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Lung Cancer Screening:

Clinical Practice Guidelines in Oncology

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Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide.^{1–4} In 2011, it is estimated that 156,900 deaths (85,600 in men, 71,300 in women) from lung cancer will occur in the United States.⁴ Five-year survival rates for lung cancer are only approximately 15.6%, partly because most patients have advanced-stage lung cancer at initial diagnosis (<http://seer.cancer.gov/statfacts/html/lungb.html>).⁵

These facts, combined with the success of screening in improving outcomes in cervical, colon, and breast cancers, have been the impetus for studies to develop an effective lung cancer screening test.^{6,7} Ideally, effective screening will lead to earlier detection of lung

cancer (before patients have symptoms and when treatment is more likely to be effective) and will decrease mortality.⁸ Currently, most lung cancer is diagnosed clinically when patients present with symptoms (such as cough, chest pain, weight loss); unfortunately, patients with these symptoms usually have advanced lung cancer.

Early detection of lung cancer is an important opportunity for decreasing mortality. Considerable interest has been shown in developing screening tools to detect early-stage lung cancer. Recent data support using spiral (helical) low-dose computed tomography (LDCT) of the chest to screen select patients who are at high risk for lung cancer (<http://www.cancer.gov/clinicaltrials/noteworthy-trials/nlst>).⁸

The NCCN Lung Cancer Screening Panel developed this new screening guideline in 2011 based on the current body of evidence.⁸ These guidelines 1) describe risk factors for lung cancer; 2) recommend criteria for selecting high-risk individuals for screening; 3) provide recommendations for evaluation and follow-up of nodules found during screening; 4) discuss the accuracy of LDCT screening protocols and imaging modalities; and 5) discuss the benefits and risks of screening.

Screening for Non–Small Cell Lung Cancer

Most lung cancers (85%) are classified as non–small cell lung cancer (NSCLC); small cell lung cancer occurs in 13% to 15% of patients (see the NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for NSCLC and Small Cell Lung Cancer, available online at www.NCCN.org). Thus, these guidelines mainly refer to detection of NSCLC. Other types of cancer can metastasize to the lungs (e.g., breast cancer), and there are also less common cancers of the lung or chest (e.g., malignant pleural mesothelioma, thymic carcinoma). Lung cancer screening may also detect other noncancerous conditions of the thorax (e.g., aortic aneurysm, coronary artery calcification) and tumors or benign disease outside of the chest (e.g., renal cell carcinoma, adrenal adenoma).

The goal of screening is to detect disease at a stage when it is not causing symptoms and when treatment is most successful. Screening should benefit the individual by increasing life expectancy and increasing quality of life. The rate of false-positive results should be low to prevent unnecessary additional testing. The large fraction of the population without the disease should not be harmed (low risk), and the screening test should not be so expensive that it places an onerous burden on the health care system. Thus, the screening test should: 1) improve outcome; 2) be scientifically validated (e.g., have acceptable levels of sensitivity and specificity); and 3) be low risk, reproducible, accessible, and cost effective.

Perhaps the most difficult aspect of lung cancer screening is addressing the moral obligation. As part of the Hippocratic oath, physicians promise to first “do no harm.”⁹ The dilemma is that if lung cancer screening is beneficial but physicians do not use it, they are denying patients effective care. However, if lung cancer screening is not effective, then patients may be harmed from overdiagnosis, increased testing, invasive testing or procedures, and the anxiety of a potential cancer diagnosis. Debates from mammography and prostate cancer

screening may provide additional insight for lung cancer screening, especially regarding the problem of overdiagnosis (see Randomized Trials on this page).¹⁰

CT as Part of a Screening Program

Lung cancer screening with CT should be part of a program of care and should not be performed in isolation as a free-standing test. Given the high percentage of false-positive results and the downstream management that ensues for many patients, the risks and benefits of lung cancer screening should be discussed with the individual before a screening LDCT scan is performed. It is recommended that institutions performing lung cancer screening use a multidisciplinary approach that may include specialties such as radiology, pulmonary medicine, internal medicine, thoracic oncology, and thoracic surgery. Management of downstream testing and follow-up of small nodules are imperative and may require the establishment of administrative processes to ensure adequate follow-up.

Randomized Trials

Disease-specific mortality (number of cancer deaths relative to number of individuals screened) is considered the ultimate test of screening effectiveness and the only test that is without bias.¹¹ Randomized controlled screening trials are essential for determining whether cancer screening decreases disease-specific mortality. Nonrandomized trials are subject to biases that may cause an apparent increase in survival (e.g., lead-time bias, length-time bias) (<http://www.cancer.gov/newscenter/qa/2002/nlstqaQA>).

If lung cancer is detected through screening before symptoms occur, then the lead time in diagnosis equals the length of time between screening detection and when the diagnosis otherwise would have occurred, either as a result of symptoms or other imaging. Even if early treatment had no benefit, the survival of the screened person is increased simply by the addition of the lead time. Length-time bias refers to the tendency of the screening test to detect cancers that take longer to become symptomatic, possibly because they are slower-growing and perhaps indolent cancers. Survival (the number of individuals who are alive after detection and treatment of disease relative to the number of individuals diagnosed with the disease) has often been reported but is subject to these biases.⁷ For further discussion of randomized and nonrandomized screening trials, see Benefits of Lung Cancer Screening on page 253.

In the 1960s and 1970s, several randomized trials assessed whether chest radiographs could improve lung cancer survival. Many of these studies were flawed in their design or power, and all were negative.¹² More recently, studies have focused on the more sensitive modality of helical LDCT-based lung cancer screening studies (see also section on Benefits of Lung Cancer Screening on page 253). However, analyses of some lung cancer screening studies using LDCT scans suggest that overdiagnosis (i.e., diagnosis of “cancer” that would never be life-threatening) and false-positive screening tests are significant concerns.^{13–15} Thus, although LDCT scanning may be a better screening test for lung cancer, it also has limitations (see Risks of Lung Cancer Screening on page 256).

Multiple ongoing randomized trials are assessing LDCT screening for lung cancer among high-risk groups, including 1) the National Lung Screening Trial (NLST), sponsored by the NCI⁷; and 2) the Dutch Belgian randomized lung cancer screening trial (NELSON).¹⁶ In November 2010, preliminary results from the NLST suggested that LDCT screening decreases disease-specific mortality, and the now-published results show that LDCT yields a decrease in lung cancer–specific mortality of 20% (95% CI, 6.8–26.7; $P = .004$) and in all-cause mortality of 7% (95% CI, 1.2–13.6; $P = .02$) when compared with chest radiograph alone.⁸

High-Risk Individuals

An essential goal of any lung cancer screening protocol is to identify the populations that are at a high risk for developing the disease. Although smoking tobacco is a well-established risk factor for lung cancer, other environmental and genetic factors also seem to increase risk. This section reviews the currently known risk factors for the development of lung cancer to identify high-risk populations that should be targeted for screening. Note that high-risk individuals who are recommended for screening do not have any symptoms suggestive of lung cancer (e.g., cough, chest pain, weight loss).

