Early Detection of Lung Cancer: Clinical Perspectives of Recent Advances in Biology and Radiology


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Abstract

Lung cancer is the most common cause of cancer death in developed countries. The prognosis is poor, with less than 15% of patients surviving 5 years after diagnosis. The poor prognosis is attributable to lack of efficient diagnostic methods for early detection and lack of successful treatment for metastatic disease. Most patients (>75%) present with stage III or IV disease and are rarely curable with current therapies. Within the last decade, rapid advances in molecular biology, pathology, bronchology, and radiology have provided a rational basis for improving outcome. These advancements have led to a better documentation of morphological changes in the bronchial epithelium before development of clinical evident invasive carcinomas. This has changed our concept of lung carcinogenesis and emphasized the multistep carcinogenesis approach on several levels. Combined with the technical developments in bronchoscopic techniques, e.g., laser-induced fluorescence endoscope (LIFE) bronchoscopy, we now have improved methods to localize preinvasive and early-invasive bronchial lesions. With the LIFE bronchoscope, a new morphological entity (angiogenic squamous dysplasia) has been recognized, which might be an important biomarker and target for antiangiogenic chemoprevention agents. To reduce the mortality of lung cancer, these new technologies have been taken into the clinic in different scientific settings. The use of low-dose spiral computed tomography in the screening of a high-risk population has demonstrated the possibility of diagnosing small peripheral tumors that are not seen on conventional X-ray. A shift in the therapeutic paradigm from targeting advanced clinically manifest lung cancer toward asymptomatic preinvasive and early-invasive cancer is occurring. The present article reviews the recent advances in the diagnosis of preinvasive and early-invasive cancer to identify biomarkers for early detection of lung cancer and for chemoprevention studies.

Introduction

Lung cancer is the most common cause of cancer deaths in the countries of North America and other developed countries, accounting for 29% of all cancer deaths and more deaths than from prostate, breast, and colorectal cancer combined in the United States (1). Lung cancer will be diagnosed in ~170,000 new patients in the United States in the year 2000, and <15% of them will survive 5 years after diagnosis (1). The prognosis for the patients with lung cancer is strongly correlated to the stage of the disease at the time of diagnosis. Whereas patients with clinical stage IA disease have a 5-year survival of about 60%, the clinical stage II-IV disease 5-year survival rate ranges from 40% to less than 5% (2). Over two-thirds of the patients have regional lymph-node involvement or distant disease at the time of presentation (3). The poor prognosis is largely attributable to the lack of effective early detection methods and the inability to cure metastatic disease. The unsatisfactory cure rates supports efforts aimed at early identification and intervention in lung cancer.

Historically, the only diagnostic tests available for the detection of lung cancer in its early stages were chest radiography and sputum cytology. The efficacy of these tests as mass screening tools was evaluated in controlled trials sponsored by the NCI (1) and conducted at Johns Hopkins University, Memorial Sloan-Kettering Cancer Center, and the Mayo Clinic during the 1970s (4–6). The principal goal of these studies was to determine whether a reduction in lung cancer mortality could be achieved by adding sputum cytology testing to annual screening by chest radiography. Results from these trials showed that both tests could detect presymptomatic, early-stage carcinoma, particularly of squamous cell type. Resectability and survival rates were found to be generally higher in the study groups than in the control groups. However, improvements in resectability and survival did not lead to a reduction in overall lung cancer mortality, the most critical end point. A subsequent study of 6346 Czechoslovakian male smokers also found no reduction in lung cancer mortality after dual screening by chest radiography and sputum cytology (7). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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The abbreviations used are: NCI, National Cancer Institute; CIS, carcinoma in situ; CT, computed tomography; ASD, angiogenic squamous dysplasia; TSG, tumor suppressor gene; LOH, loss of heterozygosity; hnRNP, heterogeneous nuclear ribonucleoprotein; SPLC, second primary lung cancer; BAL, bronchoalveolar lavage; SCLC, small cell lung carcinoma; WLB, white light bronchoscopy; LIFE, laser-induced fluorescence endoscope; ELCAP, Early Lung Cancer Action Project; PET, positron emission tomography; FDG, [18F]fluoro-2-deoxyglucose.

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and sputum cytology (7). The negative results from these screening studies lead the NCI and other health policy and research groups to conclude that mass screening programs involving periodic sputum cytological evaluation and chest radiographs could not be justified. However, controversies in the methodology and interpretation of the data from these studies have later been extensively discussed (8, 9). One additional study of annual chest X-ray screening is currently being conducted by the NCI; The Prostate-, Lung-, Colorectal-, and Ovarian (PLCO) screening trial. This trial includes individuals 55–74 years old, but they are not selected for this trial on the basis of high risk for lung cancer (e.g., smoking history with >20 pack-years).

The failure of clinical trials to demonstrate the efficacy of sputum cytology and chest radiography as mass screening tools has resulted in a search for better diagnostic approaches for early lung cancer detection that take advantage of recent developments in molecular biology, gene technology, and radiology (10). Furthermore, as has been the case for mammography screening for breast cancer, it has also been important to identify risk groups for lung cancer.

Although, much is known about predisposing factors, natural history, and the outcome based on histology and stage, our understanding remains very incomplete in many areas. What are the early premalignant changes molecularly, biochemically, and morphologically? Which changes are reversible and which are not? What research tools are available to provide answers to these questions? The identification of preinvasive lesions allows for developing promising methods for early intervention (11). The therapeutic paradigm and focus are today shifting from targeting only clinically verified lung cancer as previously toward targeting the premalignant and early-malignant lesions. Furthermore, the prospect of lung cancer screening has today become more meaningful as a consequence of recent developments in biology and radiology and better possibilities to define high-risk populations most suitable for lung cancer screening (12).

The present article will focus on the clinical perspectives of our biological knowledge of premalignant and early-malignant lesions and the potential of the recent technological advancement for early diagnosis of lung cancer.

Pathology of Preinvasive and Early Invasive Bronchial Lesions

Most of the efforts to classify lung cancer have been directed toward invasive carcinoma (13). However, better understanding of the pathogenesis of lung cancer aroused renewed interest in morphological abnormalities that fall short of invasive carcinoma but may indicate initiation of carcinogenesis. These morphological abnormalities are referred to as preinvasive lesions and are shown in Fig. 1. The last edition of the WHO classification of lung tumors included the classification of preinvasive lesions as a separate section. Numerous recent studies have indicated that lung cancer is not the result of a sudden transforming event in the bronchial epithelium but a multistep process in which gradually accruing sequential genetic and cellular changes result in the formation of an invasive (i.e., malignant) tumor. Mucosal changes in the large airways that may precede or accompany invasive squamous carcinoma include hyperplasia, metaplasia, dysplasia, and CIS (14). Hyperplasia of the bronchial epithelium and squamous metaplasia have generally been considered reversible, and not premalignant in the sense of squamous dysplasia and CIS (15).

