Authors and Disclosures

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Early Detection and Screening of Lung Cancer

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Abstract and Introduction

Abstract

Accounting for 28% of all cancer deaths and causing 1.3 million deaths worldwide every year, lung cancer is the most lethal cancer. Diagnosing and treating cancer at its early stages, ideally during precancerous stages, could increase the 5-year survival rate by three- to four-fold with a potential for cure. Thus far, no screening method has been shown to decrease disease-specific mortality rate. The present review describes the rationale and issues related to early lung cancer screening, the management of screen-detected primary cancers and different approaches that have been tested for screening. These include imaging techniques, bronchoscopies, molecular screenings from different noninvasive or invasive sources, such as blood, sputum, bronchoscopic samples and exhaled breath.

Rationale, Challenges & Issues for Lung Cancer Screening

The rationale for developing effective lung cancer screening stems from the fact that lung cancer causes 1.3 million deaths worldwide each year and accounts for more cancer deaths than breast, prostate and colon cancers combined.[1] Overall, the 5-year survival rate of a lung cancer patient is approximately 15%,[1] whereas the 5-year survival for patients with surgically resected early-stage disease is 60–80%.[2] This strong difference in lung cancer survival between those treated with early- versus late-stage lung cancer has formed the rationale for lung cancer screening.

Screening and early detection of lung cancer brings up many challenges. One is the 'lead time bias', where the screening test has no real effect on the outcome of the disease, but, due to the earlier diagnosis, there appears to be prolonged survival. Another potential confounder of screening studies is the 'length time bias', which refers to the fact that a disease with a long preclinical phase is more likely to be detected in the course of screening than a rapidly evolving disease. The 'over-diagnosis bias' occurs when a disease is diagnosed correctly, but the diagnosis is irrelevant because the disease would never cause symptoms or death during a patient's lifetime. A common consequence of all these issues is that even though early detection and intervention do not in actuality alter the course of the disease, survival would appear to be extended. For this reason the use of 'survival' as a measure of screening effectiveness, may not be the most appropriate approach. From a population perspective, the ultimate measure of screening effectiveness is 'mortality reduction'– whether screening for the disease saves lives – but this requires large randomized controlled trials. However, challenge emerges from the low frequency of the disease in the population. Lung cancer occurs on an annual basis in less than 1% of heavily tobacco-exposed individuals, making it difficult to achieve a statistically powered study size.[3]

Another challenge is to define the most optimal high-risk group for screening and early detection. It is difficult to select individuals to be considered for lung cancer screening. A balance must be found where the likelihood of developing lung cancer outweighs the harms that can result from false-positive findings, which could create complications and unnecessary costs and anxiety associated with subsequent diagnostic tests The group, consisting of patients with the highest risk for the development of lung cancers, are survivors of previous lung cancers with a standardized incidence ratio of 1.7 and a cumulative risk of 4.7% at 10 years.[4] Tobacco smoking is the major risk factor for primary lung cancer. The subgroups of patients with airflow obstruction, chronic bronchitis or chronic obstructive pulmonary disease (COPD),

which only occurs in approximately 25% of smokers, has a significantly increased incidence of lung cancer, compared with smokers with similar smoking histories but with no airflow obstruction.[5,6]

In Tockman's study, subjects with a forced expiratory volume in 1 s of less than 60% of that predicted were observed to have a six- to seven-fold increased risk for lung cancer.[6] Through the University of Colorado (USA) SPORE, we have obtained sputum cytology from a cohort of over 1900 individuals with airflow obstruction and more than 30 pack-years of cigarette smoking. Approximately 1% of these individuals had cancer on their initial sputum cytology (compared with 0.1% in the Mayo Lung Study) and 17% had moderate dysplasia (compared with 1% in the Mayo study).[7] Thus, the inclusion of airflow obstruction significantly increases the yield of both lung cancer and premalignant dysplasia. Chronic bronchitis is most commonly accompanied by airflow obstruction and, like airflow obstruction, is a marker for increased susceptibility to lung cancer.[8] Previous studies at the University of Colorado have found that approximately two out of three of patients with atypia on sputum cytology have dysplasia on a bronchial biopsy.[9] Recently, the Colorado group showed that risk for incident lung cancer was increased among those with moderate atypia or worse in sputum (adjusted hazard ratio of 2.37 [1.68–3.34]). The association was greatest for those whose sputum samples were collected 5 months or less before the diagnosis of lung cancer (odds ratio of 10.32 [5.34–19.97]). This association was substantially stronger for squamous cell carcinomas than for adenocarcinomas.[10] Other groups that did not use sputum cytologic atypia as an entrance criterion for a bronchoscopy had dysplasia rates of less than 5%.[11] In our previous studies in patients with airflow obstruction and either 30 or 40 pack-years smoking history, we have found a relationship between pack-years of smoking and the incidence of dysplasia in sputum.[7] Bach *et al.* developed a model for individual lung cancer risk based on data from patients that included a large randomized trial of lung cancer prevention. They showed that the absolute 10-year risk of developing lung cancer varies widely among smokers, mainly based on duration of smoking, average number of cigarettes smoked per day, presence and duration of abstinence, and the age of the patient.[12]

Despite the challenges and controversy of early screening for lung cancer, there is no controversy about the devastation of this disease. Prevention through smoking avoidance and cessation remains a primary goal. Nonetheless, the persistence of smoking prevalence and the fact that more lung cancers are diagnosed annually in former smokers suggests that the problem of lung cancer has a secure hold on mortality for decades. An increasing challenge is to identify risk factors among the cohort of never smokers that develop lung cancers. Today, 10% of all lung cancers are seen among never smokers.[13] Keeping in mind the challenges and issues, diagnosis and treatment at early stages, ideally in its precancerous stages, could increase the 5-year survival rate three- to four-fold.[14,15] Given the possibility for cure, effort should therefore be continued in this field of research.

Imaging-based Screening for Lung Cancer

Chest X-ray Screening Trials

Previous trials for lung cancer screening focused on chest radiographs (CXR) with or without sputum cytology evaluation.[14,16–22] In the 1970s, the US National Cancer Institute (NCI) sponsored three randomized controlled trials of lung cancer screening in male smokers. Two trials, the Memorial Sloan-Kettering Study and the Johns Hopkins Study, were identically designed to evaluate the incremental benefit of sputum cytology to annual chest radiography, but were not designed to address the efficacy of CXR screening versus an absence of any screening. There was no decrease in lung cancer mortality rates in the more intensely screened arm of either study.

The Mayo Lung Project examined the effects of intense CXR screening.[22] The intervention arm underwent CXR and sputum cytology examination at 4 months intervals; individuals in the control arm were advised at trial entry to only undergo annual CXR and sputum cytology examination. However, all participants received screening CXR and sputum cytology prior to study entry, precluding an analysis of the overall benefit of screening versus no screening on disease-specific mortality. The latest studies of the Mayo Lung Project analyzed additional mortality data through 1996.[19] During the initial six-year study period, there were 206 incident cases of lung cancer diagnosed in the screened arm and 160 in the control arm. The excess lung cancers in the screened arm were almost all early-stage lung cancers, but there was no decrease in late stage disease with screening. The 5-year survival was greater in the screened arm (33%) than in the control arm (15%), yet this did not translate into a mortality benefit from screening: lung cancer-specific mortality was 4.4 and 3.9 per 1000 person-years in the screened and control arms, respectively, (two-sided P for difference = 0.09). The results of chest x-ray studies performed in the 1970s are less relevant and probably not comparable considering new imaging technologies and greater prevalence of adenocarcinoma compared with the earlier prevalence of squamous cell carcinoma.

