binding protein, is a powerful predictor of early subclinical cancer in high-risk groups [28].

An alternative approach is based on photometric measurements of >100 features such as shape and texture extracted from the nucleus of epithelial cells found in sputum. Using these features, the cells are automatically classified into different cell types, associated with different risk pattern for developing lung cancer. This method of automated quantitative cytometry (AQC) reduces costs, improves the intra- and inter-observer variability, and is currently in the process of being validated (Perceptronix Medical, Vancouver, Canada) [29].

Analysis of circulating DNA in plasma can provide a useful marker for early lung cancer detection. In a study assessing the sensitivity and specificity of a quantitative molecular assay of circulating DNA to identify patients with lung cancer and monitor their disease, the median concentration of circulating plasma DNA in patients was almost eight times the value detected in controls [30]. This suggests that plasma DNA elevation is a strong risk factor for lung cancer [31].

(Auto-)fluorescence bronchoscopy uses the property of (pre-)neoplastic mucosa to differentially reflect incoming

Table 3. Summary of pilot LD-SCT screening results for NSCLC

Institution/reference	No. of subjects	% patients with NPN	No. of CT-detected lung cancers	Mean/median primary cancer size (mm)	Frequency of detecting post-surgical stage I tumors (%)
Cornell (prevalence) [15]	1000	23	27	14/≤10	0.85
Cornell (incidence) [18]	1000	NA	7	12/8	0.71
Mayo Clinic (prevalence) [19]	1520	51	29	NA	NA
Mayo Clinic (incidence) [19]	1000	NA	21	NA	NA
National Cancer Center (prevalence) [20]	1611	11.5	14	20/20	0.79
National Cancer Center (incidence) [21]	770	NA	22	15/20	0.82
Milan (prevalence) [22]	1035	29	11	21/NA	0.55
Milan (incidence) [22]	996	NA	11	15/NA	1.00

LD-SCT, low-dose spiral computed tomography; NSCLC, non-small-cell lung cancer; NPN, non-calcified pulmonary nodule; CT, computed tomography; NA, not available.

monochromatic light, based on differences in mucosal thickness and intracellular molecules. Although most experts agree on its high sensitivity compared with classic white-light bronchoscopy, its low specificity and the invasiveness of the procedure precludes its role as a widespread screening tool. Its potential use is as a case-finder in individuals found to have abnormalities on sputum screen techniques [32].

Sputum immunocytology, AQC and plasma DNA measurements may have their optimal use in 'prescreening' individuals for LD-SCT. A preliminary study using AQC, CT scanning and autofluorescence bronchoscopy showed that AQC of sputum cells improved the detection rate of lung cancer [33]. Further research is ongoing.

Diagnosis

In most cancer registries, tissue diagnosis of lung cancer diagnosis is required and is documented in more than 80% to 90% of patients [34]. Histological proof is obtained for up to 77% of cases, and only cytology in 17%. NSCLC represents $\sim$80% of lung cancer cases, with squamous cell lung cancer still preceding adenocarcinoma in relative frequency in most European series [35]. The latter subtype is, however, increasing, mostly in women and non-smoking cases. In 1999, the WHO adopted a new classification of lung cancer [36].

Standard light microscopy with hematoxylin–eosin stains is sufficient for histological diagnosis in most cases of NSCLC. Periodic acid–Schiff and immunohistochemical stains are necessary in only a few histological types and for differentiating subtypes of adenocarcinoma and neuro-endocrine subtypes. Morphological separation of NSCLC and small-cell lung cancer (SCLC) can be difficult even for experienced pathologists. Disagreement among the latter over the distinction may occur in up to 5% to 7% of cases [27]. Morphological subclassification of NSCLC remains imprecise. Agreement on subtype classification of adenocarcinoma occurs in only 40% of samples. Histological heterogeneity, the presence of a mixture of histological types representing a manifestation of the derivation of lung cancer from a pluripotent stem cell, is an important reason. It is hence appropriate to use the term NSCLC in small tissue specimens when it is not possible to be certain about the subtype. This heterogeneity is responsible for the observed differences between pathological diagnosis in biopsy and resection specimens. Special considerations apply in the case of a presumed diagnosis of lung cancer, synchrone or metachrone to another solid cancer. In these cases, special stains and even molecular techniques will be necessary to rule out any relationship with the other tumor [37].

Guidelines regarding reliable diagnosis of lung cancer have recently been published [38, 39]. Whenever possible, a tissue diagnosis of cancer obtained from a suspected metastasis has the advantage of proving not only the malignant character of the tumor, but also its invasiveness and dissemination. Lung cancer presents with a various clinical picture and is disseminated at first diagnosis in >40% of cases [34]. Despite this, first diagnosis is obtained most often by sampling of intrathoracic structures or tissues. Only the techniques involved in the latter will be reviewed here.

Flexible bronchoscopy

Flexible bronchoscopy is an essential part in the diagnosis of a patient with presumed lung cancer, because it is diagnostic in >70% of cases [40]. The procedure can be performed in an outpatient setting and is safe when performed by experienced hands. A number of simple techniques are available to obtain the diagnosis of endoscopically visible lesions during the procedures: bronchial biopsy, brushing and sputum aspiration are mostly used. The top part of Table 4 shows a comparison of the average diagnostic yield of the different procedures. The pooled sensitivity of these histological and cytological techniques in case of centrally located tumors is 89% [40]. Maximal results are obtained when four to five biopsies are taken.