Squamous metaplasia is a common finding, especially as a response to cigarette smoking. Peters et al. (16) studied bronchoscopic biopsies from six sites in 106 heavy cigarette smokers; Squamous metaplasia was noted at one or more biopsy sites in approximately two-thirds of the group, and one-fourth showed squamous metaplasia in three or more biopsy sites. The incidence of squamous metaplasia increased with smoking history and was highest in individuals who had smoked more than two packs of cigarettes a day. Auerbach et al. (17) noted similar findings in autopsy tissues; basal cell hyperplasia and squamous metaplasia are increased in smokers in proportion to smoking history. Hyperplasia and metaplasia are believed to be reactive changes in the bronchial epithelium, as opposed to true preneoplastic changes (17, 18). The reasons for this include: (a) they are frequently found in association with chronic inflammation, and may be induced by mechanical trauma; (b) they spontaneously regress after smoking cessation; (c) in chronic smokers, the molecular changes present in these lesions are similar to those present in histologically normal epithelium; and (d) there are no reports linking their presence to increased risk for developing lung cancer. In contrast, moderate-to-severe dysplasia and CIS lesions seldom regress after smoking cessation (19).

Dysplasia and CIS are changes that frequently precede squamous cell carcinoma of the lung. Saccomanno et al. (20) studied more than 50,000 samples from 6,000 men, many of whom had worked in the uranium mining industry. Both smoking and uranium mining (radon exposure) were found to be associated with increased incidence of dysplasia, CIS, and invasive cancer. The studies of Saccomanno et al. established that increasing degrees of sputum atypia may be recognized an average of 4–5 years before the development of frank lung carcinoma.

Another question is: which grades of sputum atypia progress to cancer? From the Johns Hopkins cohort of the NCI chest X-ray/sputum screening trial, we know that among individuals with moderate atypia on sputum screening, ~10% developed known cancer up to 9 years later. Among individuals with severe atypia on the sputum screening, >40% developed known cancer during the same time period (21). Although there are data in the literature showing the relationship between sputum atypia and subsequent invasive cancer, there is still very little information about the histological progression in the bronchial mucosa in the high risk populations. In a recent publication, nine patients with CIS were followed with autofluorescence bronchoscopy at regular intervals, and 5 (56%) had progression to invasive cancer despite endobronchial therapy (22). The number of invasive cancers might even have been higher if treatment had not been not given. Ongoing studies of high-risk subjects (e.g., the Colorado sputum cohort study) including serial follow-up bronchoscopies will provide evidence related to the frequency of development of invasive lung cancer as it relates to smoking history, airflow obstruction, and sputum atypia.

Since the previous WHO-classification was published in

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Fig. 1  A, squamous metaplasia. The cells are widely dispersed, with a regular maturation from the basal region to the top. There is keratinization, and the nuclei/cytoplasmic ratio is low. B, moderate dysplasia with ASD. Hypercellularity of the epithelium with incomplete maturation and micropapillary invasion of capillaries are seen. The nuclei/cytoplasmic ratio is high. C, severe dysplasia. There is marked pleomorphism of the cells with irregularity and prominent nucleoli.
1981, two nonsquamous lesions have been added to the WHO classification of premalignant lesions: atypical alveolar hyperplasia and diffuse idiopathic neuroendocrine cell hyperplasia (13). Both of these lesions are diagnosed rarely. The former consists of lesions <5 mm in diameter and composed of a peripheral epithelial cell proliferation with minimal cytological atypia or stromal response and resembles bronchioloalveolar carcinoma. The lesion has been seen in lung specimens resected for lung cancer, but no prospective significance of this lesion has been reported. However, this morphological lesion may play a role for the pathogenesis of peripheral lung adenocarcinomas (23, 24). The resolution of spiral CT (currently about 3 mm) approaches the diameter of these lesions, and it is anticipated that atypical alveolar hyperplasia will be increasingly encountered in subjects undergoing this procedure (25). Diffuse idiopathic neuroendocrine cell hyperplasia consists of a patchy increase in the number of well-differentiated neuroendocrine cells in the bronchioles. This process may result in the formation of small carcinoid tumors, and for this reason it is considered “preinvasive.” To date, small cell carcinomas have not been associated with this lesion (13).

Recently, the use of fluorescence bronchoscopy (see below) has increased the recognition of dysplastic lesions in the large airways and a new morphological entity, ASD, was identified (26). Dysplasia of bronchial epithelium in “micropapillomatosis” and the possible link between angiogenesis and preinvasive bronchial epithelial dysplasia were recognized as early as 1983 by Muller and Muller (27), who also described the ultrastructure of these lesions. It has been suggested that this angiogenesis, which is recognized as capillary loops projecting into the dysplastic bronchial lining, is responsible for the reduced fluorescence seen in dysplastic lesions by LIFE bronchoscopes (Figs. 1 and 3; Ref. 26). Future prospective studies will show whether this morphological entity is correlated with a progression to lung cancer so as to be a target for the use of antiangiogenic agents for chemoprevention.

In general, there are several questions/problems relating to premalignant lesions, which will be addressed in future studies:

(a) The morphological criteria for premalignant and early-malignant changes, both on sputum cytology and in bronchial biopsies, have to be validated for intra- and interobserver reproducibility.

(b) Uniform and reproducible morphological/cytological criteria have to be published more extensively, and a training set of slides should be available. By the use of Internet technology, this could be more easily facilitated (28).

(c) The correlation of sputum atypia and histological changes in the bronchi in high-risk population is not well defined.

(d) The natural course of preinvasive changes in the bronchi from the high risk subjects needs to be clarified through longitudinal, prospective studies with reference to histological changes in the bronchi. Ongoing longitudinal studies with fluorescence bronchoscopy and multiple biopsies with histology and other biomarkers will define the ability of these markers to assess for risk.

(e) What is the pathology/biology of the small, often peripherally located, tumors (3 mm in diameter), which are more often diagnosed with newer radiological techniques (e.g., low-dose spiral CT)?

(f) Optimization of the tissue procurement and processing techniques are important. Distinction of reactive from neoplastic processes is usually straightforward, but diagnostic difficulties may arise in the case of (a) inadequate or poorly prepared histological material to evaluate and (b) the presence of cytological atypia in epithelium stimulated by inflammation, viral infection, radiation, or chemotherapy.

(g) DNA array analyses of gene expression: will it be useful? How to collect proper mRNA? Can mRNA extracted from microdissected cells obtained at bronchoscopy be globally amplified and still remain representative of RNA present in situ?

Biology of Lung Carcinogenesis and Potential Early Detection Markers

Lung cancer is the end-stage of multiple-step carcinogenesis, in most cases driven by genetic and epigenetic damage caused by chronic exposure to tobacco carcinogens. The genetic instability in human cancers appears to exist at two levels: at the chromosomal level, including large scale losses and gains; and at the nucleotide level including single or several base changes (29). Lung cancers harbor many numerical chromosomal abnormalities (aneuploidy) and structural cytogenetic abnormalities including deletions and nonreciprocal translocations (30). At least three classes of cellular genes are involved: proto-oncogenes, TSGs, and DNA repair genes. Oncogenic activation often occurs via point mutations, gene amplification, or chromosomal rearrangement, whereas TSGs are classically inactivated by the loss of one parental allele combined with a point or small mutation or aberrant methylation of a target TSG in the remaining allele. Additionally, dysregulated gene expression (either increased or decreased expression) can occur by other, as yet unknown, mechanisms (30). Present studies have not yet confirmed a prominent role for abnormalities of DNA repair genes in lung cancer.