In 1992, the NCI initiated the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. This was a large

randomized controlled trial to definitively assess the ability of multiple screening modalities to reduce disease-specific cancer mortality. An annual comparison of CXR screening versus no screening for lung cancer was included.[22] PLCO enrolled 154,934 men and women aged from 55 to 74 years, who were randomized to be screened or to receive their usual medical care. Participants in the intervention arm were offered either three (never smokers) or four (ever smokers) annual CXR screens. Participants are followed for at least 14 years. The trial has 90% powered to detect a 10% difference in lung cancer mortality, even considering conservative estimates of noncompliance and contamination. Only lung cancer detection results from the CXR baseline screening round has been published.[23] Among the participants in the intervention arm, the rate of a positive (abnormal) screen was 8.9% (5991 out of 67,038 participants that received a baseline chest x-ray) and 126 lung cancers were diagnosed within 12 months of the screen. As expected, detection rates were highest among current smokers (6.3 per 1000 screens) and lowest among never smokers (0.4 per 1000 screens). In the future, optimal evaluation of CXR screening should include more accurate digital radiography.

Computed Tomography Screening Trials

Multidetector helical computed tomography (CT) represents a major advance in cross-sectional imaging due to increased scan speed, improved z-axis spatial resolution and the capacity to reconstruct multiple series from a single data acquisition. Advances in acquisition techniques and speed have made it more practical as a potential screening tool for early lung cancer detection. The advancement of CT technology has renewed interest in screening for lung cancer using low-dose spiral CT. Japanese and USA investigators began using spiral CT for lung cancer screening in the late 1980s and early 1990s, respectively.[24–27] Clinical trials were conducted with observation models. These trials clearly demonstrated that smaller nodules could be detected by CT compared with chest radiographs and more lung cancers were detected at stage 1. This resulted in a better survival rate of patients.[24–27] However, these studies also concluded that too many lung nodules were seen by CT, resulting in false positives, which resulted in follow-up studies including increased morbidity and mortality from unnecessary procedures and a presumed increase in participant's anxiety (quality of life and cost–effectiveness issues). Given the lead time bias, length time bias and possibility of over-diagnosis inherent in the single-arm models of these clinical trials, many questions remain unanswered.[28] Will CT for lung cancer screening result in a decrease in mortality from lung cancer? Does the size and radiographic phenotype of a nodule determine clinical outcome or is biology of lung cancer the real determinant of cure in a given patient? The seventh edition of the tumor node metastasis staging system reflects that tumor size (T descriptor) is one of the determinants of prognosis and clinical outcome. To answer some of these important questions, the NCI sponsored a randomized controlled trial, the National Lung Cancer Screening Trial,[201] at multiple institutions in the USA. The recruitment started at the end of September 2002. The goal to recruit 50,000 participants was reached in February 2004. Each eligible participant received three annual CTs screening or three annual chest x-rays and are then followed clinically for another 5–7 years.

Multidetector CT as a screening tool for early lung cancer detection is being evaluated in large ongoing trials, in the USA (NLST) and in Europe (NELSON trial). The studies designs are slightly different in these two major randomized trials, specifically related to the control arms. In the NELSON trial, typical care without imaging is used in the control arm while in the NLST trial, imaging with CXR is used. The rationale for using the CXR is that if the PLCO trial shows that CXR did decrease lung cancer-specific mortality, compared with usual care, NLST will then compare the new standard with CT. If CXR does not turn out to be an effective screening test in the PLCO trial as in the older CXR trials in the 1970s, then it would be nearly the same as usual care.

Given isometric datasets, volume-rendered techniques can be applied for calculating the volume of a nodule. Since lung nodules often grow in a nonlinear fashion, volumetric growth assessment is reported to be more accurate than 2D measurements.[29] Recently, investigators reported the use of volume and volume-doubling time of a noncalcified nodule as the main criteria for determining whether or not to act further. In this population-based screening study (NELSON), the test was considered negative if the nodules were less than 50 mm^3 (4.6 mm), or the doubling volume was more than 600 days. The test was considered positive if the nodule volume was greater than 500 mm^3 (9.8 mm) or the doubling time was less than 400 days. Nodules with volumes between 50 and 500 mm^3, and doubling times between 400 and 600 days were considered indeterminate.[30] Using these criteria, a positive test result was reported in 2.6 and 1.8% of the participants, in the first and second rounds of screening, respectively. In round one, the sensitivity of the screen was 94.6% (95% CI: 86.5–98.0) and the negative predictive value 99.9% (95% CI: 99.9–100). However, this methodology is not commercially available and given large number of variables further validation is warranted.

The widespread availability of multidetector CT and abundance of new information obtained from both observational and randomized controlled trials, CT lung cancer screening programs have increased our understanding of the management, and types of, small peripheral lung nodules encountered in daily clinical practice. In particular, concerning the importance and prevalence of sub-solid pulmonary nodules (Table 1). Sub-solid nodules include both pure ground glass, and part

solid nodules. Ground glass opacities (GGOs) are defined as focal nodular areas of increased lung attenuation through which normal parenchymal structures, such as airways, vessels and interlobular septa, can be defined. Sub-solid nodules are now known to frequently represent the histological spectrum of peripheral adenocarcinomas.[31] Pending revisions in multidisciplinary classifications of these lesions, this includes premalignant atypical adenomatous hyperplasia, carcinoma *in situ* (CIS) or bronchiolalveolar carcinoma, minimally invasive and invasive adenocarcinoma.[32]

Table 1. Recommended follow-up and management of nodules smaller than 8 mm detected incidentally at nonscreening computed tomography.

Nodule size (mm)	Low-risk patient†	High-risk patient
≤4	No follow-up needed	Follow-up CT at 12 months; if unchanged, no further follow-up
>4–6	Follow-up CT at 12 months; if unchanged, no further follow-up	Initial follow-up CT at 6–12 months then at 18–24 months if no change
>6–8	Initial follow-up CT at 6–12 months then at 18–24 months if no change	Initial follow-up CT at 3–6 months then at 9–12 months and 24 months if no change
>8	Follow-up CT at around 3, 9 and 24 months, dynamic contrast-enhanced CT, PET and/or biopsy	Same as for low-risk patient

†Low-risk patient = age ≤35 years, <12 pack-years smoking, no history of previous malignancy, no family history of aerodigestive tract malignancy.
CT: Computed tomography.
‡Data taken from.[159]

Routine screening for lung cancer using imaging is not yet recommended by any major medical organization.[33] However, more scientific evidence is awaited from ongoing randomized controlled trials (including the NLST, PLCO and NELSON trials) before deciding for or against imaging based screening for lung cancer. One of the limitations of ongoing trials is that they do not adequately consider what are probably major genetic differences among the various populations, likely accounting for the high percentage of nonsmoking women with peripheral adenocarcinoma in Japan, for example. Discussion about the impact of single versus multiple nodules and new information about early lung cancer in the new seventh edition of tumor node metastasis staging system is beyond the scope of this article.