Tobacco Smoke

Active Tobacco Use: Tobacco smoking is a major modifiable risk factor in the development of lung cancer, and accounts for 85% of all lung cancer–related deaths.^{1,6} The causal relationship between tobacco smoking and lung cancer was first reported in 1939. Since then, the risk of developing lung cancer from smoking tobacco has been firmly established. Tobacco smoke contains more than 4500 compounds, and more than 50 of these are known carcinogens that increase the risk of cancerous mutations at the cellular level, especially among individuals with a genetic predisposition. A dose–response relationship exists between smoking tobacco and the risk of developing lung cancer; however, there is no risk-free level of tobacco exposure (http://cancercontrol.cancer.gov/tcrb/monographs/7/m7_6.pdf). The relative risk (RR) for lung cancer is approximately 20-fold higher^{1,17} for smokers than for nonsmokers. Cessation of tobacco smoking decreases the risk of lung cancer.¹⁸ However, even reformed former smokers have a higher risk of lung cancer compared with never-smokers (<http://cancercontrol.cancer.gov/tcrb/monographs/8/index.html>). As a result, current or past history of tobacco smoking is considered a risk factor for the development of lung cancer, irrespective of the magnitude of exposure and the time since smoking cessation.

In the algorithm, individuals (aged 55–74 years) with a 30 or more pack-year history of smoking tobacco are selected as the highest-risk group for lung cancer and are recommended for screening (category 1) based on criteria for entry into the NLST.^{7,8} Pack-years of smoking history is defined as the number of packs of cigarettes smoked every day multiplied by the number of years of smoking. Individuals with a 30 pack-year smoking history who quit smoking less than 15 years ago are still in this highest-risk group.

Exposure to Second-Hand Smoke: The relationship between lung cancer and exposure to second-hand smoke (also known as *environmental tobacco smoke*, *passive*

smoke, and *involuntary smoke*) was first suggested in epidemiologic studies published in 1981.¹⁹ Since then, several studies and pooled RR estimates suggest that second-hand smoke causally increases the risk for lung cancer among nonsmokers (<http://www.surgeongeneral.gov/library/secondhandsmoke/factsheets/factsheet6.html>).²⁰ However, the NCCN Lung Cancer Screening Panel does not consider second-hand smoke to be an independent risk factor, because the association is either weak or variable. Thus, second-hand smoke does not confer a great enough risk for exposed individuals to be considered for lung cancer screening in these guidelines.

A pooled analysis of 37 published studies found an estimated RR of 1.24 (95% CI, 1.13–1.36) for adult nonsmokers who live with a smoker.²¹ A pooled estimate from 25 studies found an RR of 1.22 (95% CI, 1.13–1.33) for lung cancer risk from exposure to second-hand smoke at the workplace.²⁰ The pooled estimate for 6 studies suggests a dose–response relationship between number of years of second-hand smoke exposure and lung cancer risk.²⁰ The data are inconsistent for second-hand smoke exposure during childhood and subsequent lung cancer risk in adulthood. For childhood tobacco smoke exposure, pooled RR estimates for the development of lung cancer were 0.93 (95% CI, 0.81–1.07) for studies conducted in the United States, 0.81 (95% CI, 0.71–0.92) for studies conducted in European countries, and 1.59 (95% CI, 1.18–2.15) for studies conducted in Asian countries.²⁰

Occupational Exposure

Approximately 150 agents are classified as known or probable human carcinogens (IARC 2002). The 8 agents that are identified specifically as carcinogens targeting the lungs are arsenic, chromium, asbestos, nickel, cadmium, beryllium, silica, and diesel fumes.^{22–25} These agents are listed in order of their presumed risk.²² The calculated mean RR for development of lung cancer is 1.59 for individuals in the United States who have a known occupational exposure to these agents.^{22,25} Among those who are exposed to these carcinogens, smokers have a greater risk for lung cancer than nonsmokers.²⁶

Residential Radon Exposure

Radon (a gaseous decay product of uranium-238 and radium-226) has been implicated in the development of lung cancer.²⁷ The risk of lung cancer from occupational exposure among uranium miners is well established.²⁸ However, the risk associated with residential radon is uncertain. A meta-analysis in 1997 of 8 studies yielded an estimated RR of 1.14 (95% CI, 1.0–1.3).²⁹ However, a 2005 meta-analysis of 13 studies (using individual patient data) reported a linear relationship between the amount of radon detected in a home and the risk of developing lung cancer.³⁰ Among those exposed to radon, smokers have a greater risk for lung cancer than nonsmokers.³⁰

Cancer History

Evidence shows an increased risk of new primary cancers among patients who survive lung cancer, lymphomas, cancers of the head and neck, or smoking-related cancers (e.g., esophageal cancer). Patients who survive small cell lung cancer have a 3.5-fold increase in the risk for developing a new primary cancer (predominantly NSCLC).³¹

The risk for subsequent lung cancers is increased in patients who continue to smoke and who have been previously treated with either chest irradiation or alkylating agents. Patients previously treated with chest irradiation have a 13-fold increase in risk for developing new primary lung cancer, and those previously treated with alkylating agents have an estimated RR of 9.4. In patients previously treated for Hodgkin's lymphoma, the RR for new primary lung cancer is 4.2 if previously treated with alkylating agents, and 5.9 if previously treated with 5 Gy or more of radiation therapy.³²

In patients with head and neck cancers, subsequent new primary lung cancer may occur synchronously or metachronously. New primary tumors are seen in approximately 9% of patients. Most of these tend to be squamous cell cancers and a third of them occur in the lung. However, data do not suggest that previous treatment for head and neck cancers increases the risk of subsequent new primary lung cancer independent of tobacco exposure.^{33,34}

Evidence suggests that patients who are successfully treated (i.e., cured) for an initial smoking-related lung cancer and who stop smoking will have a decreased risk of a subsequent smoking-related cancer compared with those who continue smoking.³⁵

Family History of Lung Cancer

Several studies have suggested an increased risk for lung cancer among first-degree relatives of patients with lung cancer, even after adjustment for age, gender, and smoking habits.^{36,37} A meta-analysis of 28 case-control studies and 17 observational cohort studies showed an RR of 1.8 (95% CI, 1.6–2.0) for individuals with a sibling/parents or a first-degree relative with lung cancer.³⁸ The risk is greater in individuals with multiple affected family members or who had a cancer diagnosis at a young age.

Although no high-penetrance inherited syndrome has been described for lung cancer (either small cell lung cancer or NSCLC), several groups have identified genetic loci that may be associated with an increased risk of developing lung cancer. The Genetic Epidemiology of Lung Cancer Consortium conducted a genome-wide linkage analysis of 52 families who had several first-degree relatives with lung cancer. Linkage disequilibrium was shown on chromosome 6, localizing a susceptibility locus influencing lung cancer risk to 6q23–25.³⁹ Subsequently, 3 groups performed genome-wide association studies in patients with lung cancer and matched controls. They found a locus at 15q24–25 associated with an increased risk of lung cancer, nicotine dependence, and peripheral artery disease.^{40–42} It was noted that subunits of the nicotinic acetylcholine receptor genes are localized to this area (CHRNA5, CHRNA3, and CHRN4). Other investigators recently found that a variant at 15q24/25 is associated with spirometric bronchial obstruction and emphysema as assessed with CT.⁴³ Patients with classic familial cancer susceptibility syndromes (such as retinoblastoma, Li-Fraumeni syndrome) have a substantially increased risk for lung cancer if they also smoke tobacco.^{44–46}

History of Lung Disease in the Patient

Chronic Obstructive Pulmonary Disease: A history of chronic obstructive pulmonary disease (COPD) is associated with lung cancer risk,^{47–53} and this association may be largely caused by smoking. Yang et al.⁵⁴ found that COPD accounts for 12% of lung cancer cases among heavy smokers. However, even after statistical adjustment, evidence suggests that the association between COPD and lung cancer may not be entirely caused by smoking.⁵⁵ For example, 1) family history of chronic bronchitis and emphysema is associated with increased risk of lung cancer, and 2) COPD is associated with lung cancer among never-smokers.^{54–56} Yang et al.⁵⁴ found that COPD accounts for 10% of lung cancer cases among never-smokers. Koshiol et al.⁵⁵ found that when they restricted their analyses to adenocarcinoma (which is more common among nonsmokers, particularly women), COPD was still associated with an increased risk of lung cancer.