Pneoplastic cells contain several molecular genetic abnormalities identical to some of the abnormalities found in overt lung cancer cells (Fig. 2). These include allele loss at several loci (3p, 9p, 8p, and 17p), myc and ras up-regulation, cyclin D1 overexpression, p53 mutations, and increased immunoreactivity, bcl-2 overexpression and DNA aneuploidy (31–35). Allelotyping of precisely microdissected, pneoplastic foci of cells suggests that the earliest changes in the bronchial epithelium is allele loss at chromosome regions 3p, then 9p, 8p, 17p, 5q, and then ras mutations (36–39). The biological meaning of LOH is only vaguely understood. Recent evidence suggests that LOH may be a consequence of mitotic recombination, that there is only infrequent physical loss of genetic loci, and that LOH probably precedes chromosomal duplication (40). Allelic loss would thus be significant primarily in the presence of mutation in the retained allele, and gene dosage would not be expected to exert a phenotypic effect in LOH. Some reports have indicated that ras activation occurs at early carcinoma stages (34). Histologically normal bronchial epithelium adjacent to cancers has also been shown to have certain genetic losses. Atypical adenomatous hyperplasia, the potential precursor lesion of adenocarcinomas, often have Ki-ras mutations (41).
Molecular changes have been found not only in the lungs of patients with lung cancer, but also in the lungs of current and former smokers without lung cancer (18, 42, 43). These observations are consistent with the multistep model of carcinogenesis and “field cancerization” process, whereby the whole region is repeatedly exposed to carcinogenic damage (tobacco smoke) and is at risk for developing multiple, separate, clonally unrelated foci of neoplasia. The widespread aneuploidy that occurs throughout the respiratory tree of smokers supports this theory (44). However, the presence of the same somatic p53 point mutation at widely dispersed preneoplastic lesions in a smoker without invasive lung cancer indicates that expansion of a single progenitor clone may spread throughout the respiratory tree (45). These molecular alterations might thus be important targets for use in the early detection of lung cancer and for use as surrogate biomarkers in the follow-up of chemoprevention studies. Detection of these mutant cells should be possible with the different molecular techniques in accessible specimens. The prospects of diagnosing these biological abnormalities in multiple types of clinical specimens are discussed below.

**Specimens for Clinical Testing: Sputum**

Since the 1930s, cytological examination of sputum has been used for the diagnosis of lung cancer (46). Cytological examination of sputa, especially multiple samples, is helpful for the detection of central tumors arising from the larger bronchi (e.g., squamous cell- and small cell carcinomas). Exfoliated cells from peripheral tumors, such as adenocarcinomas, arising from the smaller airways (small bronchi, bronchioles, and alveoli), especially those less than 2 cm in diameter, can be detected only occasionally in sputum samples. This has become of greater importance because the changes in cigarette exposition...
The sensitivity of sputum cytology for early lung cancer is only in the 20%–30% range from screening studies, but by adhering to proper specimen collection, and processing and interpreting criteria, the yield can be substantially improved (50, 51). The data on the reliability of the sputum are conflicting (52–54). Browman et al. (50, 51) reported low agreement within observers (27–60%) and across observers (13–50%). Within-1-category intraobserver agreement was also the case for interobserver agreement. The variation in intra- and interobserver agreement seems to depend on experience among the cytotechnicians/cytopathologists and the composition of categories studied. A higher degree of agreement is obtained for higher grades of dysplasia (54). Risse et al. (55) showed that the ability to detect premalignant conditions is dependent on the number and type of cells present in the deeper airways, suggesting a mode of improvement that is unrelated to observer reliability. MacDougall et al. (56) concluded that sputum cytology was too insensitive and insufficiently accurate to be included in the routine work-up of any patient suspected of having lung cancer. To improve the reliability of sputum cytology examinations a simplification of the diagnostic categories from 6 (normal; squamous metaplasia; mild, moderate, and severe atypia; and carcinoma) to 2–3 categories have been proposed (54). Future clinicopathological studies will be required to validate this concept.

To improve the sensitivity of sputum examination as a population-screening tool for the detection of early lung cancer, several approaches are currently under development.

**Immunostaining.** Annual sputum specimens obtained from individuals screened at Johns Hopkins were obtained, and the patients were monitored for 8 years (57). Because the clinical outcome of these patients was known, archival sputum specimens were screened for the presence of biomarkers that could indicate the presence of lung tumors in an early, preinvasive stage. In an attempt to distinguish the pattern of marker expression Tockman et al. (58) studied two monoclonal antibodies. Positive staining predicted subsequent lung cancer approximately 2 years before clinical recognition of the disease, with a sensitivity of 91% and a specificity of 88% (58). One of these antibodies (703 D4) had a higher sensitivity and was later identified as recognizing hnRNP A2/B1 (59). The role of hnRNP A2/B1 overexpression for detecting preclinical lung cancer has been studied in a large high-risk population including 6000 Chinese tin miners who were heavy smokers and who had an extraordinary rate of lung cancer (60). The results from this study indicated that detection of hnRNP A2/B1 overexpression in sputum epithelium cells was 2- to 3-fold more sensitive for detection of lung cancer than standard chest X-ray and sputum cytology methods. The method was particularly effective in identifying early disease (60). The sensitivity was 74% versus 21% for cytology and 42% for chest X-ray. However, the biomarker had a lower specificity (70%) compared with cytology (100%) and chest radiograph (90%). An ongoing clinical trial is evaluating the performance of the A2/B1 protein as a biomarker for the early detection of SPLC. The patients at risk for SPLC have the highest incidence of lung cancer (2–5%) among asymptomatic populations (61). In this trial, 13 SPLCs were identified by A2/B1, and the sensitivity and specificity were 77–82% and 65–81%, respectively. Among the cases identified as positive by immunocytochemistry and image cytometry, 67% developed SPLC within 1 year (62). Whereas the previous immunocytochemistry studies on material from the older screening material from the NCI-supported screening studies were made on sputum cells cytologically classified with moderately or gravely atypical metaplastic appearance, the latter studies have been done on cytologically “normal appearing” cells. More recently Squeka et al. (63) reported the confirmation of the value of overexpression of hnRNP A2/B1 to detect preclinical lung cancer in Japan. Efforts to improve the sensitivity of hnRNP markers are ongoing (64).