Bronchoscopy

Bronchoscopy for Early Detection & Screening for Lung Cancer

CT scans are good at detecting small peripheral lesions, especially adenocarcinoma. However, CT scans are not suitable for detecting preinvasive lesions and early lung cancer in the central airways, specifically small-cell lung cancer (SCLC) and the early stages of squamous cell carcinoma, which comprise 17–29% of all lung cancers.[34] Centrally located preinvasive and very early stages bronchial malignancies (e.g., severe dysplasia and CIS) are occult to the CT scans. McWilliams *et al.* found 28 lung cancers cases in a screened cohort of 561 high-risk patients (5%).[35] Seven (25%) of the detected malignant cases were found by bronchoscopy, but not by image evaluation. However, this study used computer-generated cytologic evaluation for assessing sputum, again a technology not generally available. Centrally located tumors require direct inspection for diagnoses, namely bronchoscopy, with or without biomarker prescreening such as abnormal sputum cytology analysis. Thus, the main challenge is to detect pre-invasive or early invasive disease. White light bronchoscopy (WLB) is insufficient to detect such lesions; therefore autofluorescence bronchoscopy (AFB) was developed to address this limitation. AFB is now the gold standard for detecting pre-invasive lesions.[36] Lam *et al.* were the first to use AFB in 1992 and the light-induced fluorescence endoscopy device became commercially available in 1998.[37] The light-induced fluorescence endoscopy system uses a helium–cadmium laser to illuminate the bronchial mucosa with 442-nm light. The red and green auto-fluorescence emitted light is captured by a photo-amplifier camera and diplayed as green for normal areas and red-brown for abnormal areas.

In a European multicenter randomized controlled trial,[38] 1173 high risk patients were randomized to undergo WLB or WLB plus AFB diagnosis. Overall, preinvasive lesions (moderate dysplasia or greater and CIS) were detected in 3.9% of

the patients, while the prevalence with WLB was 2.7% and with AFB 5.1% (p = 0.037). Adding AFB increased the rate of detecting moderate to severe dysplasia and CIS by a factor of 2.1 and 1.25, respectively. The sensitivity to detect moderate dysplasia or greater increased from 57.9 to 82.3% by the use of AFB. Numerous other studies comparing the sensitivity of WLB to WLB plus AFB are summarized in Table 2. These studies show that adding AFB to WLB increases the sensitivity from 9 to 65% and 4 to 100% for moderate-to-severe dysplasia and CIS, respectively.[9,11,37–52] However, AFB still hasn't been adopted in most of the clinics.

Table 2. The additive value of autofluorescence bronchoscopy to white light bronchoscopy to detect moderate/severe dysplasia and carcinoma *in situ*.

Study (year)	Patients (n)	Biopsies (n)	Sensitivity (%) - WLB	Sensitivity (%) - AFB ± WLB	Ref.
Lam *et al.* (1993)	94	328	48	73	[39]
Lam *et al.* (1994)	223	451	39	79	[40]
Lam *et al.* (1998)	173	700	9	56	[37]
Kurie *et al.* (1998)	39	245	NA	43	[11]
Venmans *et al.* (1999)	95	681	59	85	[41]
Ikeda *et al.* (1999)	158	997	58	92	[42]
Vermylen *et al.* (1999)	34	142	25	94	[43]
van Rens *et al.* (2001)	72		20	100	[44]
Hirsch *et al.* (2001)	55	391	18	79	[9]
Shibuya *et al.* (2001)	64	212	69	91	[45]
Sato *et al.* (2001)	63		61	89	[46]
Moro-Sibilot *et al.* (2002)	244	354	36	86	[47]
Beamis *et al.* (2004)	293	821	11	66	[48]
Chhajed *et al.* (2005)	151	343	63	95	[49]
Chiyo *et al.* (2005)	32	62	62	85	[50]
Haussinger *et al.* (2005)	1173	1978	58	82	[38]
Lam *et al.* (2006)	62	91	58	91	[51]
Ikeda *et al.* (2006)	154	166	65	90	[52]

AFB: Autofluorescence bronchoscopy; WLB: White light bronchoscopy.

Within the past few years, a new bronchoscope, the narrow-band imaging bronchoscope (NBI), has been evaluated to detect bronchial dysplasia and CIS. While AFB uses blue light (390–440 nm wavelength), the NBI uses two bandwidths of light: 390–445 nm (blue) light that is absorbed by superficial capillaries and 530–550 nm (green) light that is absorbed by blood vessels below the mucosal capillaries. These narrow wavelengths reduce the scattering of light and enable enhanced visualization of blood vessels.[53] Vincent *et al.* showed that NBI detected one cancer and four dysplastic cases in 22 patients that appeared normal by WLB.[54] Peled *et al.* evaluated 104 postoperative patients 1 year after lung cancer surgery.[55] All cases were evaluated by WLB and, of those, 47 cases were also evaluated by NBI. While they found 4% of early local recurrence with local stumpal polyp, adding NBI detected seven cases of bronchial dysplasia and metaplasia. A comparison between AFB and NBI has been reported recently by Herth *et al.*.[53] In 57 high-risk patients, the sensitivity of WLB to detect intra-epithelial neoplasia is 18%. The relative sensitivities (compared with WLB) of AFI and NBI were 3.7 (p = 0.005) and 3.0 (p = 0.03), respectively. Combining AFI and NBI did not increase diagnostic yield significantly.

Two other new tools have been developed: optical coherence tomography (OCT) and confocal fluorescence microscopy (CFM).

Optical coherence tomography is an optical imaging method that can offer microscopic resolution for visualizing cellular and extracellular structures at and below a tissue surface.[56–60] OCT is similar to ultrasound imaging, but uses light rather than acoustical waves. In ultrasound, the imaging is accomplished by measuring the delay time (echo delay) for an incident ultrasonic pulse to be reflected back from structures within tissue. Lam reported that quantitative measurement of the epithelial thickness showed that invasive carcinoma was significantly different than CIS ($p = 0.004$) and dysplasia was significantly different than metaplasia or hyperplasia ($p = 0.002$).[61] The autofluorescence endoscopy-guided OCT imaging of bronchial lesions is technically feasible. OCT appears to have great potential for management of early lung cancer and precancerous lesions.

Confocal fluorescence microscopy is a new technique that procedures microscopic imaging of a living tissue and that enables *in vivo* microscopic observation of the airways and alveoli. Similar to autofluorescence bronchoscopy, the device utilizes a blue laser. The small probe is integrated into the working channel of a bronchoscope into the distal airway and alveoli. The magnification and resolution of the images is such that alveolar structures and intra-alveolar cells can be clearly visible.[62] Thiberville *et al*. reported early findings of fiberoptic CFM in 29 patients at high risk for lung cancer and healthy controls with premalignant and benign airway pathology.[62] They found several microscopic patterns that may help in the recognition of dysplastic lesions. Then, they studied fiberoptic CFM in 41 healthy patients, including 17 current smokers.[63] They reported a strong correlation between the number of cigarettes smoked per day and the amount of large and mobile macrophages observed *in vivo*, as well as with the intensity of the macrophage alveolitis. Fiberoptic CFM enables accurate exploration of the peripheral lung *in vivo* in both smokers and nonsmokers.

To summarize, development of new bronchoscopy techniques has improved the early detection of lung cancer, mainly for the central airways, and increased sensitivity compared with WLB, while more studies should be done to compare the yield of NBI to the AFB.