Pulmonary Fibrosis: Patients with diffuse pulmonary fibrosis seem to be at a higher risk for lung cancer even after age, gender, and a history of smoking are taken into consideration (RR, 8.25; 95% CI, 4.7–11.48).^{57,58} Among patients with a history of exposure to asbestos, those who develop interstitial fibrosis are at a higher risk of developing lung cancer than those without fibrosis.⁵⁹

Hormone Replacement Therapy

Whether hormone replacement therapy (HRT) use affects the risk of lung cancer in women is currently unclear. More than 20 studies have been published and the results have been inconsistent. Most of the currently available information comes from case-control and cohort studies. Cumulatively, these studies are variable; they have found associations ranging from an increased risk of lung cancer, no effect on risk, and a protective effect against lung cancer risk. However, in a large randomized controlled study,⁶⁰ no increase in the incidence of lung cancer was found among postmenopausal women treated with estrogen plus progestin HRT, but deaths from lung cancer (especially NSCLC) were higher among patients receiving HRT.

Selection of High-Risk Individuals for Screening

Well-known risk factors exist for the development of lung cancer, especially smoking tobacco. Results from the recently concluded NLST support screening select individuals who are at high risk for lung cancer.⁸ The NCCN Lung Cancer Screening Panel recommends that high-risk individuals should be screened; however, moderate- and low-risk individuals should not be screened currently. Patients are selected for the different risk categories using the NLST inclusion criteria, nonrandomized studies, and/or observational studies. Based on the available data, the NCCN Lung Cancer Screening Panel recommends using the following criteria to determine whether individuals are at high, moderate, or low risk for lung cancer.

High-Risk Individuals

The NCCN Lung Cancer Screening Panel recommends lung cancer screening using helical LDCT for individuals with the following high-risk factors:

- Age 55 to 74 years; 30 or more pack-year history of smoking tobacco; and, if former smoker, have quit within 15 years (category 1).^{7,8} Some high-risk individuals in the NLST also had COPD and other risk factors. This is a category 1 recommendation because these individuals are selected based on the NLST inclusion criteria.^{7,8} An NCCN category 1 recommendation is based on high-level evidence (i.e., randomized controlled trial) and uniform consensus among panel members. Annual screening is recommended for these high-risk individuals until they are 74 years of age based on the NLST.⁸ However, uncertainty exists about the appropriate duration of screening and the age at which screening is no longer appropriate.
- Age 50 years or older, 20 or more pack-year history of smoking tobacco, and one additional risk factor (category 2B).⁶¹ This is a category 2B recommendation, because these individuals are selected based on nonrandomized studies and observational data.⁶¹ These additional risk factors were previously described and include cancer history, lung disease history, family history of lung cancer, radon exposure, and occupational exposure. Note that the NCCN Lung Cancer Screening Panel does not currently believe that exposure to second-hand smoke is an independent risk factor, because the data are either weak or variable (see Exposure to Second-Hand Smoke on page 248).

Moderate-Risk Individuals

NCCN defines moderate-risk individuals as those aged 50 years or older and have a 20 or more pack-year history of smoking tobacco or second-hand smoke exposure but no additional lung cancer risk factors.⁶¹ The NCCN Lung Cancer Screening Panel does not recommend lung cancer screening for these moderate-risk individuals. This is a category 2A recommendation based on nonrandomized studies and observational data.

Low-Risk Individuals

NCCN defines low-risk individuals as those younger than 50 years and/or with a smoking history of fewer than 20 pack-years.⁶¹ The NCCN Lung Cancer Screening Panel does not recommend lung cancer screening for these low-risk individuals. This is a category 2A recommendation based on nonrandomized studies and observational data.

Accuracy of LDCT Protocols and Imaging Modalities

As shown in the algorithm, LDCT is recommended for detecting noncalcified nodules that may be suspicious for lung cancer depending on their type and size (e.g., solid, part-solid, and ground glass nodules). Li et al.⁶² found that the prevalence of malignancy was as follows: ground glass opacities (GGOs; 59%), mixed GGOs and solid (48%), and solid (11%). GGOs have the highest incidence of malignancy; 75% of persistent GGOs are cancer.⁶³ However, the GGOs are mainly adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA), formerly known as *bronchioloalveolar carcinomas* (BAC), which have 100% 5-year disease-free survival if completely resected.^{63,64} Solid and part-solid nodules are more likely to be invasive and faster-growing cancers, factors that are reflected in the increased suspicion and follow-up of these nodules.¹⁴

Helical multidetector CT (MDCT) of the chest has made it possible to detect very small lung nodules, both benign and malignant. The ability to acquire thinner slices, the use of maximum intensity projection (MIP) or volume-rendered (VR) images, and computer-aided diagnosis (CAD) software have increased the sensitivity of small-nodule detection.^{65–74} The use of thinner images has also improved the characterization of small lung nodules.⁷⁵

For lung cancer screening, LDCT without intravenous contrast is currently recommended instead of standard-dose CT to decrease the dose of radiation. Although there is no strict definition of LDCT of the chest, it is usually considered to be approximately 10% to 30% of standard-dose CT. In most cases, LDCT has been shown to be as accurate as standard-dose CT for detecting solid pulmonary nodules, although nodule detection with LDCT may be limited in larger patients.^{76,77} However, LDCT seems to be less sensitive for detecting very low-density non-solid nodules or GGOs.⁷⁸ Decreasing the radiation dose does not significantly affect the measurement of nodule size when using 1-mm thick slices.⁷⁹ These low-dose scans require radiologists to assess images that are much noisier than they are currently used to seeing. Studies suggest that some variation occurs in interpretation of LDCT scans among radiologists.^{80,81}

Recent LDCT lung cancer screening studies using MDCT have reported that lung cancer mortality is decreased when compared with unscreened cohorts or those receiving chest radiographs.^{8,82} However, studies using multidetector LDCT screening for lung cancer in high-risk patients have applied various different protocol algorithms for detection and follow-up of pulmonary nodules/lesions (<http://www.ielcap.org/professionals/docs/ielcap.pdf>).^{7,83–89} These protocols have been based on the positive relationships among 1) nodule size and/or nodule consistency/density and likelihood of malignancy; 2) nodule size and tumor stage; and 3) tumor stage and survival. They also take into account the average growth rate of lung cancer (i.e., doubling time).^{61,90–96} Most of these protocols recommend dynamic contrast-enhanced CT and/or PET/CT be considered for nodules that are at least 7 to 10 mm, because these technologies have been shown to increase specificity for malignancy.^{97–101} In the workup of pulmonary nodules detected with CT in a high-risk lung cancer screening population, the roles of contrast-enhanced CT and PET/CT are still in evolution.^{102,103}