**PCR Techniques.** PCR techniques have been used for the evaluation of molecular biomarkers for early lung cancer detection. In a pilot study with selected patients from the Johns Hopkins Lung Project (JHLP), 8 (53%) of 15 patients with adenocarcinoma or large cell carcinoma were detected by mutations in sputum cells from 1 to 13 months before clinical diagnosis (65). However, the method seemed to be less sensitive than the protein marker described above, and the identification of specific gene abnormalities is further limited by the need to know the specific mutation sequence with which to probe the sputum specimens. Currently, this approach is not practical for screening undiagnosed individuals. Future advances in gene chip technology may permit testing for all possible mutations of common onecogens and TSGs in clinical specimens of asymptomatic individuals (62).

Microsatellite markers are small repeating DNA sequences found in the noncoding regions of a gene. PCR amplification of these repeat sequences provides a rapid method for assessment of LOH and facilitates the mapping of suppressor genes (66, 67). Microsatellite alterations are extension or deletions of these repeated elements. Detection of microsatellite alterations in histological or cytological specimens may facilitate the detection of clonal preneoplastic or neoplastic cell populations. Although the detection of microsatellite alterations does not indicate the specific genetic change in the tumor, detection of clonal cell populations might serve as a cancer screening marker (65). Identical alterations have been found in lung cancers and corresponding sputum samples demonstrating minimal atypia (68).

The p16 gene is located on the short arm of chromosome 9(9p21) and is frequently mutated or inactivated in tumors and cell lines derived from lung cancer (69, 70). Belinsky et al. (71) measured hypermethylation of the CpG islands in the sputum of lung cancer patients and demonstrated a high correlation with early stages of non-small cell lung cancer, which indicated that p16 CpG hypermethylation could be useful in the prediction of future lung cancer. However, prospective studies are needed to evaluate the role of p16 hypermethylation as a marker for early lung cancer detection. Multiple other genes are inactivated by hypermethylation in lung cancer (72), and the detection of hypermethylation may be useful for risk assessment and early diagnosis.

**Computer-assisted Image Analysis.** Computer-assisted image analysis was initially used to detect malignancy-associated changes (e.g., subvisual or nonobvious changes in the
distribution of DNA in the nuclei of histologically normal cells in the vicinity of preinvasive or invasive cancer; (73). In a retrospective analysis of sputum cytology slides, malignancy-associated changes alone correctly identified 74% of the subjects who later developed squamous cell carcinoma (74). The technique has been improved, and recent data showed sensitivities of 75% for stage 0/l lung cancer and 85% for adenocarcinomas with a specificity of 90% (75). This quantitative microscopy technique allows the examining of thousands of cells per slide within a relative short time. Similar techniques have been approved in the United States for cervical cancer screening, and might, in the future, play a role for lung cancer screening. However, no prospective clinical studies has evaluated this technology in a larger lung cancer screening setting.

**High Throughput Technology.** With future advances in gene chip technology, it might become feasible to probe for expression of multiple genes in sputum specimens of asymptomatic individuals. However, this requires a large amount of undegraded RNA from respiratory tract cells. With the high throughput technology, a higher sensitivity might be achieved by using multiple markers at the cost of achieving a lower specificity, which would be undesirable for a screening study.

In conclusion, we need to reevaluate the role of sputum cytology for screening and early detection of lung cancer because of advances in biomarkers and technology. Ongoing studies with standard and biomarker analysis in high-risk groups might change the previous negative attitude and provide a new perspective on sputum cytology as a mass screening tool when applied in a high-risk population. Adding different molecular diagnostic tests gives the possibility for early diagnosis far in advance of clinical presentation. However, validation of the tests in larger prospective studies is necessary, and the individual tests have to be compared with each other to define the role of early diagnosis in the overall management of high-risk subjects. Furthermore, health economic issues have to be considered.

**Specimens for Clinical Testing: BAL**

BAL involves the infusion and reaspiration of a sterile saline solution in distal segments of the lung via a fiberoptic bronchoscope. Ahrendt et al., (76) examined a series of 50 resected non-SCLC tumor patients and compared the tumor and BAL with regard to molecular markers including p53 mutations, K-ras mutation, the methylation status of the CpG island of the p16 gene, and microsatellite alteration (Tables 1 and 2). With the possible exception of the test for microsatellite alteration, all of the tests had relatively high sensitivity and could detect mutant cells in the presence of a large excess of normal cells. The frequencies of these changes in the tumors ranged from 27% (for K-ras mutations) to 56% (for p53 mutations). As expected, p53 mutations were more frequent in central (predominantly squamous cell) tumors, and K-ras mutations were more frequent in peripheral (predominantly adenocarcinoma) tumors. The specificity was high (nearly 100%) because, with the exception of microsatellite alterations, the same genetic change in BAL sample as in tumors was always found, but the sensitivity was low, and in only 53% of tumors that contained molecular lesions were the same abnormalities detected in corresponding BAL fluids. Specifically, the tests were least helpful in the group of patients in whom improved diagnostic abilities are most needed, those with small, peripherally located tumors (77). Unfortunately, the investigators were not able to compare the molecular tests with routine cytopathological analysis of the BAL specimens. The sensitivity of the molecular tests in BAL specimens has to be improved, and we need to know the results from subjects at increased risk (current and former smokers without lung cancer and survivors of previous cancer of the upper respiratory tract) and subjects with chronic lung diseases as well as results from healthy never smokers.

A European group has previously shown that genetic alterations detected in DNA from bronchial lavage of individuals with lung cancer were also found in individuals with no evidence of malignant disease (78), which raises the question about the specificity of such molecular damage in neoplastic conditions. To improve the sensitivity and specificity of detecting allelic imbalance in lung tumors, high throughput PCR-based microsatellite assays have been established (79). In a recent study by Fielding et al. (80), the up-regulation of hnrNP A2/B1 was found to be a promising marker in BAL for the detection of premalignant and malignant bronchial lesions with a diagnostic sensitivity of 96% and a specificity of 82%.

It is too early yet to make conclusions as to whether BAL examinations will add to other pathological/molecular biological clinical studies. To obtain diagnostic material for BAL bronchoscopy is required, and we do not have any data that compare BAL examinations with biopsies. Thus, we do not know whether BAL is a valuable adjunct to the biopsies taken under the same bronchoscopy procedure.

**Specimens for Clinical Testing: Peripheral Blood**

For many years scientists have searched for a lung cancer-specific tumor marker that could be detected in peripheral blood. Optimism was raised in the “early” immunocytochemistry era by the use of monoclonal antibodies raised against more-or-less specific epithelial epitopes. In the search for epithelial cells in peripheral blood and bone marrow, monoclonal antibodies against cytokeratin have been used. However, these reactions are clearly not cancer-specific, and some antibodies have been shown to cross-react with normal blood or bone marrow elements (81, 82). Another explanation could be that cells from the macrophage/monocyte system may contain proteins derived from the primary tumor that have undergone necrosis and apoptosis and that these processed proteins are recognized by the antibodies (82). On the basis of “traditional” immunocytochemistry, no markers have been able to detect premalignant or early-malignant disorders based on a peripheral blood sample. However, with the development of DNA technologies, new possibilities have been raised, and, with the use of PCR techniques, some promising reports have been published.