Sputum Cytology & AFB

Sputum cytology has been shown to be effective in detecting early squamous carcinomas of the major bronchi.[64] In the update by the Colorado Lung Cancer group, the risk for lung cancer was increased when sputum atypia was graded moderate or greater (hazard ratio of 2.37 [1.68–3.34]), with a stronger association if the sputum sample was collected 5 months or less before the diagnosis of lung cancer (odds ratio of 10.32 [5.34–19.97]).[10] Lam *et al.* recently reported that sputum cytology in high-risk patients has a sensitivity of 69% and specificity of 40% for lung cancer.[65] The positive and negative predictive values of sputum atypia for lung cancer were 8 and 94%, respectively. They recommended sputum cytology followed by AFB as a screening regimen for high-risk groups.

Similarly to AFB, sputum cytology is rarely performed, especially not as a screening device, despite decades of reports regarding its efficacy.

Molecular Screening: The New Era

Advances in molecular biology have led to new insights regarding lung cancer biology. Blood, sputum bronchoalveolar lavage, bronchoscopic brushing or biopsies, and exhaled breath are sources for the identification and detection of various molecular abnormalities.

Blood (Serum/Plasma) Analyses

Different genetic abnormalities are observed in serum and/or plasma by examining circulating DNA, promoter hypermethylation, microsatellite instability, loss of heterozygosity (LOH), tumor-associated antibodies, proteomic profiles, circulating mRNAs and microRNAs (miRNAs).

Circulating DNA Circulating cell-free DNA, released by lung cancer cells, can be detected at higher levels in patients with lung cancer compared with a control group. Many studies have indeed assessed the circulating cell-free DNA for lung cancer detection.[66] Sozzi *et al.* performed one of the first large scale studies on this topic, which included 100 cases and 100 controls (24.3 ng/ml vs 3.1 ng/ml of circulating DNA). The control group included current, former and never-smokers. With a cutoff value of 4, 9 or 25 ng/ml, the sensitivity was 97, 90 and 46%, and the specificity was 60, 86 and 99%, respectively. The level of circulating DNA decreased after tumor resection and a bigger reduction was prognostic for the absence of recurrence.[67] Recently, another group assessed 155 patients with lung cancer, using 79 healthy patients as a control. The concentration of circulating plasma DNA was approximately four-times higher in patients with lung cancer with respect to the control group. Furthermore, depending on the cutoff level, sensitivity ranged between 32 and 86% and specificity between 75 and 92%.[68] Zhang *et al.* recently made a meta-analyses of the studies including at least ten lung

cancer patients and providing both the sensitivity and specificity of the level of circulating plasma DNA for the diagnosis between lung cancer and healthy controls.[66] In total, ten studies published between 1997 and 2009 were included in this meta-analyses.[67–76] Using a cutoff value from 2 ng/ml up to 50 ng/ml, the sensitivity and specificity ranged between 48 and 91% and 47 and 100%, respectively, while the pooled sensitivity and specificity was 80% (95% CI: 77–83%) and 77% (95% CI: 74–80%), respectively. We could expect more clinical application of the measure of circulating DNA for the diagnosis of lung cancer as many studies have been published on this topic, but there is a lack of standardization and of reproducibility, that is, a large range of thresholds used in the different studies, thus making any clinical application impossible so far.

Promoter Hypermethylation Promoter hypermethylation, a mechanism of silencing tumor-suppressor genes, has been detected in the serum of lung cancer patients. In a study of 22 patients with non-small-cell lung cancer (NSCLC), Esteller *et al.* detected promoter hypermethylation in at least one of four tumor-suppressor genes in 68% of primary tumors versus 73% of matched serum samples. No conclusion was drawn about the sensitivity of promoter hypermethylation detection for the early detection of lung cancer or for its prognostic value on mortality.[77] Adenomatous polyposis coli (*APC*)[78] as well as *RASSF1A* [79] have also been detected in lung cancer patient's serum in 42 out of 89 (47%) and 27 out of 80 (34%) patients, respectively. Both *APC* and *RASSF1A* were unmethylated in the serum of the control's healthy patients. Thus, the hypermethylations of these two genes seem to be very specific for cancer patients but have a low sensitivity.

Microsatellite instability Several studies have detected microsatellite instability due to replication errors in short tandem repeat sequences, and LOH in the blood of patients with lung cancer. Cuda *et al.* studied 21 patients with NSCLC with at least one genetic abnormality detected in 12 of the primary tumors and nine of the matched serum.[80] Andriani *et al.* assessed p53 mutations, *FHIT* LOH and 3p microsatellite instability or LOH. At least one abnormality was found in the serum of half of the lung cancer patients whereas none were positive in any of the 43 controls.[81] Sozzi *et al.* also tested microsatellite instability or LOH at several loci. In a cohort of 87 patients, at least one abnormality was detected in 56% of primary tumors and 40% of matched serum samples globally, and 45, 43 and 67% of patients with tumors less than 2 cm, stage I and stage IIIB–IV, respectively. Cancer recurrence did not correlate with abnormal serum samples.[82]

Tumor-associated antibodies Zhong *et al.* identified a set of five tumor-associated antibodies in the plasma of patients with NSCLC based on a training set of 23 patients with stage I NSCLC and 23 risk-matched controls. In the validation set there were 46 plasma samples from patients with early-stage NSCLC and 56 risk-matched controls. The panel of five antibodies identified patients with cancer with a sensitivity and a specificity of 82.6 and 87.5%, respectively.[83] More recently, Chapman *et al.* analysed plasma from 50 normal controls, 82 patients with NSCLC and 22 with SCLC for the presence of 7 antibodies (p53, c-myc, HER2, NY-ESO-1, CAGE, MUC1 and GBU4–5). Raised levels of autoantibodies were seen to at least one out of seven antigens in 76% of patients with lung cancer and 89% of node-negative patients, with a specificity of 92%.[84] The detection rate was higher in squamous cell carcinoma (92%). Tan *et al.* recently published a review of the use of serum autoantibodies as biomarkers for early detection of cancers, including lung cancer.[85]

Proteomic Using MALDI mass spectrometry to analyze unfractionated serum from a total of 288 cases and matched controls, Yildiz *et al.* showed that a signature of seven features reached an accuracy of 78 and 72.6%, a sensitivity of 67.4 and 58% and a specificity of 88.9 and 85.7% in the training (n = 182) and the blinded test sets (n = 106), respectively.[86] Patz *et al.* assayed six serum proteins and found that a panel of four of them (carcinoembryonic antigen, retinol binding protein, α1-antitrypsin and squamous cell carcinoma antigen) correctly classified the majority of the lung cancer versus control patients in the training set (n = 50 patients in each group, sensitivity 89.3%, specificity 84.7%) and in the independent validation set (49 lung cancer patients and 48 matched controls) with a sensitivity and a specificity of 77.8% and 75.4%, respectively.[87] More recently, using antibody microarrays, Han *et al.* found that six proteins (AQP5, ARTN, CKB, MCM3, TAF9 and TGIF2) were distinctly downregulated in sera of 28 lung cancer patients compared with sera from eight healthy persons. In the validation set (17 cases and 15 controls), these proteins identified cancer patients sera with a sensitivity of 88% and a specificity of 80%.[88]