Optimally, these lung cancer screening methods will maximize detection of early-stage lung cancer and minimize false-positive results, unnecessary invasive procedures, radiation exposure, and cost. In at least one medical center, improvement in CT equipment and change in screening protocol have been shown to increase early lung cancer detection, decrease the surgery rate, and improve cancer-specific survival.¹⁰⁴ Strict adherence to a screening protocol may also significantly reduce unnecessary biopsies.¹⁰⁵

Currently, the most accurate protocol for lung cancer detection using LDCT is difficult to determine because of differing patient populations, methodologies, lengths of follow-up, and statistical analyses among lung cancer screening studies. Recent LDCT screening programs (with multiple years of follow-up) report that 65% to 85% of their detected lung cancers are stage I.^{88,101} The I-ELCAP (International Early Lung Cancer Action Program) and NLST are the largest recent series examining lung cancer detection using LDCT in high-risk

patients (see Benefits of Lung Cancer Screening 253).^{7,61} Differences in screening algorithms or recommended diagnostic pathways between these studies are summarized in Table 1 (available online, in these guidelines, at www.NCCN.org [MS-19]).^{7,61}

In 2005, the Fleischner Society published guidelines for the management of small pulmonary nodules detected on LDCT scans.¹⁰⁶ Most radiologists in the United States are aware of these guidelines and/or work in a practice that uses them.¹⁰⁷ However, these recommendations do not specifically address the management of part-solid or nonsolid pulmonary nodules. Although understanding of the histology and behavior of nonsolid and part-solid nodules has changed recently, interim guidelines for the assessment and management of subsolid nodules were recently proposed.¹⁴

Because of the familiarity and/or acceptance of the Fleischner Society guidelines among radiologists, pulmonologists, and thoracic surgeons, these same principles have been incorporated into the NCCN recommendations for lung cancer screening. The NCCN recommendations in the algorithm are an adaptation of the Fleischner Society guidelines, proposed guide lines for subsolid nodules by Godoy, NLST data, and the I-ELCAP protocol guidelines (<http://www.ielcap.org/professionals/docs/ielcap.pdf>).^{14,106} The currently proposed NCCN recommendations are less aggressive (i.e., less-frequent LDCT) than the I-ELCAP protocol for the workup of baseline and new solid and part-solid nodules 6 mm or smaller. However, the NCCN recommendations are slightly different (i.e., consider PET/CT and/or contrast-enhanced CT) from the I-ELCAP protocol (see Table 1, available online, in these guidelines, at www.NCCN.org [MS-19]) in the evaluation of solid and part-solid nodules larger than 8 mm, because the NCCN Guidelines recommend considering short-term assessment with PET/CT (to increase nodule specificity) rather than longer-term assessment with LDCT.

The NCCN definition of *nodule growth* is 1) an increase in mean diameter of 2 mm or more for nodules 15 mm or smaller or in the solid portion of a part-solid nodule when compared with the baseline scan, or 2) an increase of 15% in mean diameter if the nodule is 15 mm or more when compared with the baseline scan. *Mean diameter* is the mean of the longest diameter of the nodule and its perpendicular diameter when compared with the baseline scan. This definition of nodule growth is based on intraobserver and interobserver variability when measuring small pulmonary nodules, and on the minimum change in diameter that can be reliably detected using conventional methods (excluding volumetric analysis software).¹⁰⁸ This definition of nodule growth is simplified compared with the formula used by I-ELCAP (see Table 1, available online, in these guidelines, at www.NCCN.org [MS-19]), which requires nodule growth of 1.5 to 3.0 mm in mean diameter for nodules 3 to 15 mm, depending on their diameter. The NCCN definition of nodule growth should also result in fewer false-positive diagnoses compared with the NLST suggested definition of nodule growth ($\geq 10\%$ increase in nodule diameter).⁸

Currently, the NCCN recommendations do not take into consideration other possibly relevant nodule features, such as proximity to the pleura or fissure.^{109–111} Currently, the topics of nodule volumetric analysis and/or calculations of tumor doubling time have not been addressed. In some cases, it may be appropriate to perform standard-dose CT with or

without intravenous contrast for follow-up or further evaluation of lung or mediastinal abnormalities detected on screening LDCT.

The recommended LDCT acquisition parameters in these NCCN Guidelines (see Table 2, available online, in these guidelines, at www.NCCN.org [MS-20–21]) are similar to many of the recent and ongoing lung cancer screening studies using low-dose MDCT. Use of MIP, VR, and/or CAD software is highly recommended in addition to evaluation of conventional axial images for increased sensitivity of small nodule detection. A detector collimation of 1.5 mm or less is necessary for optimal use of these 3-dimensional applications. For accurate nodule volumetric analysis, some radiologists feel that a detector collimation of 1 mm or less is needed. Measurement and evaluation of small nodules are more accurate and consistent on 1-mm thick images compared with 5-mm images.⁷⁵ There may be a similar but less-pronounced benefit in evaluating nodules on 1-mm reconstructed images after detecting them on 2.5- to 3.0-mm thick slices. Because slice thickness, reconstruction algorithms, and postprocessing filters affect nodule size measurement, the same technical parameters should be used for each screening LDCT. Ultra-low-dose chest CT currently produces lower sensitivity for nodule detection, especially in larger patients.⁷⁷ However, new LDCT technologies may soon make it possible to significantly decrease the radiation dose without compromising nodule detection and evaluation.^{112–115}

Benefits of Lung Cancer Screening

This section summarizes current information about the possible or projected benefits of screening for lung cancer using helical LDCT scans, including 1) decreased lung cancer mortality, or improvement in other oncologic outcomes, 2) quality-of-life benefits from screening and early detection (compared with standard clinical detection), 3) cost-effectiveness of screening, and 4) detection of disease, other than lung cancer, that requires treatment.

Oncology Outcomes

After a clinical diagnosis of NSCLC, survival is directly related to stage at diagnosis.⁵ Although patients with earliest-stage disease (IA) may have a 5-year survival rate of approximately 75% with surgery, the outcomes quickly decrease with increasing stage (e.g., 5-year survival is 71% for stage IB; 58% for IIA; 49% for IIB; and < 25% for stages III and IV).¹¹⁶ Note that staging for NSCLC was recently revised in January 2010 (see the NCCN Guidelines for NSCLC, available online at www.NCCN.org).¹¹⁷ Although it is intuitively appealing to conclude that earlier detection of disease will improve outcome, screen-detected lung cancers may have a different natural history from that of clinically detected cancers,^{118,119} and an apparent improvement in survival from early detection itself (lead-time bias). Pathology results of resected lung cancers detected through prior screening trials suggest that screening increases the detection of indolent cancer. However, randomized trial data from the NLST show that LDCT screening decreases lung cancer mortality.⁸

Nonrandomized Trials: Of the single-armed screening studies (i.e., nonrandomized), the I-ELCAP study is the largest. It included 31,567 high-risk patients from around the world, all of whom were to be screened with baseline and annual LDCT scans analyzed centrally in

New York.⁶¹ In the I-ELCAP study, Henschke et al.⁶¹ reported that a high percentage of stage I cancers (85%) were detected using LDCT, with an estimated 92% actuarial 10-year survival rate for stage I cancers resected within 1 month of diagnosis (62% of all cancers detected). The authors noted that 8 participants with clinical stage I cancer who opted not to undergo treatment all died within 5 years, findings similar to those of published medical literature examining the natural history of stage I NSCLC.¹²⁰ They concluded that annual helical LDCT screening can detect lung cancer that is curable. Important caveats about I-ELCAP include that it was not randomized, the median follow-up time was only 40 months, and fewer than 20% of the subjects were observed for more than 5 years. Given the limited follow-up, the 10-year survival estimates may have been overstated.