Nanogram quantities of DNA circulating in blood are present in healthy individuals (83, 84). Tumor DNA is also released into the plasma component in increased quantities (85, 86). Thus, the plasma and serum of cancer patients is enriched in DNA, an average four times the amount of free DNA as compared with normal controls (87). In a study by Chen et al. (88), a comparison of microsatellite alterations in tumor and plasma DNA was done in SCLC patients, and 93% of the patients with
In conclusion, the limited direct accessibility of lung carcinomas has led to efforts to identify tumor-associated soluble markers in serum or plasma. Many of the currently recognized soluble markers were first identified as “tumor” markers but, when evaluated in nonneoplastic tissue, have often been found in normal cells as well as in tumors. For early detection of lung cancer, we need more clinical data evaluating these new molecular biological markers from multiple sites, especially in high-risk groups.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Ref.</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Tumor tissue</td>
<td>Numerous</td>
<td>Mixture of cell types, may require microdissection (139). Extensively used for most studies. Alcohol-fixed fine-needle aspirates may be used for mutational and other studies.</td>
</tr>
<tr>
<td>Sputum</td>
<td>65, 68, 71, 74</td>
<td>Respiratory cells usually in small minority. Most samples fixed in Saccomanno’s fixative. Several studies have been performed on these specimens many years later.</td>
</tr>
<tr>
<td>Surrogate organ</td>
<td>140</td>
<td>Predominantly squamous epithelial cells. Buccal smears, brushings of tongue or tonsil may be explored as potential surrogate organs resulting from the field effect of tobacco damage of the entire upper aerodigestive tract. This concept needs to be confirmed.</td>
</tr>
<tr>
<td>Bronchial brush/wash</td>
<td>141, 142, 143</td>
<td>Predominantly respiratory cells. Fresh, frozen, or alcohol-fixed samples are suitable for multiple studies including FISH.†</td>
</tr>
<tr>
<td>Bronchial tissues</td>
<td>42, 43, 45, 144, 145</td>
<td>Usually from bronchial biopsies, but may be obtained from surgical resection specimens. Formalin fixation and paraffin embedding required for histological diagnosis, although EASI preps may permit identification and isolation of subpopulations. Paraffin sections may be used for genotyping polymorphisms, for allelotyping, and for in situ hybridization.</td>
</tr>
<tr>
<td>BAL fluids</td>
<td>76, 78, 146, 147, 148</td>
<td>BAL fluids are useful for examining the peripheral airway cells, which are the precursor cells of most adenocarcinomas. Numerous mononuclear cells present. Enrichment of epithelial cells desirable.</td>
</tr>
<tr>
<td>Blood components</td>
<td>72, 92, 149</td>
<td>Analysis of circulating tumor cells and genetic material shed by dying tumor cells into the plasma component may yield useful biological and diagnostic information. Gene mutations and presence of epithelial cell markers have been used to detect circulating tumor cells. Gene mutations, allelic loss, microsatellite alterations, and aberrant methylation have been used to identify tumor cell DNA released into the fluid compartment.</td>
</tr>
<tr>
<td>Tissue for molecular staging</td>
<td>150, 151</td>
<td>Although little data exists for lung cancers, regional lymph nodes, sentinel lymph nodes, and surgical resection margins have been used in other tumor types for molecular staging.</td>
</tr>
<tr>
<td>Tumor cell lines</td>
<td>152, 153</td>
<td>Provide an unlimited self-replicating source of high-quality molecular reagents and have been used for numerous studies. Cell lines may or may not reflect the properties of the tumors from which they were derived (26), although they probably represent cellular subpopulations (27). Aggressive metastatic tumors are more likely to be successfully cultured (28) resulting in skewed data.</td>
</tr>
<tr>
<td>Cultures of nonmalignant tissues</td>
<td>154, 155</td>
<td>Epithelial cultures may be useful for studying molecular changes during multistage pathogenesis. Temporary as well as a few immortalized cultures from nonmalignant epithelial cells have been established. B-lymphoblastoid cultures are useful for linkage analysis, for genetic susceptibility studies, and for allelotyping corresponding tumors.</td>
</tr>
<tr>
<td>Nonmalignant tissue from patients and from cancer-free relatives</td>
<td>156, 157, 158</td>
<td>Tissues such as buccal smears, tumor-free lymph nodes, and peripheral blood mononuclear cells are useful as controls for linkage analysis, for genetic susceptibility studies, and for allelotyping corresponding tumors.</td>
</tr>
</tbody>
</table>

† FISH, fluorescence in situ hybridization; EASI, epithelial aggregate separation and isolation.
have been eliminated, but it remained a significant problem. Differences by autofluorescence from normal tissue should then be overcome. To reduce autofluorescent signals compared with normal tissue autofluorescence (500–580 nm), and interference with tissue autofluorescence, a new laser photodynamic diagnostic system was developed (101). This system detected tumor-specific drug fluorescence at 630 nm wavelength, which is far from normal tissue autofluorescence (500–580 nm), and interference by autofluorescence from normal tissue should then have been eliminated, but it remained a significant problem (102).

Another approach was developed by Palcic et al. (103), who noticed the lack of autofluorescence in the tumor lesions by using blue light (442 nm) rather than white light to illuminate the bronchial surface. They amplified the difference in autofluorescence between normal, premalignant, and tumor tissue for the bronchial surface. They amplified the difference in autofluorescence between normal, premalignant, and tumor tissue for the bronchial surface. Using a high-quality-charge coupled device and special algorithm, the LIFE was developed, taking advantage of the principle that dysplastic and malignant tissues have different optical properties. Western blotting often used for detection of protein expression. In situ hybridization for message expression can be performed on paraffin-embedded tissues and, thus, can be used to investigate multistage pathogenesis. Microarray techniques offer promise of examining all or most of the genome but currently require relatively large amount of high-quality RNA from purified cell populations. Sage technique useful for investigation and identification of expressed genes. Similarly, advances in proteomics will permit simultaneous detection of multiple proteins. Numerous immunohistochemical studies of oncogene expression have been used to study multistage pathogenesis. Of particular interest, hnrnp expression on exfoliated epithelial cells in sputum samples may predict for development of cancer.