Circulating mRNA Circulating mRNA can also be detected in cancer patients.[89] In particular for lung cancer, Fleischhacker *et al.* were able to detect all patients with lung cancer in 18 cases by serum examination for presence of hnRNP-B1 or HER2/Neu mRNA.[90] Investigating tyrosinase mRNA, Kopreski *et al.* detected 5T4 (trophoblast glycoprotein) in the sera of 43% (six out of 14) but also 12% (three out of 25) of healthy controls.[91] By using real-time-PCR, Matsunaga *et al.* could detect at least one out of five tested transcripts (cytokeratin 19, collagen 1, syndecan 1 and 2 novel genes) in peripheral blood from 79% of patients with adenocarcinoma and 69% of patients with squamous cell compared with one out of 20 (5%) of blood samples from healthy volunteers.[92]

Circulating miRNAs Recently, miRNAs, small noncoding RNAs that inhibit translation, were found to be stable blood markers for cancer detection.[93,94] Rabinowits *et al.* detected miRNAs in the circulating exosomes of lung adenocarcinoma patients. The mean concentration of both circulating exosomes and miRNA were significantly higher ($p < 0.001$) in cancer ($n = 27$) than in control patients ($n = 9$).[95]

Sputum Analyses

In addition to the classical cytology assessment, different molecular biomarkers (chromosomal aneusomy, promoter hypermethylation, tumor-associated antigens) have been assessed in sputum.

Promoter Hypermethylation Many authors have studied promoter hypermethylation in sputum of lung cancer patients.[96] In particular and more recently, Belinsky *et al.* assessed the promoter methylation of 14 genes in the DNA isolated from sputum of 98 cases and 92 controls from the Colorado high-risk cohort. The best discrimination between cases and controls was obtained with six loci. The concomitant methylation of three or more of these six genes was associated with a 6.5-fold increased risk of lung cancer and with a sensitivity and specificity of 64%.[97]

Chromosomal Aneusomy A recent nested case–control study showed that a multitarget test detecting chromosomal aneusomy with LAVysions probes for EGF receptor (*EGFR*), *MYCC*, *5p15* and *CEP6* in sputum by FISH, in association with cytology, could predict lung cancer in samples colleted within 18 months prior to diagnosis, with a sensitivity and a specificity of 76 and 88%, respectively.[98]

Bronchoscopy Samples

Detection of molecular abnormalities in bronchoscopy samples (bronchoalveolar lavage [BAL], bronchoscopic brushings and bronchial biopsies), although more invasive than blood and sputum analyses, can significanlty increase the sensitivity of a detection test when compared with classical cytological evaluations.

Loss of Heterozygosity Examining 80 BAL's from patients with lung cancer and control, Liloglou *et al.* showed that the detection of LOH in four of eight loci defined cancer with a sensitivity and specificity of 73.9 and 76.5%, respectively. When combining the results of this molecular assay with cytological examination, the sensitivity reached 82.6%.[99]

Tumor-associated Antigens HnRNP A2/B1 antigen has also been detected in BAL. In a total of 195 patients, 23 showed malignant cells and only one of them tested negative for hnRNP A2/B1. Among the 172 others, 80 displayed metaplastic cells and 41 of them were positive for hnRNP. In total 33 out of 41 hnRNP A2/B1-positive patients and one out of 39 negative-patients were subsequently diagnosed with lung cancer. Globally, detection of hnRNP A2/B1 in BAL containing metaplastic or cancer cells predicts the presence of a neoplasm with a sensitivity and specificity of 96 and 82%, respectively.[100]

Chromosomal Aneusomy Cytological and FISH methods utilizing LAVysion probes were also performed on bronchoscopic brushings and washings in 137 patients, of whom 89 were subsequently diagnosed with lung cancer. The sensitivities of cytology, FISH, or the combination of both, were 44, 49 and 61%, respectively, in brushing and 51, 71 and 75%, respectivtely, in BAL. The combination of both methods was significantly more effective of a test ($p < 0.001$) than cytology alone.[101] Another study showed the advantage of an additional FISH test performed on specimens diagnosed as negative, atypical or suspicious by cytology, mainly for peripheral lung lesions.[102]

Gene Expression Analyses Another approach to identify biomarkers for the early detection of lung cancer consists of using high-throughput techniques to study the molecular biology of bronchial epithelium and thus determine the molecular signatures that allow one to discriminate high-grade preinvasive lesions and/or invasive carcinoma from benign bronchial epithelium. The first data were obtained on normal bronchial airways epithelial cells collected in bronchoscopic brushings. Spira *et al.* show that the genomic profile of bronchial epithelial cells could classify patients as either having or not having lung cancer. Using 80 genes obtained on the training set ($n = 770$), they distinguished patients with and without cancer in the validation set ($n = 52$) with an accuracy of 83%, a sensitivity of 80% and a specificity of 84%.[103] The same team further evaluated the independence of these biomarkers from other clinical risk factors. Using training ($n = 76$) and test ($n = 62$) sets of smokers undergoing bronchoscopy for suspicion of lung cancer at five medical centers, their so-called clinicogenomic model increased sensitivity to 100% and specificity to 91%.[104] A potential alternative to bronchial airway brushings could be to use cells lining the oral or nasal mucosa. Indeed, the same group,[105] as well as others,[106,107] showed that the components of the genomic response to tobacco smoke are shared between nasal and bronchial epithelium, suggesting that the nasal epithelial gene expression may be used as a relatively noninvasive surrogate measure of tobacco smoke effects.

The second type of approach for the study of genomic profiling, used to obtain signatures suitable for early detection, is based on bronchial biopsy samples obtained during fluorescence bronchoscopy at all stages of lung squamous carcinogenesis. Mascaux *et al.* showed that miRNA[108] and mRNA signatures,[109] performed on 60 and 122 samples, respectively, at all stages of lung squamous carcinogenesis, were shown to discriminate high-grade bronchial biopsies (severe dysplasia and CIS) and invasive squamous cell carcinoma from normal bronchial mucosa and low-grade bronchial biopsies (moderate dysplasia or lower) with a sensitivity and specificity of 83–100% for the mRNA and 93–88% for the 381-gene signatures, respectively. A new study performed on a multinational independent set of patients, which aimed to validate these signatures, as well as to assess the potential to use them in peripheral blood test, is presently ongoing. If validated and also detected in noninvasive obtainable biologic samples like plasma, these biomarkers would constitute a tool for the noninvasive screening and early diagnosis of lung cancer.

The different studies performed on blood, sputum and bronchoscopy samples and reporting sensitivity and specificities are summarized in Table 3.

Table 3. Studies assessing sensitivity and specificity of testing molecular markers for early detection of lung cancer.