A study by Bach et al.¹²¹ raised concern that LDCT screening may lead to overdiagnosis of indolent cases without substantially decreasing the number of advanced cases or the overall attributable deaths from lung cancer. However, although overdiagnosis did occur with LDCT in the NLST, the magnitude was not large when compared with radiographic screening (83 vs. 17 stage IA BAC, also known as AIS or MIA).^{8,64,122} Data from the ELCAP suggest that baseline CT scans find more indolent cancers, and subsequent annual scans find more rapidly growing cancers.¹²³

Another recent analysis of 7995 participants in the NY-ELCAP single-arm screening trial (the precursor to the I-ELCAP) compared the observed death rate from lung cancer among ELCAP subjects with that seen in participants in large cancer prevention cohort studies who were not undergoing prescribed lung cancer screening with LDCT scans.⁸² The analysis was adjusted for age, gender, and smoking status, and suggested a significant reduction in deaths from lung cancer of 40% to 60% among the screened cohort.

Randomized Trials: To address the concerns of bias and overdiagnosis from single-arm screening (i.e., nonrandomized) studies, the NCI launched the NLST in 2002.⁷ The NLST was a prospective, randomized lung cancer screening trial comparing annual LDCT scan with annual chest radiograph for 3 years; this trial was designed to have 90% power to detect a 21% decrease in the primary end point of lung cancer–specific mortality in the screened group. The investigators enrolled 53,454 high-risk participants aged 55 to 74 years who had smoking history of at least 30 pack-years. If subjects were no longer smoking tobacco, they had to have quit within the previous 15 years. All screening examinations were completed by mid-2007, and the study mandated a Data Safety Monitoring Board (DSMB) that met twice annually to evaluate follow-up information. In October 2010, the DSMB concluded that sufficient information was available to assess the primary outcome of the study. A NCI press release about the NLST findings was issued in November 2010. The NLST results were recently published and showed a substantial reduction in lung cancer–specific mortality and a reduction in all-cause mortality (<http://www.cancer.gov/newscenter/pressreleases/2011/NLSTprimaryNEJM>).⁸

The NLST participants were similar to a United States census population of heavy smokers in terms of gender, but the NLST population was generally younger, better educated, and less likely to be current smokers. Subjects in both the LDCT screening and chest radiograph screening arms were very compliant (> 90%) with their designated screening tests. The

screening tests were deemed positive if there was a finding that was suspicious for lung cancer (i.e., suspicious nodule).⁷ Overall, 24% of the LDCT scans and 7% of the chest radiographs performed were positive screens, an imbalance that was expected based on prior data. In each of the 3 years of screening, positive LDCT scan screens were determined to be actual lung cancer cases (i.e., true-positive) 4%, 2%, and 5% of the time, compared with 6%, 4%, and 7% for positive chest radiographs.

Based on the published NLST results, 356 participants died of lung cancer in the LDCT arm and 443 participants died of lung cancer in the chest radiograph arm.⁸ Thus, LDCT screening yielded a 20% reduction in lung cancer–specific mortality. In addition, a 7% improvement was seen in all-cause mortality. These results are impressive, and the NLST represents the first randomized study showing an improvement in either disease-specific or overall mortality when using a lung cancer screening program. The NLST results indicate that to prevent one death from lung cancer, 320 high-risk individuals must be screened with LDCT. The NLST results will likely change medical practice in the United States. Results of the NELSON trial are anxiously awaited to ensure the NLST findings are validated in a separate cohort; further analysis of the NLST, including comparative effectiveness modeling, is underway.

The 20% reduction in mortality from LDCT screening (compared with chest radiograph) may actually be greater in clinical practice, because chest radiographs are not currently recommended for lung cancer screening as standard practice (by either the American Thoracic Society or the American College of Chest Physicians).¹²⁴ In addition, if annual lung screening is continued for more than 3 years, this increased screening may yield mortality reductions of more than 20% (which was reported by the NLST after annual lung screening for only 3 years). Recent findings suggest that showing the benefit of breast cancer screening requires follow-up of at least 20 years.¹²⁵

Quality of Life

The NLST assessed quality of life among participants at the time of each annual screening study, but these results are not yet available. Possible quality-of-life benefits from early lung cancer detection (as opposed to detection at the time of clinical symptoms) include 1) reduction in disease-related morbidity, 2) reduction in treatment-related morbidity, 3) alterations in health affecting lifestyles, and 4) reduction in anxiety and psychological burden.

Reduction in Disease-Related Morbidity: It is a reasonable assumption that the disease-related symptom burden would be decreased in patients whose lung cancer is detected early (via screening) compared with late (via clinical presentation). Most patients whose lung cancer is detected early are asymptomatic, and detection is often either incidental or part of a screening protocol.⁷ Historically, most patients with lung cancer presented with symptoms of the disease (including cough, dyspnea, hemoptysis, pain, weight loss, and cachexia), and thus their lung cancer was detected clinically. An important analysis of the NLST quality-of-life data will be to assess the 2 cohorts for differences in the

types of symptoms experienced at the time of lung cancer diagnosis to see if screening truly can decrease the lung cancer symptom burden.

Reduction in Treatment-Related Morbidity: Patients with early-stage lung cancer primarily are treated surgically, sometimes with adjuvant chemotherapy, whereas those with more advanced disease are treated with a combination of chemotherapy and radiation, or chemotherapy alone (see the NCCN Guidelines for NSCLC, available online at www.NCCN.org).^{126,127} Patients with early-stage lung cancer who undergo an R0 resection have increased survival compared with those with more advanced disease who undergo definitive chemoradiation therapy.¹²⁸ However, few data have been published comparing the treatment burden of surgery versus chemoradiation therapy. It seems reasonable to assume that a patient with stage I lung cancer requiring a lobectomy alone probably has less treatment-related morbidity than a patient with stage III lung cancer requiring combined-modality therapy (i.e., chemotherapy, radiation, and a possible lung resection).¹²⁹ However, this has not been shown.