**Table 2 Molecular approaches for lung cancer investigation**

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Ref.</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene mutations</td>
<td>159, 160, 161</td>
<td>Widely used technique, especially for p53 and ras genes. Often used to determine the role of a newly discovered gene in the pathogenesis of lung cancer. May be of diagnostic and prognostic significance. Multiple methodologies available.</td>
</tr>
<tr>
<td>Allelotyping</td>
<td>18, 158</td>
<td>Useful as a partial substitute for mutational analysis and for determining the chromosomal locations of putative tumor suppressor genes. Widely used to study multistage pathogenesis. Readily performed on formalin-fixed and microdissected tissues. Increasing use of genotyping using automatic sequencers.</td>
</tr>
<tr>
<td>Gene expression at RNA and protein level</td>
<td>145, 162, 163, 164, 165, 166</td>
<td>Northern blotting and reverse transcription-PCR are widely used to investigate gene expression. Western blotting often used for detection of protein expression. In situ hybridization for message expression can be performed on paraffin-embedded tissues and, thus, can be used to investigate multistage pathogenesis. Microarray techniques offer promise of examining all or most of the genome but currently require relatively large amount of high-quality RNA from purified cell populations. Sage technique useful for investigation and identification of expressed genes. Similarly, advances in proteomics will permit simultaneous detection of multiple proteins. Numerous immunohistochemical studies of oncogene expression have been used to study multistage pathogenesis. Of particular interest, hnrnp expression on exfoliated epithelial cells in sputum samples may predict for development of cancer.</td>
</tr>
<tr>
<td>Molecular cytogenetics</td>
<td>40, 167, 168, 169, 170</td>
<td>In situ hybridization studies of fixed materials or using smears has provided considerable information about numerical and structural changes.</td>
</tr>
<tr>
<td>Comparative genomic hybridization</td>
<td>171, 172</td>
<td>Useful for detection of gene amplifications. Less sensitive for the detection of regions of allelic loss.</td>
</tr>
<tr>
<td>Morphometric studies</td>
<td>74, 173, 174</td>
<td>May be applied to paraffin-embedded tissues. Useful for determining aneuploidy and for measuring a number of nuclear and cytoplasmic parameters.</td>
</tr>
</tbody>
</table>

**Specimens for Clinical Testing: Bronchoscopy**

WLB is the most commonly used diagnostic tool for obtaining a definite histological diagnosis of lung cancer. Bronchoscopy has major diagnostic limitations for premalignant lesions. Because these lesions are only a few cells thick (0.2–1 mm) and have a surface diameter of only a few millimeters, they rarely are observed as visual abnormalities. Woolner (95) reported that squamous cell CIS was visible to experienced bronchoscopists in only 29% of cases. To address this limitation, fluorescence bronchoscopy was developed. Early studies of fluorescence bronchoscopy entailed the use of fluorescent drugs (hematoporphyrin dyes) that were preferentially retained in malignant tissue (96). Although, studies evaluating this approach did, in fact, show that early invasive and in situ cancers could be localized, the detection of dysplasia remained problematic (97–100). Furthermore, the development of photodynamic diagnostic systems was hampered by problems including skin photosensitizing and interference with tissue autofluorescence. To overcome these problems, a new laser photodynamic diagnostic system was developed (101). This system detected tumor-specific drug fluorescence at 630 nm wavelength, which is far from normal tissue autofluorescence (500–580 nm), and interference by autofluorescence from normal tissue should then have been eliminated, but it remained a significant problem (102).
strated by Venmans et al. (107). In their study, the diagnostic sensitivity increased from 67 to 80% when comparing the first and the second half of the study. The use of the LIFE device in conjunction with WLB improved the detection rate of preneoplastic lesions and CIS significantly (Table 3). Kurie et al. (106) looked for more subtle tissue transformation, but their study included few patients with moderate dysplasia or worse. No improvement in the evaluation of metaplasia index was observed by the use of LIFE bronchoscopy. Thus, differences in the study population might explain the different conclusion. There are still no clinical studies with sufficient long-term data showing that moderate dysplasia is the most relevant clinical predictor of eventual malignancy. Limitations in making conclusions from the existing studies are also the potential methodological bias related to the order in which the different bronchoscopy procedures are done and whether the same examiner has performed both procedures. To address these issues, a prospective randomized study between LIFE bronchoscopy and WLB was done at the University of Colorado Cancer Center. The study design included a randomization with regard to the order of procedure as well as the order of the individual bronchoscopist (109). The order of the procedure and of the individual bronchoscopist did not affect the results. The study also demonstrated a significantly higher sensitivity in detecting premalignant lesions visualized by the LIFE, but at the cost of a lower specificity (109). The reason for the low diagnostic specificity found with the LIFE bronchoscopy in the different studies might be attributable to the visualization of more abnormal foci with the LIFE bronchoscope, with the consequence that a larger number of biopsies were taken and, thus, there was a higher risk of more false-positive results. The use of LIFE bronchoscopy has led to the identification of a new morphological entity, the ASD, which is described above. In a recent morphological study angiodysplastic changes were frequently found in preneoplastic

Fig. 3 A, normal WLB and normal LIFE bronchoscopy. B, WLB shows inflammatory changes in the bronchial mucosa but no suspicion of malignancy (left). LIFE bronchoscopy shows diffuse reduced autofluorescence (visualized by diffuse red-brownish colorization; arrows). Biopsy demonstrated diffuse severe dysplasia.
and early-malignant lesions in the bronchi (26). The morphological entity has been confirmed in preneoplasias among smokers, and the perspectives of this finding have been extensively discussed (110). The prognostic significance of this morphological entity is currently studied in ongoing long-term follow-up studies. Future studies have to evaluate the role of ASD as a biomarker for early lesions and whether it can be used as a marker for treatment effect or therapeutic target for chemoprevention.

The LIFE bronchoscope may play an important role in the screening and follow-up of subjects at high risk of developing lung cancer. At this stage, however, it is unknown whether the LIFE bronchoscope will lead to a reduction in lung cancer mortality. There are also no data on cost-effectiveness and cost-benefit analyses available for this new diagnostic procedure. The use of the LIFE bronchoscope may also in the future be extended to other indications, e.g., patients staged as having resectable lung cancer on one side. Whether LIFE bronchoscopy of the contralateral lung will disclose abnormalities, which would change the therapeutic decision, is not yet reported.

Recent Advances in Radiology

The previous NCI-sponsored screening trials failed to demonstrate any reduction in the lung cancer mortality by sputum cytology and yearly chest radiography as mass screening tools for lung cancer screening. Limitations of design and execution of the studies, however, have been discussed extensively (8, 111, 112). An extended follow-up (median, 20.5 years) of the Mayo Lung Project was recently published (113). There was still no difference in lung cancer mortality between the intervention arm and the control arm (4.4 versus 3.9 deaths per 1000 person-years). However, the median survival for patients with resected early-stage disease was 16.0 years in the intervention arm versus 5.0 years in the usual-care arm ($P < 0.05$). The latter findings have raised the question as to whether some small lesions with limited clinical relevance may have been identified in the intervention arm, and the question of “overdiagnosis” was discussed in accompanying editorials (114).

Mass screening for lung cancer has been performed in Japan for many years and has been performed in over 500,000 people in about 80% of the local communities (115). Sobue et al. (116) observed that annual clinic-based chest X-ray screening for lung cancer in Japan showed reduced lung cancer mortality by about one-fourth among individuals who underwent screening once a year. In this screening program, the relative odds ratio of dying from lung cancer within 12 months was 0.535 and in the 12–24-month period was 0.638 (117). However, many studies have focused on the pitfalls in the detection of abnormalities by radiography (118–122). The limit of chest radiographic sensitivity for nodule detection is roughly 1 cm in diameter, by which time the tumor has over $10^9$ cells and may already have violated bronchial epithelium and vascular epithelium. CT has been shown to be more effective in the detection of peripheral lung lesions compared with plain radiography or conventional tomography of the whole lung (123, 124).