Study (year)	Source	Biomarker tested	Technique	Sensitivity (%)	Specificity (%)	Ref.
Sozzi *et al.* (2003)	Plasma	Free circulating DNA	PCR	90†	86†	[67]
Xie *et al.* (2004)	Plasma	Free circulating DNA	Pico green method	80.6†	86.4†	[69]
Herrera *et al.* (2005)	Plasma	Free circulating DNA	PCR	48†	100†	[70]
Ludovini *et al.* (2008)	Plasma	Free circulating DNA	PCR	80†	61†	[74]
Ulivi *et al.* (2008)	Serum	Free circulating DNA	PCR	83†	92†	[76]
Paci *et al.* (2009)	Plasma	Free circulating DNA	PCR	85.8†	46.8†	[68]
Yoon *et al.* (2009)	Plasma	Free circulating DNA	PCR	91.2†	57.1†	[73]
Zhong *et al.* (2006)	Plasma	Tumor associated antibodies	Customized diagnostic chips	82.6‡	87.5‡	[83]
Yildiz *et al.* (2007)	Serum	Proteomic profiles	MALDI MS	67.4† 58‡	88.9† 85.7‡	[86]
Patz *et al.* (2007)	Serum	Proteins	ELISA	89.3† 77.8‡	84.7† 75.4‡	[87]
Belinsky *et al.* (2006)	Sputum	Promoter methylation of DNA	Methylation-specific PCR	64†	64†	[97]
Varella-Garcia *et al.* (2010)	Sputum	Chromosomal aneusomy	FISH	76†	88†	[98]
Liloglou *et al.* (2001)	BAL	LOH	PCR	73.9†	76.5†	[99]
Fielding *et al.* (1999)	BAL	hnRNP A2/B1 antigen	IHC	96†	82†	[100]
Voss *et al.* (2010)	BB and BW	Chromosomal aneusomy	Cytology + FISH	61†	75†	[102]
Spira *et al.* (2007)	BB	Gene expression	Microarrays	80‡	84‡	[103]
Beane *et al.* (2008)	BB	Clinicogenomic model	Microarrays	100‡	91‡	[104]

Mascaux *et al.* (2009)	Bronchial biopsies	Gene expression	Microarrays	93†	88†	[109]
Mascaux *et al.* (2009)	Bronchial biopsies	microRNAs	RT-PCR	83†	100†	[108]

†Test set.
‡Validation set.
BAL: Bronchoalveolar lavage; BB: Bronchoscopic brushings; BW: Bronchoscopy washings; IHC: Immunohistochemistry; LOH: Loss of heterozygosity; MALDI MS: MALDI mass spectrometry; RT-PCR: Real-time PCR.

In conclusion, detection of molecular abnormalities in different fluids, some being noninvasive (blood, sputum), other being more invasive (bronchoscopy), showed some interesting results with sensitivity and specificity of up to 95 and 100%, respectively. However, so far, none of these biomarker-based detection tests have been validated beyond the validation set within the same study and thus could not be recommended as a screening procedure. Even in some specific fields in which many studies have been published, such as in the detection of circulating DNA, there is a deep lack of effort to standardize the technique to measure the biomarkers as well as to validate the results in prospective independent cohorts.

Exhaled Breath Analysis of Volatile Organic Compounds

Exhaled breath analysis links specific volatile organic compounds (VOCs) to medical conditions, but has not yet been adopted for cancer diagnosis and screening.[110–113] The principle behind this approach is that cancer-related metabolism is reflected in the circulation from the onset of the disease.[114] These changes are manifested as a measurable increase or decrease in the levels of certain VOCs in the breath via air exchange in the lung, thus producing a unique 'smell' signature.

The association of breath VOCs with lung cancer was recently reviewed and showed that organic compounds in the range of C_4–$C_{20,}$ straight and mono-methylated alkanes, in addition to certain benzene derivatives, are mostly associated with lung cancer and these have the ability to classify subjects as having cancer or not.[115–117] The compounds of interest are generally found at 1–20 parts per billion (ppb) in healthy human breath, but can be seen in distinctively different mixture compositions and at elevated levels (10–100 ppb) in the breath of diseased patients. An interesting breakthrough has been reported recently by the TECHNION (Israel) group showing that the breath VOC profile discriminates not only between lung cancer and healthy breath but also between lung cancer and other cancer types, including breast, colon and prostate cancers.[113]

This new technology in breath analysis, eNose, was recently developed and can rapidly distinguish the breath of lung cancer patients from the breath of healthy individuals and could even discriminate between NSCLC and SCLC through VOC sampling of cell line headspace atmosphere.[118]

The main potential usage of breath analysis is for screening high-risk cohorts, as the breath medium is a completely noninvasive method, extremely available and without any side effects. Such a screening tool, together with other noninvasive biomarker panels, would serve as a first-step screening method preceding further investigation that might include image techniques, such as chest CT scans, and invasive procedures, such as bronchoscopy and needle biopsies. Early detection of lung cancer is hampered by inaccessibility of sites of tumor origin and the multiplicity of sites from which tumors may arise. Clinically, this leads to late-stage diagnosis with incurable disease.[119]

Breath analysis has been proposed to identify inflammatory and tumor processes.[120,121] However, the cellular and biochemical origin of VOCs is still poorly known. The released VOC can come from the tumor, form the environmental response, or from the human response. Therefore, *in vitro* studies that investigate isolated components, like cancer cell lines, might tease out the contribution of the cancer cells' general signature.[118,122]

Volatile organic compounds in human breath were first described by Pauling *et al.* in 1971.[123] The identification of VOCs by gas chromatography/mass spectrometry in the exhaled breath of lung cancer patients was initially reported in the 1970s and 1980s.[124,125] It is now known that exhaled breath contains thousands of different VOCs, most of them in picomolar concentrations.[114] Different concentration combinations of exhaled breath VOCs have been proposed by different groups aiming to detect lung cancer, for example, Phillips *et al.* have published a list of 22 VOCs[126] and later a

combination of nine VOCs[114] with a detection sensitivity of 89% and a specificity of 83%. Chen *et al.* have further isolated 11 specific VOCs from cellular activity of lung cancer cells, but their list was only partially related to Phillips's combination.[127]

Advanced technology based on arrays of chemical vapor sensors improved the ability to discriminate and to identify gaseous samples in a complex mixture, and seems to be the leading technology in that field. Machado *et al.* have reported 71% sensitivity and 92% specificity for detecting lung cancer by this system in 14 patients,[128] while Peng *et al.* have reported a recent accuracy of greater than 86% and a reproducibility of greater than 90%.[113]

The field of breath analysis is growing with the hope of having such a noninvasive tool that would be of great advantage to early-detection screening. However, clinical comparison with other diagnostic techniques has not been done yet.

Management of Screen-detected Primary Cancers

Surgical Approach

The purpose of early diagnosis is to provide the possibility of early radical treatment of lung cancer. The curative treatment of choice for early-stage NSCLC is usually surgical resection. The gold standard for the surgical resection has been lobectomy with lymphadenectomy.[129] However, as a result of the development of radiographic screening tools, such as high-resolution (HR) CT, the frequency of detection of early-stage lung cancer has been increasing. Most of them have a characteristic appearance on HRCT known as GGO and small sized (diameter ≤2 cm) peripheral malignancies (Figure 1). The pathologic features of GGO are characterized by nonmucinous-bronchioloalveolar carcinoma or atypical adenomatous hyperplasia, according to WHO criteria.[130] The peripheral small lung adenocarcinoma discovered in HRCT has a remarkable 5-year survival rate of 95% and is different from conventional lung adenocarcinoma.[131–133] Several studies suggested that survival is significantly better in patients whose tumors are 2.0 cm or smaller in size.[134,135] For these tumors, sublobar resection might be the treatment of choice provided that they are located in the outer third of the lung parenchyma. Otherwise, there might be no other choice than a lobectomy. However, the main issue of performing HRCT for the early screening of lung cancer is the very high rate of false-positive results being followed by invasive procedure, including surgery with resulting morbidity and mortality.