The NLST found that 40% of the cancers detected in the CT-screening group were stage IA, 12% were stage IIIB, and 22% were stage IV.⁸ Conversely, 21% of the cancers detected in the chest radiograph group were stage IA, 13% were stage IIIB, and 36% were stage IV. These results suggest that LDCT screening decreases the number of cases of advanced lung cancer, and therefore may decrease treatment-related morbidity. Lung cancer screening may reduce the number of patients who require pneumonectomy for treatment of lung cancer, which will reduce treatment-related morbidity and mortality. Several series have shown that pneumonectomy is performed in only 1% of cases of lung cancer diagnosed in CT screening programs, in contrast to the 20% to 30% rate of pneumonectomy in symptom-detected cases.^{130–133}

Alterations in Health That Affect Lifestyles: The process of lung cancer screening itself has been suggested to increase smoking cessation rates. Conversely, it has also been suggested that negative results on a lung cancer screening test may provide a false sense of security to smokers and result in higher smoking rates. Neither hypothesis has been supported by any substantial evidence. A nonrandomized screening study reported that smoking cessation rates were higher when more follow-up LDCT scans were ordered for abnormal findings, regardless of ultimate diagnosis of cancer, suggesting that patients became “scared” into quitting.¹³⁴ In a controlled study, however, smoking abstinence rates were similarly higher than expected in both screened and unscreened arms. This result suggests that the positive effect on smoking cessation was likely unrelated to the screening test results and may reflect a higher desire to be healthy among volunteers participating in screening clinical trials.¹³⁵

Smokers, including those undergoing lung cancer screening, should always be encouraged to quit smoking tobacco (<http://www.smokefree.gov/>).¹³⁶ Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful (see *Quick Reference Guide for Clinicians: Treating Tobacco Use and Dependence*; <http://www.surgeongeneral.gov/tobacco/tobaqrg.htm>).

Reduction in Anxiety and Psychological Burden: As with mammogram screening for breast cancer, whether lung cancer screening causes anxiety or improves overall quality of life has been a topic of discussion. The randomized NELSON screening study recently published health-related quality-of-life data from 733 participants. In the short term, recipients of an indeterminate result from the LDCT scan experienced increased distress, whereas relief was experienced after a negative baseline screening examination.¹³⁷ After 2 years of follow-up, data from the NELSON trial suggest that lung screening did not adversely affect quality of life.¹³⁸ However, further longitudinal studies are needed to determine the long-term effect. Patients' attitudes toward risk in their life (risk perception) also greatly affect their anxiety when undertaking cancer screening examinations.¹³⁹ Little definitive research is available to support or refute effects on quality of life from lung cancer screening.

Cost-Effectiveness

Only a small number of preliminary cost-benefit analyses have been performed with respect to lung cancer screening, and many are based on modeled predictive systems because randomized clinical trials have been completed only recently.¹⁴⁰ In fact, a current fundamental flaw with cost-benefit analyses for lung cancer screening is that because the true benefit of screening requires more years of follow-up and more years of screening to realize the full potential, this crucial factor in prior analyses has been arbitrarily assigned or assumed.¹²⁵ The types of assumptions made can significantly affect the conclusions of the analysis. Furthermore, many cost-benefit analyses do not adequately represent the detrimental effects of false-positive test results on screening. For a person undergoing lung cancer screening with 2 sequential annual examinations, the cumulative risk of a false-positive test result was 33%.¹⁴¹ The economic effect of false-positive cancer screening results has been estimated to be at least \$1000 per incident.¹⁴²

The original ELCAP study constructed a decision analysis model from its data.¹⁴³ The investigators documented that diagnostic procedure costs and hospital/physician costs in the first year after the diagnosis of lung cancer proportionally increased with increasing stage. Because they detected primarily early-stage cancers, they estimated that a baseline screening LDCT scan could increase survival by 0.1 year at an incremental cost of approximately \$230 (this study was published in 2003). The incremental cost per life-year gained ratio is also very sensitive to the fraction of the patients screened and found to have early-stage disease; the higher the percentage of patients found with early-stage disease, the lower the incremental cost ratio.¹⁴⁴ The emerging NSLT data must be carefully examined to ascertain the proportion of patients diagnosed with early-stage disease, their comparative mortality and morbidity, and the associated costs. Additional studies to examine other cohorts at risk will also be helpful in future cost-effectiveness analysis models.

Risks of Lung Cancer Screening

Lung cancer screening with LDCT has inherent risks and benefits. These risks must be understood to determine whether screening is beneficial. The possible or projected risks of screening for lung cancer using LDCT scans include 1) false-positive results, leading to

unnecessary testing, unnecessary invasive procedures (including surgery), increased cost, and decreased quality of life because of mental anguish; 2) false-negative results, which may delay or prevent diagnosis and treatment because of a false sense of good health; 3) futile detection of small aggressive tumors (which have already metastasized, preventing meaningful survival benefit from screening); 4) futile detection of indolent disease (i.e., overdiagnosis), which would never have harmed the patient who subsequently undergoes unnecessary therapy; 5) indeterminate results, leading to additional testing; 6) radiation exposure; and 7) physical complications from diagnostic workup. Patients with several comorbid conditions may be at greater risk than those with few or none.

False-Positive Results

Lung cancer screening studies (which have included only high-risk populations) have found a high rate of noncalcified nodules larger than 4 mm on LDCT screening, with false-positive rates ranging from 10% to 43%.^{132,141,145–148} In the NLST, the false-positive rate was 96.4% for the CT screening group.⁸ The cumulative risk of a false-positive result was 33% for a person undergoing lung cancer screening with 2 sequential annual examinations.¹⁴¹ These results then require follow-up, which may include surveillance with chest LDCT scans, percutaneous needle biopsy, or even surgical biopsy. Each of these procedures has its own risks and potential harms.¹⁴⁹ Approximately 7% of individuals with a false-positive result will undergo an invasive procedure (typically bronchoscopy).¹⁴¹ However, in the NLST, the rate of major complications after an invasive procedure was very low (only 0.06%) after workup for a false-positive result in the CT screening group.⁸

The NCCN lung cancer screening protocol may avoid much of the most-invasive follow-up for noncalcified nodules that are detected on baseline screening with LDCT (see the algorithm). The NCCN protocol uses the NLST and I-ELCAP protocols/recommendations (see Table 1, available online, in these guidelines, at www.NCCN.org [MS-19]) and the Fleischner Society guidelines and is based on expert opinion from the NCCN panel members.¹⁵⁰ However, even repeat chest LDCT scanning is associated with risk for 1) increased radiation exposure; 2) increased cost of follow-up scans and clinic visits; and 3) ongoing anxiety to the individual, who must wait for the results of repeat chest LDCT scans. Bach et al.¹²¹ also provide insight into the potential harms of LDCT screening, which results in a 3-fold increase in lung cancer diagnosis and a 10-fold increase in lung cancer surgery, this representing substantial psychological and physical burdens. Although the I-ELCAP investigators reported a surgical mortality rate of only 0.5% (when surgery is performed by board certified thoracic surgeons at cancer centers), the average surgical mortality rate for major lung surgery across the United States is 5%, and the frequency of serious complications is greater than 20%.¹⁵¹ These potential harms associated with thoracic surgery^{151–153} mandate that the effectiveness of LDCT screening be accurately assessed.

False-Negative Results

Sone et al.¹⁵⁴ published 2 reports on lung cancers missed at screening.^{155,156} Of the 88 lung cancers diagnosed, 32 were missed on 38 LDCT scans; 23 from detection errors (with a mean size of 9.8 mm) and 16 from interpretation errors (with a mean size of 15.9 mm). Detection errors included 1) subtle lesions (91%) appearing as GGOs; and 2) lesions (83%)

that were overlapped with, obscured by, or similar in appearance to normal structures (such as blood vessels). Interpretation errors (87%) were seen in patients who had underlying lung disease, such as tuberculosis, emphysema, or fibrosis.