Spiral CT scan is a relatively new technology with the ability to continuously acquire data resulting in a shorter scanning time, a lower radiation exposure, and improved diagnostic accuracy compared with those of plain radiography (125–127). Spiral CT allows the whole chest to be imaged in one or two breath-holds, reducing motion artifacts and eliminating respiratory misregistration or missing nodules. Although there is greater radiation exposure with CT than with chest radiography, low-dose techniques (lower mA of 30–50 compared with 200 for conventional CT) have achieved calculated exposure doses that are 17% that of conventional CT and 10 times that of chest radiographs. Further reduction in radiation dose while maintaining diagnostic accuracy is a topic of current research. Furthermore, for the baseline screening, low-dose spiral-CT-scan i.v. contrast is not administered. Nodules as small as 1–5 mm can be shown with modern spiral CT technology (25, 128). The obvious advantages with this new technology led some groups in Japan and in the United States to look to low-dose spiral CT as a tool for screening (Refs. 129–131; Tables 4 and 5).

In a Japanese report, spiral CT scans and chest radiographs were done twice a year in 1369 individuals (129). Peripheral lung cancer was detected in 15 (0.3%) of 3457 examinations, and, among the 15 lung cancer cases detected, the results of chest X-ray were negative in 11 (73%), and the tumors were detected only by low-dose spiral CT. The detection rates of low-dose spiral CT and chest X-ray were 0.43% (15 of 3457 examinations) and 0.12% (4 of 3457 examinations), respectively. Furthermore, 14 (93%) of the 15 lung cancers were stage I disease. The histology showed that 11 of the 15 lung cancer cases were adenocarcinoma, and 4 had squamous cell carcinoma. The effective exposure dose with spiral CT scan in that study was calculated to about one-sixth that of conventional CT.

The ELCAP in New York was designed to determine: (a) the frequency with which nodules were detected; (b) the frequency with which detected nodules represent malignant disease; and (c) the frequency with which malignant nodules are curable (131). In the ELCAP study, 27 lung cancers were found among 1000 subjects screened. Among the 27 patients with cancer, 85% had stage I disease (Table 5).

Another population-based study on low-dose CT screening has been published by Sone et al. (130), using a mobile low-dose spiral CT scanner. The detection rate was 0.48% (i.e., 4–5

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**Fig. 4** Seventy-one-year-old man with a spicular nodule in upper left lobe demonstrated on low-dose helical CT (picture), but not visible on chest X-radiography. CT-guided biopsy showed adenocarcinoma.
cases per 1000 examinations). Surprisingly, there was no difference in the detection rate among smokers (0.52%) versus nonsmokers (0.46%). The results from the three population-based studies are summarized in Tables 4 and 5. The conclusion from these studies is that 85% of the lung cancers detected by low-dose CT were in stage I, offering improved possibility for curative treatment and better prognosis in general. However, the issue of “false-positive” scans has to be taken into consideration. Thus far, up to 20% of the participants with nodules on the scan had no malignancy during the follow-up period. The possibility that the cancers found represent incidental cancers as in the Mayo Lung Project must also be considered (114). The results from these studies confirm the expectation that low-dose CT increases the detection of small noncalcified nodules and, that lung cancer at an earlier and more curable stage are detected. The mobile CT screening study by Sone et al. (130) showed that low-dose CT increased the likelihood of detection of malignant disease 10 times as compared with radiography. The overall rate of malignant disease was lower in the Japanese studies (129, 130) compared with the ELCAP study (Ref. 131; detection rates of malignant disease was lower in the Japanese studies (129, 130) compared with the ELCAP study (Ref. 131; detection rates of 0.43–0.48% versus 2.7%). This could be because the Japanese studies screened individuals from the general population ages 40–74, whereas ELCAP screened people at high risk, ages ≥60, with a tobacco history of at least 10 pack-years. Thus, as expected, the risk of the population to be screened affects the rate of cancer detection.

Questions remaining to be answered include: (a) what are the diagnostic sensitivity and specificity of this procedure; and (b) does screening reduce lung cancer mortality? The spiral CT has not been as sensitive for small central cancers as it is for small peripheral cancers (129, 131). Minute nodules of lung cancer that are near the threshold of detectability may be overlooked at spiral CT screening (132). A prospective study of the diagnostic sensitivity of spiral CT has recently shown that the diagnostic sensitivity exceeded the sensitivity of conventional CT in previous reports (25). However, there were limitations in the detection of intrapulmonary nodules smaller than 6 mm and of pleural lesions. Compared with surgery (thoracotomy with palpation of deflated lung, resection, and histology), the sensitivity of spiral CT was 60% for intrapulmonary nodules of <6 mm and 95% for nodules of ≥6 mm and was 100% for neoplastic lesions ≥6 mm. Furthermore, a marked difference in the sensitivities of two independent observers was found for nodules smaller than 6 mm, whereas agreement was much better for

### Table 3 Bronchoscopy versus WLB in diagnosing premalignant and early-malignant lesions

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of biopsies</th>
<th>Life+LIFE</th>
<th>Life+WLB</th>
<th>Relative sensitivity</th>
<th>Life+LIFE</th>
<th>Life+WLB</th>
<th>Relative specificity</th>
<th>PPV*</th>
<th>NPV*</th>
<th>PPV*</th>
<th>NPV*</th>
<th>PPV*</th>
<th>NPV*</th>
<th>PPV*</th>
<th>NPV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lam et al. (105)</td>
<td>700</td>
<td>0.67</td>
<td>0.25</td>
<td>6.3 (2.7)</td>
<td>0.66</td>
<td>0.90</td>
<td>NR</td>
<td>0.33</td>
<td>0.89</td>
<td>NR</td>
<td>0.39</td>
<td>0.83</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurie et al.</td>
<td>234</td>
<td>NR</td>
<td>0.38</td>
<td>NR</td>
<td>NR</td>
<td>0.56</td>
<td>NR</td>
<td>NR</td>
<td>0.16</td>
<td>0.81</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venmans et al.</td>
<td>139</td>
<td>NR</td>
<td>0.89</td>
<td>1.43</td>
<td>NR</td>
<td>0.61</td>
<td>0.88</td>
<td>NR</td>
<td>0.20</td>
<td>0.99</td>
<td>0.32</td>
<td>0.98</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vermulen et al.</td>
<td>172</td>
<td>NR</td>
<td>0.25</td>
<td>3.75</td>
<td>0.21</td>
<td>NR</td>
<td>0.87</td>
<td>NR</td>
<td>0.13</td>
<td>0.96</td>
<td>NR</td>
<td>0.19</td>
<td>0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kennedy et al.</td>
<td>394</td>
<td>0.79</td>
<td>0.22</td>
<td>3</td>
<td>0.3</td>
<td>0.43</td>
<td>0.78</td>
<td>0.38</td>
<td>0.21</td>
<td>0.85</td>
<td>0.25</td>
<td>0.87</td>
<td>0.17</td>
<td>0.80</td>
<td></td>
</tr>
</tbody>
</table>

* PPV, positive predictive value; NPV, negative predictive value; NR, not reported.