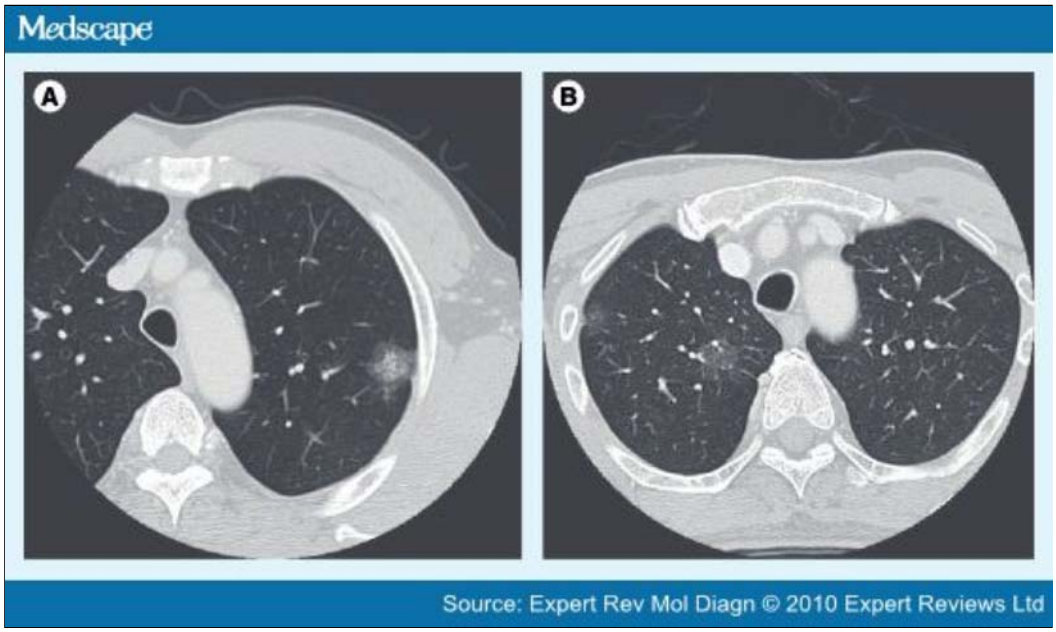

Figure 1. Detection of early stages of lung cancer based on imaging. (A) Part-solid nodule in left upper lobe. The pathological diagnosis was bronchoalveolar carcinoma with invasive components. The central solid portion corresponded to invasion. **(B)** Multiple ground-glass nodules in the right upper lobe. The pathological diagnosis was bronchoalveolar carcinoma (or adenocarcinoma *in situ*).

Two large randomized trials, CALBG140503 (Figure 2)[202] and JCOG0802/WJOG4607L,[136] comparing lobectomies with sublobar resection are ongoing. Preliminary data from these studies suggest equivalency of these surgical strategies with respect to overall and disease-free survival in patients with small tumors.

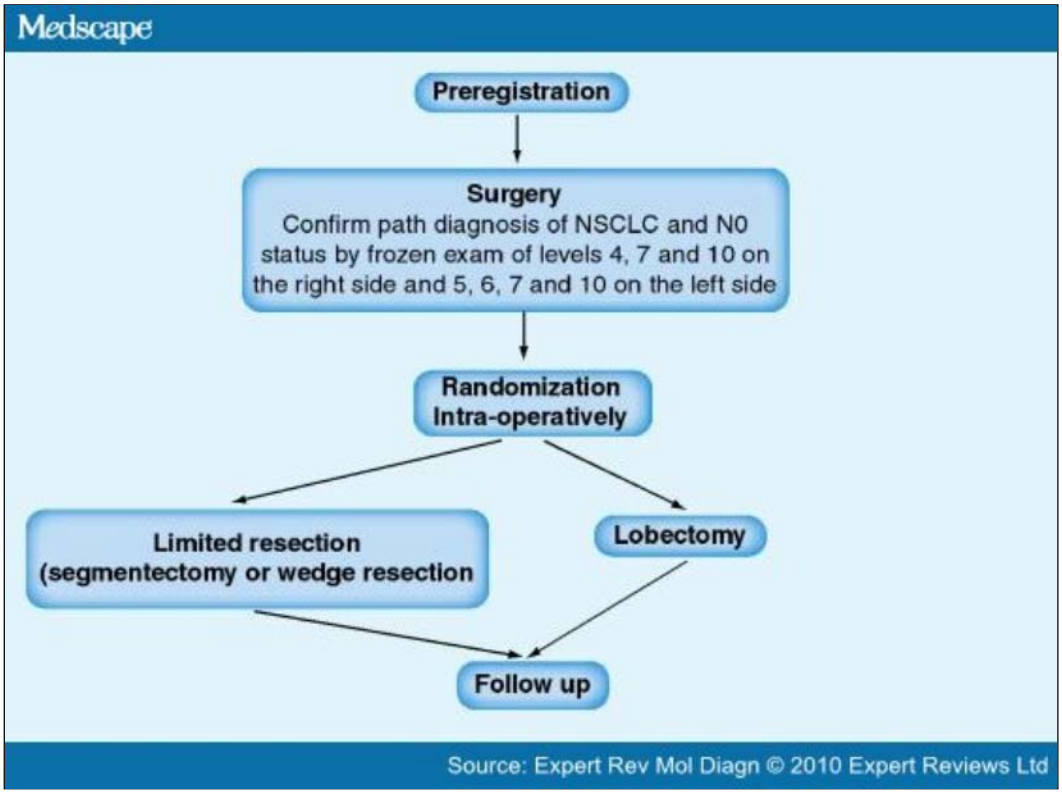

Figure 2. CALGB140530 study design.
NSCLC: Non-small-cell lung cancer

Nonsurgical Approach

A significant proportion of patients, particularly elderly patients with low cardiopulmonary function, are not candidates for surgery. Therefore, these patients either receive no treatment or are treated with conventional external-beam radiotherapy. Recently, the effectiveness of stereotactic radiation therapy (SRT) and radiofrequency ablation (RFA) was reported for these patients.

Stereotactic radiation therapy was first developed in the 1950s for the treatment of intracranial lesions. Technological developments have led to the application of this technique to extra-cranial sites, including the chest. In recent years, SRT has become available as a good treatment alternative for medically inoperable patients with stage I lung cancer.[137] Excellent local controls exceeding 85% can be obtained using SRT with low toxicity.[138–140] The largest trials of SRT treatment in stage I lung cancer were reported from Japan,[140,141] the USA,[142] Scandinavia[143,144] and The Netherlands.[138]

Radiofrequency ablation is a well-established modality in the treatment of unresectable liver tumors, in both primary malignancies and metastases.[145] Recently, several authors have evaluated RFA for the treatment of small primary lung tumors and lung metastases in patients who are medically inoperable.[146,147] During RFA, a radiowave-emitting probe is inserted into the tumor under CT guidance and is used to heat the tumor to 90–100°C, resulting in focal coagulative necrosis. The largest reported series showed that local control at 2 years ranged from 25% for T2 tumors to 64% for T1 tumors.[148] Zhu *et al.* performed a systematic review to assess the safety and efficacy of RFA.[149] All studies were classified as level-IV evidence and the conclusion is that RFA appears to be safe and may have a potential role in the treatment of unresectable lung tumors. A randomized controlled study comparing systemic chemotherapy alone versus percutaneous lung RFA and systemic chemotherapy would potentially provide meaningful information on this subject.