The second report revealed that 84% of missed cancers in that database were subsequently detected using an automated lung nodule detection method. The CAD method involved the use of gray-level thresholding techniques to identify 3-dimensionally contiguous structures with the lungs, which were possible nodule candidates. The problem is that CAD systems are not universally deployed, and the success of detecting disease can vary greatly among radiologists. The variability and success of CAD and volumetric analysis systems may also affect the success of screening trials. Although these issues are partly being addressed through NCI-sponsored programs (such as the RIDER and PAR 08–225 programs), the range in variability at various centers, particularly outside of academic institutions, may lead to significant differences in results compared with those published from clinical trials. False-negative results from a screening test may provide an individual patient with a false sense of security, causing a patient to perhaps ignore symptoms that may have otherwise led to more evaluation.

Futile Detection of Small Aggressive Tumors

Early detection using lung cancer screening may not be beneficial if a small tumor is very aggressive and has already metastasized, with a loss of opportunity for effective treatment. Studies show that a 5-mm lung cancer has undergone approximately 20 doublings yielding 10^8 cells, whereas patient death typically occurs with a tumor burden of 10^{12} cells.¹⁵⁷ Even small tumors may have already metastasized. Studies have also shown that metastases can occur at the time of angiogenesis, when lesions are approximately 1 to 2 mm.¹⁵⁸ Human tumors grown in nude mouse models can shed 3 to 6 million cells per gram of tissue every 24 hours,¹⁵⁹ providing the potential for early metastasis.

However, the NLST trial results show that lung cancer screening is effective in select high-risk patients.⁸ The data from this trial show that detecting and treating lung lesions lead to a reduction in lung cancer–specific mortality. Therefore, the likelihood of futile therapy in patients with screen-detected tumors is much less, albeit not zero. However, because the natural history of lung cancer is heterogeneous and not completely predictable or linear,¹⁶⁰ the potential remains for futile treatment in patients with an aggressive tumor that is already incurable at the time of screening diagnosis.

Futile Detection of Indolent Disease

Although lung cancer specialists generally have a strong opinion of the uniform fatality of untreated lung cancer, recent studies of some low-grade lung cancers (i.e., BAC) show a potential for prolonged survival in some patients with NSCLC, even without therapy.^{161,162} Note that a new lung adenocarcinoma classification has recommended that the term *BAC* should not be used anymore. Newly defined entities of AIS and MIA, which are likely to present as ground glass nodules (GGN), should have 100% 5-year disease-free survival rate if completely resected.^{64,161} A greater percentage of the lepidic pattern (formerly BAC

pattern), which corresponds with the ground glass component in a part-solid nodule, is correlated with a more favorable prognosis.^{64,161,162}

Furthermore, experience in lung cancer screening has raised the question of increased identification of indolent tumors in the screened population.^{121,163} These indolent tumors may not cause symptoms or cancer mortality; therefore, patients do not benefit from screening and subsequent workup and treatment. A percentage of these patients will be exposed to the risk, morbidity, and mortality of surgical resection that, in retrospect, will not increase their life expectancy. As the newly defined entities of AIS and MIA (formerly BAC) with excellent survival have been separated from overtly invasive adenocarcinomas, the potential exists to learn how to minimize surgical intervention for pure GGNs through CT screening studies and long-term follow-up.⁶⁴

Bach et al.¹²¹ found an increase in the number of patients with lung cancer detected through screening, yet no evidence of a decline in the number of deaths from lung cancer. Their nonrandomized study raised concern that LDCT screening may lead to overdiagnosis of indolent cases and to the morbidity of treatment, without a survival benefit. However, the recent randomized NLST found that LDCT does decrease lung cancer mortality.⁸

Quality of Life

What effect a lung cancer screening trial will have on the quality of life (see Benefits of Lung Cancer Screening on page 253) is not fully known. A study by van den Bergh et al.¹⁶⁴ found no measured adverse effects, although approximately half of the participants reported discomfort while waiting for the results. However, others have reported significant personal and physical quality-of-life issues from screening tests (<http://health.usnews.com/usnews/health/articles/030519/19diagnosis.htm>). Several studies (including the NLST and NELSON trial) will be measuring quality-of-life issues.^{137,138} Recent data from the NELSON trial suggest that lung screening did not adversely affect quality of life.¹³⁸ False-positive and indeterminate results may decrease quality of life because of mental anguish and additional testing.

Unnecessary Testing

Any lung cancer screening program will result in additional testing. In a report by Croswell et al.¹⁶⁵ (from the Prostate, Lung, Colorectal, and Ovarian trial), the cumulative risk of having one false-positive result was 60% for men and 49% for women. The cumulative risk of undergoing an invasive diagnostic procedure prompted by the false-positive test was 29% for men and 22% for women. The NLST is a carefully supervised, randomized, controlled trial. In a less-controlled environment, the rate of additive studies may be higher. Siström et al.¹⁶⁶ reviewed the recommendations for additional imaging in more than 5.9 million radiology reports; they reported additional imaging of 35.8% for chest LDCT. The issue of incidental findings on screening examinations is problematic, and some organizations are attempting to address the issue, but regional and physician variations remain.¹⁶⁷

Radiation Exposure With LDCT

Current MDCT scanners provide a significantly enhanced capability for detecting small nodules through allowing thinner slice images. Using low-dose techniques, the mean effective radiation dose is 1.4 mSv (SD, 0.5 mSv) compared with an average of 7 mSv for conventional CT.¹⁶⁸ However, the radiation dose of LDCT is 10 times that of chest radiography.

There may be even more reason to be concerned about use of chest LDCT scans for lung cancer screening, because these individuals, who are already at high risk for lung cancer, may experience adverse effects from increased radiation exposure. In fact, the effects of repeated exposure to radiation at regular intervals are not known. Brenner¹⁶⁹ estimated a 1.8% increase in lung cancer cases if 50% of all current and former smokers in the United States between 50 and 75 years of age were to undergo annual LDCT scans for lung cancer screening. However, lower doses of radiation are now used for LDCT scans and these lower doses may be less dangerous.¹⁷⁰ The risk of radiation exposure over long periods will have to be considered when screening guidelines are developed, especially when recommending how frequently the scans should be performed.

Increased Cost

Many are concerned about the effect of lung cancer screening on medical resources, including the cost of LDCT screening and additional testing. For each LDCT screen for lung cancer, the Medicare reimbursement rate is approximately \$300 in the United States (<http://www.cancer.gov/newscenter/pressreleases/2011/NLSTFastFacts>). Therefore, with the number of high-risk individuals eligible for lung cancer screening at approximately 7 million (using NLST data), the annual cost in the United States would be about \$2.1 billion.⁸

Helical LDCT screening will lead to false-positive results, detection of indeterminate nodules, and detection of potential disease other than lung cancer. In the NLST, although 24.2% of the LDCT scans were positive, most were false-positive (96.4%). In 2004, the economic effect of false-positive cancer screening results was estimated to be at least \$1000 per incident.¹⁴² Therefore, a conservative estimate of the costs of workup after 1 year for only the false-positive results would be \$1.63 billion (7 million \times 24.2% = 1.694 million \times 96.4% = 1.633 \times \$1000). This estimate does not include costs of workup for other potential abnormalities detected during screening, such as cardiac and upper abdominal pathology. Of individuals with a false-positive result, approximately 7% will undergo an invasive procedure (typically bronchoscopy).¹⁴¹

Limiting screening to only high-risk patients not only helps avoid unnecessary risks in individuals with a lower risk of cancer but also is important for keeping the screening program cost-effective. "Pre-screening" based on age, smoking history, appropriate medical history, family history, and occupational history is important to determine which patients are high risk.