In cases of peripherally located tumors or extrabronchial enlarged lymph nodes, other techniques are available requiring a more skilled physician: broncho-alveolar lavage, transbronchial biopsy and/or fine needle aspiration (TBNA). The latter two are preferably carried out under fluoroscopic guidance. The lower part of Table 4 shows a comparison of the average diagnostic yield of the different procedures. Pooled sensitivity of flexible bronchoscopy techniques in case of a peripheral tumor is 69%. Ideally, six to 10 specimens should be obtained for optimal diagnostic yield. If the lesion is <2 cm diameter the diagnostic accuracy is only 33%, and CT-guided puncture is far more preferable (see below). Although rapid on-site evaluation (ROSE) seems to improve the diagnostic yield of TBNA, its cost-effectiveness remains unclear.

Cytological examination of sputum is preferably reserved to patients whose general condition precludes a bronchoscopy.

Table 4. Diagnostic yield of individual bronchoscopic procedures for endoscopically visible lung cancers and peripheral cancers

Procedure	No. of patients	Diagnosis	Average diagnostic yield (%)	Range (%)
Endoscopically visible lung cancers				
BW	1535	1041	68	27–90
BR	1578	1131	72	44–94
EBB	1934	2418	80	51–97
EBNA	456	365	80	68–91
Peripheral cancers				
BW	704	196	28	4–43
BR	1174	528	45	6–83
BAL	225	136	60	33–69
TBB	1509	786	52	13–83
TBNA	792	473	60	40–69

Adapted from Mazzone et al. [40].
BW, bronchial washing; BR, bronchial brushing; EBB, endobronchial biopsy; EBNA, endobronchial needle aspiration; BAL, broncho-alveolar lavage; TBB, transbronchial biopsy; TBNA, transbronchial needle aspiration.

Its sensitivity is 71% for central and 49% for peripheral tumors [40].

Transthoracic needle techniques

Advances in needle technology have improved safety and increased the accuracy of transthoracic needle biopsy (TNB). Needles vary according to size, tip design and sampling mechanism. Small gauge aspiration needles provide specimens suitable for cytological evaluation. Small- or large-bore cutting needles are capable of providing histology samples. The choice of needle relates to the location of the lesion, the amount of tissue required for a diagnosis and the operator's comfort. Studies comparing cutting with aspiration needles have demonstrated a similar or lower yield for malignant lesions for the former, but a higher yield for specific benign diagnoses and lymphoma, with little increase in complications [40]. Sensitivity for the diagnosis of peripheral primary lung cancer by TNB is 90%. The yield depends on the size of the lesion, and is highest in lesions with a diameter >2 cm and lower for smaller lesions (95% and 78%, respectively). CT guidance has a higher sensitivity than fluoroscopic guidance (92% versus 88%). The most frequent complication is pneumothorax, occurring in approximately one out of four patients. In only 5% to 10% of these, thoracic drainage is required. Bleeding is the second most common complication, occurring in $\sim$5% of patients, and is almost always self-limited; there have been sporadic reports of needle tract implantation of tumor cells [41].

Thoracentesis

With 35% of cases, lung cancer is the most frequent cause of malignant pleural fluid [42]. In 7% to 10% of patients with lung cancer, malignant pleural fluid will be a presenting feature or will develop during the course of disease. Not every case of pleural fluid is necessarily malignant. Paramalignant effusions occur, and can be due to obstructive pneumonitis, paraneoplastic pulmonary embolism, chylothorax or transudates caused by cardiogenic or hypoproteinaemic comorbidity. The presence of malignant cells in pleural fluid classifies the tumor as T4, hence at least stage IIIB, and not amenable to radical treatment [34]. Pleural fluid visible on chest X-ray of a lung cancer patient should be analyzed by thoracentesis of at least 30 ml of fluid. Its diagnostic yield depends of the extent of pleural involvement and ranges from 62% to 90%. Repeated thoracentesis and concentration techniques, e.g. cell block preparation, increases the sensitivity [43]. The majority of malignant effusions are detected with two specimens [44]. Examination of more than three specimens is of little value. Through the utilization of cell block preparations and a panel of antibodies appropriate for the differential diagnosis in question, immunocytochemistry conditions utilized in surgical pathology can be most closely replicated [45]. In those cases still negative after two thoracenteses and in whom radical treatment is considered, a thoracoscopy should be performed to inspect closely and biopsy the pleural cavity [38].

New developments in the diagnosis of lung cancer

A number of new and innovative techniques in association with conventional bronchoscopic procedures are being developed to improve the diagnostic yield of flexible bronchoscopy. Among these are the bronchoscopic ultrasonography, esophageal ultrasonography with fine-needle aspiration with ROSE, and virtual bronchoscopy-guided transbronchial needle aspiration [40]. Their application awaits further validation in prospective series.

Finally, gene expression profiling techniques will provide further improvements in the present light-microscopical classification by identifying subsets with discrete molecular characteristics [46].

Conclusions

Screening for lung cancer in risk groups with sputum cytology, chest X-ray or spiral CT scan is not advised until a definite reduction in lung cancer mortality is shown to occur in the screened group. Patients should be taught to seek medical advice in case of a change in coughing pattern, hemoptysis or dyspnea. Their physicians should unrelentingly continue their smoking cessation advice and be aware that lung cancer also occurs in ex-smokers presenting with these symptoms.

Once a presumed diagnosis is made, tissue diagnosis is to be pursued, even if treatment options are bleak at first glance. Modern endoscopic and transthoracic puncture techniques are highly accurate in experienced hands and have an acceptable morbidity and a low mortality. When confronted with a non-diagnostic procedure or a peripheral lung lesion with high *a priori* suspicion of cancer, pretreatment tissue diagnosis should only be pursued if the latter will impact on treatment. The decision to continue with diagnostic procedures hence depends on whether or not a radical treatment can be offered and sustained.

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