Therapy of Preinvasive Lesions

The clinical studies performed by an endoscopic follow-up showed that 32–37% of severe dysplasia and 56–78% of CIS are progressing to invasive SCC, while less than 10% of the lesions at stages lower or equal to moderate dysplasia follow this course.[142–144]

Early-stage lung cancers can be divided into two categories, the central and the peripheral type, depending on the site of origin of the tumor. In the peripheral type, the tumor is less than 2 cm in diameter and is located in a subsegmental or

more peripheral bronchus with no metastasis. In the early-stage central type, the tumor is located not beyond the level of a segmental bronchus, and is a CIS or shows only limited invasion of the bronchial wall; most patients with central type tumors have symptoms such as cough, sputum production and blood-tinged sputum (hemoptysis). Indeed, a whole range of successive histological grades has been shown for the central tumors: basal cell hyperplasia, squamous metaplasia, mild, moderate and severe dysplasia and CIS. Most investigators believe that these stages could be simplified into two major stages: lesions leading up to moderate dysplasia are called low grade, and lesions from severe dysplasia and up to CIS are high grade.

Patients with centrally located early lung cancer are often heavy smokers and have a considerably high risk of a second primary lung cancer. Therefore, these patients require treatment that will preserve their cardiopulmonary function. It has been reported that 70% of CIS is not detected during WLB, and that the prevalence of synchronous occult lesions after fluorescence bronchoscopy assessment might be higher than the previously reported values of 7–14%.[51,52,150]

Photodynamic therapy (PDT), a potential treatment for these cancers, uses a photosensitizer and laser irradiation to produce reactive oxygen in cells. In Japan,[151,152] the USA,[153] and many other countries, PDT is a treatment option for stage 0 (TisN0M0) and stage I (T1N0M0) centrally located early-stage lung cancer.[154] A prospective Phase II study on PDT with Photofrin for centrally located early-stage lung cancer was conducted in Japan[155] from 1989 to 1992. A total of 54 patients with 64 early-stage lung cancers were treated. The results were complete response in 50 (84.8%), partial response in six, and no response in three. This study demonstrated PDT with photofrin had an excellent effect on patients with centrally located early-stage lung cancer who have limited tumor invasion extending over a small area (≤1 cm). The major side effect of Photofrin is cutaneous photosensitivity. A second-generation photosensitizer, mono-l-aspartyl chlorin e6 (NPe6) has shown antitumor efficacy and rapid clearance from skin. In 1997, a multicenter II clinical study of centrally located early-stage lung cancer using NPe6 was conducted.[156] A total of 40 patients with 45 lesions were eligible for efficacy evaluation. Complete response was obtained in 84.6% of lesions (82.9% patients). This study demonstrated excellent antitumor effects and safety, especially low skin photosensitivity in patients with early-stage lung cancer.

Photodynamic therapy for 264 centrally located early-stage lung cancer lesions yielded an initial complete response rate of 84.8%.[26] It is useful for extending the therapeutic options and improving the prognosis of patients with centrally located early lung cancer. However, using PDT should be limited to small (<1 cm in diameter), superficial and visual lesions.[36] It has never been tested and validated in randomized controlled studies.

External-beam radiotherapy and intraluminal low-dose rate brachytherapy are likely to be done to the early central cancer in recent years though these were done to the advanced cancer as airway stenosis so far. This method can be irradiated to be deeper than the bronchial mucous layer.[157,158] A further number of cases and the term of the surveillance are necessary to evaluate effectiveness.

So far, the impact of these techniques remains limited as there are little data to suggest that there is a current role for these types of therapy in all but research instutions.

Perspective

Cancer screening is conceptually a good strategy for reducing the mortality rate of lung cancer. So far, none of the tested approaches have improved the specific mortality rate. The various techniques described have proven to have limited impact for detection and some with a high rate of false positive and consequent morbidity and mortality. The majority of these techniques are currently not in use clinically despite, in some cases, there being a long history of research. Considerable further research seems to be required to allow this field to mature. The use of CT, for example, is currently a highly controversial topic, as CT screening results in false positives, which drive to a presumed increase in the participant's anxiety (quality of life and cost–effectiveness issues), morbidity and mortality. Given the lead time bias, length time bias and possibility of over-diagnosis inherent in the single-arm models of these clinical trials, many questions remain unanswered for CT screening. Currently, ongoing randomized control trials of CT screening will hopefully lead to a reduction in mortality with CT screening. Advances in bronchoscopy and the expanding prevalence of sputum cytology have helped to detect central early lung cancer, but conventional bronchoscopy provides only a 30% chance to detect central early lung cancer. Recent endoscopic techniques, such as magnetic navigation bronchoscopy, improved the ability to diagnose distal nodules. These new tools are AFB, NBI, OCT and CFM. Bronchoscopy is rapidly developing. Advanced bronchoscopy will be able to help the diagnosis and staging in minimum-invasive tools with higher specificity.

New potential approaches such as new spiral CT technologies, new bronchoscopy technologies and noninvasive biomarker assays are promising. However, combining several techniques might lead to improved sensitivity and specificity

and it is expected that the early detection of lung cancer will be based on a sequential approach. In the future we could utilize early detection tests, both sensitive and noninvasive, followed by possible more specific and invasive tests that should be necessary. These tests would confirm the diagnosis of cancer and specify the histology and other characteristics of each specific tumor, identifying predictive biomarkers for response to treatment. However, there is a real need, mainly in the biomarker research, for a standardization of the measure and an effort towards validation of the tests in independent prospective cohorts.

Expert Commentary

Cancer screening is conceptually a good approach for reducing the mortality of lung cancer. So far, none of the tested approaches have improved the specific mortality rate. Further research is required to encourage this field to grow. Results of ongoing, prospectively randomized CT trials are expected. However, promising new approaches, such as new technologies of spiral CT and the development of noninvasive biomarkers tests, are underway. A sequential approach could be proposed in the future, from the most sensitive and the least invasive tests, to the most specific and if necessary more invasive.

Five-year View

The results of the ongoing randomized control trials of CT screening are expected to show that spiral CT could improve lung cancer mortality. New spiral CT technology should emerge, as well as the development of noninvasive biomarkers testing.

Sidebar

Key Issues

- The strong difference in lung cancer survival between treated early- and late-stage lung cancer has formed the rationale for lung cancer screening and better systemic therapy. Cancer screening is a conceptually good approach for reducing lung cancer mortality.
- When considering results of screening studies, several challenges, biases and issues should be kept in mind.
- From a population perspective, the ultimate measure of screening effectiveness is mortality reduction and not increased life spans.
- Routine screening for lung cancer using imaging is not yet recommended by any major medical organization. However, more scientific evidence is awaited from ongoing randomized control trials before deciding for or against imaging-based screening for lung cancer.
- Detection of molecular abnormalities in different clinically accessible specimens shows sensitivity and specificity up to 95 and 100%, respectively. However, none of these biomarker-based tests are recommended as a screening procedure. Further investigations and validations are required before their results can be used in any clinical application.
- A sequential approach could be the future using different tests starting from the less invasive and ending with the most invasive procedure.
- Surgical resection is the standard treatment in resectable
- Photodynamic therapy can be an option for the treatment of carcinoma *in situ* but should be limited to small (<1 cm in diameter) superficial lesions of which all margins can be visualized.

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Papers of special note have been highlighted as:

• of interest

•• of considerable interest

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