### Table 4 Results from three population-based screening studies with low-dose spiral CT (LDCT)

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of individuals studied</th>
<th>True positive n</th>
<th>False positive %</th>
<th>Predictive value %</th>
<th>Detection rate %</th>
<th>Age incl. yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaneko et al.</td>
<td>1369</td>
<td>15</td>
<td>15.6</td>
<td>6.6</td>
<td>0.43</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Sone et al.</td>
<td>3967</td>
<td>19</td>
<td>5.0</td>
<td>8.8</td>
<td>0.46–0.5</td>
<td>&gt;30*</td>
</tr>
<tr>
<td>Kaneko et al.</td>
<td>1000</td>
<td>27</td>
<td>20.1</td>
<td>11.6</td>
<td>2.7</td>
<td>&gt;10*</td>
</tr>
</tbody>
</table>

* Defined as individuals with “test-positive,” in whom further workup gave no suspicion of malignancy.
* The study also included a group of nonsmokers.
* Average = 45 (not reported in the other studies).

### Table 5 Histology, stage, and size of primary lung cancer detected by low-dose spiral CT

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of cancers/No. screened</th>
<th>Histology %</th>
<th>TNM %</th>
<th>Average</th>
<th>Range</th>
<th>&lt;10</th>
<th>11–20</th>
<th>&gt;21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeno</td>
<td>Squam.</td>
<td>Other</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaneko et al. (129)</td>
<td>15/1369 (1.1%)</td>
<td>73</td>
<td>17</td>
<td>93</td>
<td>7</td>
<td>12</td>
<td>8–18</td>
<td></td>
</tr>
<tr>
<td>Sone et al. (130)</td>
<td>19/5483 (0.3%)</td>
<td>63</td>
<td>5</td>
<td>84</td>
<td>16</td>
<td>17</td>
<td>6–47</td>
<td></td>
</tr>
<tr>
<td>Henschke et al. (131)</td>
<td>27/1000 (2.7%)</td>
<td>67</td>
<td>30</td>
<td>85</td>
<td>4</td>
<td>15</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

* Adeno, adenocarcinoma; Squam., squamous cell carcinoma; TNM, tumor-node-metastasis.
6–10-mm nodules (25). Given these promising preliminary clinical results, further research is needed to determine the optimal technique for spiral CT screening, which includes collimation, reconstruction interval, pitch, and viewing methods. Decreasing the slice thickness to 3 mm, monitoring the viewing of examinations, and computer-aided diagnosis have been used to improve the diagnostic capability of spiral CT in the detection of pulmonary nodules (133–136).

Future large scale randomized studies have to confirm whether in fact spiral CT screening will lead to a reduction in lung cancer mortality. In a randomized study, the following questions arise: (a) what is the optimal high-risk group to study and what should be the control arm? (b) what should be the end points (goals) of the studies? The ultimate goal is to reduce the lung cancer mortality. However, although this is a long-term goal, intermediate end points from such studies should be evaluated. The change to more curable stages at diagnosis for the lung cancer patients is one such immediate goal; (c) what is the optimal workup and the morbidity of this program? (d) what is the cost of such a screening program? and (e) what is the false-positive rate of the screening findings? Incorporation of smoking cessation programs should be included in the future design of screening studies because it has been shown that screening with low-dose CT in participants who are still smoking provides substantial motivation for smoking cessation (137).

The studies with spiral CT-scan have demonstrated the superior diagnostic ability in the detection of small peripherally located tumors, most of the malignant ones of adenocarcinoma type of histology. The diagnostic sensitivity of spiral CT for more centrally located tumors (mostly squamous cell carcinoma) is significantly lower than for the peripherally located ones. Through these spiral CT studies, we will learn about the biology, pathology, and clinical course of these small tumors, which might be different from what we know about clinically more evident tumors detected routinely in previous studies.

Because lung cancer is so common, the introduction of any new screening technique in this area has to be underpinned by careful definition of the cost implications and must be justified by compelling evidence. The cost-effectiveness of the spiral CT approach should be assessed by evaluating the rate of over-diagnosing nonmalignant, relatively common abnormalities and comparing CT imaging to other diagnostic technologies.

PET with FDG has recently emerged as a practical and useful imaging modality in the preoperative staging of patients with lung cancer. However, whereas CT is most frequently used to provide additional anatomical and morphological information about lesions, the FDG PET imaging provides physiological and metabolic information that characterizes lesions that are indeterminate by CT. FDG PET imaging takes advantage of the increased accumulation of FDG in transformed cells and is sensitive (~95%) for the detection of cancer in patients who have indeterminate lesions on CT (138). The specificity (~85%) of PET imaging is slightly less than its sensitivity because some inflammatory processes avidly accumulate FDG. The high negative predictive value of PET suggests that lesions considered negative on the study are benign, biopsy is not needed, and radiographic follow-up is recommended. Several studies have documented the increased accuracy of PET compared with CT in the evaluation of the hilar and mediastinal lymph node status in patients with lung cancer (138). However, the PET resolution is sufficient only for nodules ≥6 cm and will not be helpful in detecting the very small nodules. Compared with low-dose spiral CT, the FDG PET scan is more expensive and time consuming. The role of PET scan in early diagnosis of lung cancer in an asymptomatic high-risk population is not yet evaluated. However, future studies have to include PET evaluation to define its role in a population screening setting.

Conclusion

Recent advances in molecular biology and pathology have led to a better understanding and documentation of morphological changes in the bronchial epithelium before development of clinical evident lung carcinomas. Combined with technical developments in radiological and bronchoscopic techniques, these procedures offer great promise in diagnosing lung cancer far in advance of clinical presentation. Any of these individual procedures could be incorporated into the routine management of individuals at risk for developing primary or secondary lung cancer, and for several of these methods, clinical studies are under way. Preliminary reported data are very promising for the early detection of lung cancer. Future studies must incorporate the different methods in a multidisciplinary scientific setting to evaluate the role of the individual method in the overall management for individuals at high risk for developing lung cancer. Several of these tests might diagnose the disease at the stage of clonal expansion before invasive carcinoma has developed. A management and intervention strategy appropriate to that stage of disease have to be developed. Preliminary studies of chemoprevention agents are reported, and new agents based on other biological mechanisms are under development and ready for clinical trials. It is now time to plan clinical trials that evaluate both diagnostic and therapeutic approaches to access their impact on the incidence of clinical lung cancer.

Acknowledgments

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Review: Advances in Early Detection of Lung Cancer


Clinical Cancer Research

Early Detection of Lung Cancer: Clinical Perspectives of Recent Advances in Biology and Radiology


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