Lack of well-defined guidelines can lead to overuse of screening. Excessive screening and/or interpretations of studies by unskilled individuals may occur without strict guidelines (as with mammography). Other factors, such as the interval at which screening should be

performed, will also affect calculations of cost. In the recent screening studies using helical LDCT, 23% of the ELCAP and 69% of the 1999 Mayo Clinic study had at least one indeterminate nodule. Depending on the size and characteristics of the indeterminate nodule, further evaluation may include serial follow-up LDCT, dynamic contrast-enhanced nodule densitometry, PET, or biopsy. False-positive results also lead to additional unnecessary testing and increased cost. The financial burden, potential complications from invasive procedures, and psychological effect of investigating these indeterminate and false-positive lesions are not fully understood.

Lung screening also leads to detection of disease other than lung cancer, such as infection; coronary artery calcification; and renal, adrenal, and liver lesions. Although detection of other diseases may frequently provide a clinical benefit to the patient, certainly costs will be further increased with additional testing and treatment.

Cost-Effectiveness

The cost-effectiveness of lung cancer screening is also important to consider. LDCT imaging is more expensive than many other screening programs, and therefore it is important to validate the effectiveness first. Each LDCT screen for lung cancer costs approximately \$300 (<http://www.cancer.gov/news-center/pressreleases/2011/NLSTFastFacts>). In contrast, a mammogram costs \$80 to \$150. Several cost analyses of LDCT lung cancer screening have been undertaken, but all have some limitations because they used simulation modeling.^{144,171,172} The Mahadevia study concluded that false-positive results are a major obstacle to LDCT screening and may prevent it from being cost-effective.¹⁷¹ However, Wisnivesky et al.¹⁴³ have argued that LDCT lung cancer screening is potentially highly cost-effective and that the cost-effectiveness ratios are not different from those of other screening programs. The NLST cost-effectiveness evaluation will be extremely beneficial in understanding this issue.

Summary

Lung cancer screening with LDCT is a complex and controversial topic, with inherent risks and benefits. Results from the large, prospective, randomized NLST show that lung cancer screening with LDCT can decrease lung cancer–specific mortality by 20% and even decrease all-cause mortality by 7%.⁸ The NLST results indicate that to prevent one death from lung cancer, 320 high-risk individuals must be screened with LDCT. However, the NLST findings have not been replicated yet in a separate cohort. Further analysis of the NLST is underway, including comparative effectiveness modeling. The cost-effectiveness and true benefit-to-risk ratio for lung cancer screening still must be determined. At some point, an acceptable level of risk will have to be deemed appropriate for the benefits of screening.

The NCCN Lung Cancer Screening Panel recommends helical LDCT screening for select patients at high risk for lung cancer based on the NLST results, nonrandomized studies, and observational data. These guidelines discuss in detail the criteria for determining which patients are at high risk, and the algorithm provides recommendations for evaluating and following-up nodules detected on LDCT screening (e.g., solid and part-solid nodules).

Smokers should always be encouraged to quit smoking tobacco (<http://www.smokefree.gov/>). Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful (see *Treating Tobacco Use and Dependence: Quick Reference Guide for Clinicians*; <http://www.surgeongeneral.gov/tobacco/tobaqrg.htm>).

When considering lung cancer screening, it is important to have a full understanding of all risks and benefits related to screening with LDCT. As policies for implementing lung screening programs are designed, a focus on multidisciplinary programs (incorporating primary care doctors, pulmonologists, radiologists, thoracic surgeons, medical oncologists, and pathologists) will be helpful to optimize decision-making and minimize interventions for patients with benign lung disease.

NCCN Clinical Practice Guidelines in Oncology for Lung Cancer Screening

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, lung cancer, screening, LDCT, smoking, carcinogen, tobacco (*JNCCN* 2012;10:240–265)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines[®] is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network[®] (NCCN[®]) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

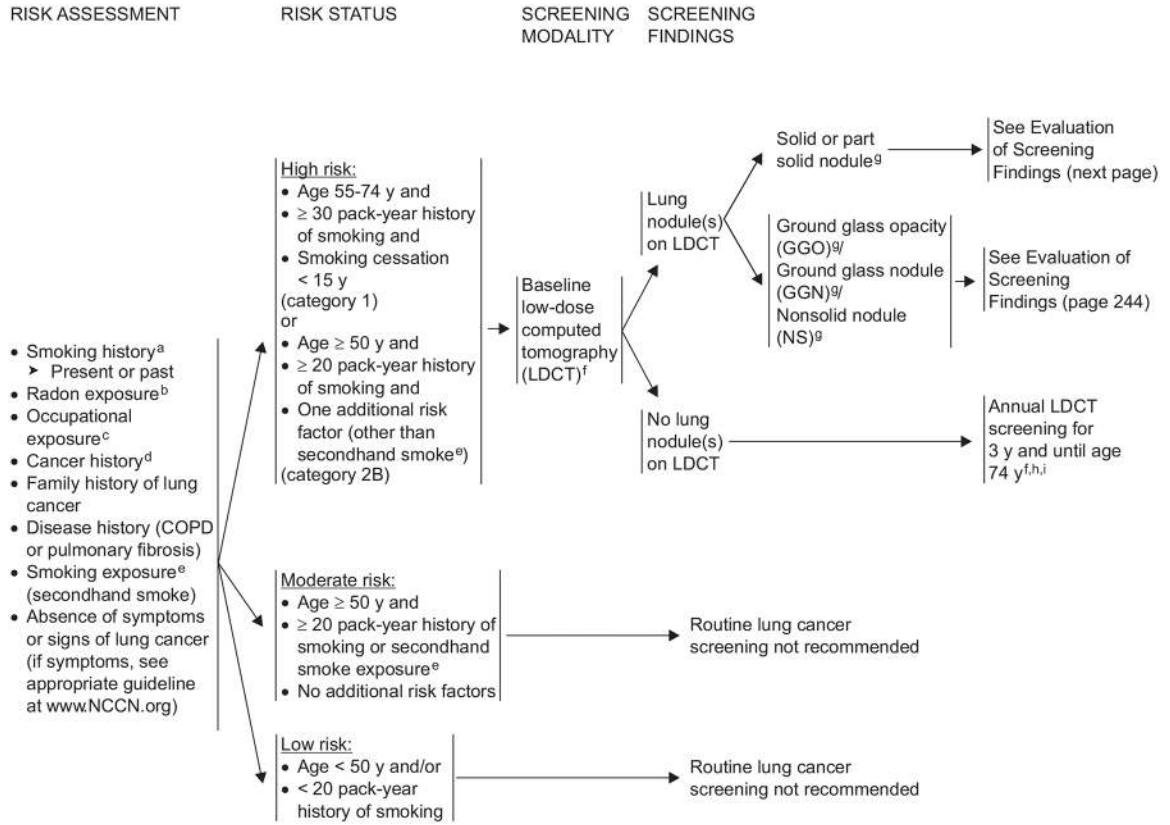
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Disclosures for the NCCN Guidelines Panel for Lung Cancer Screening

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Lung Cancer Screening Panel members can be found on page 265. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit www.NCCN.org.

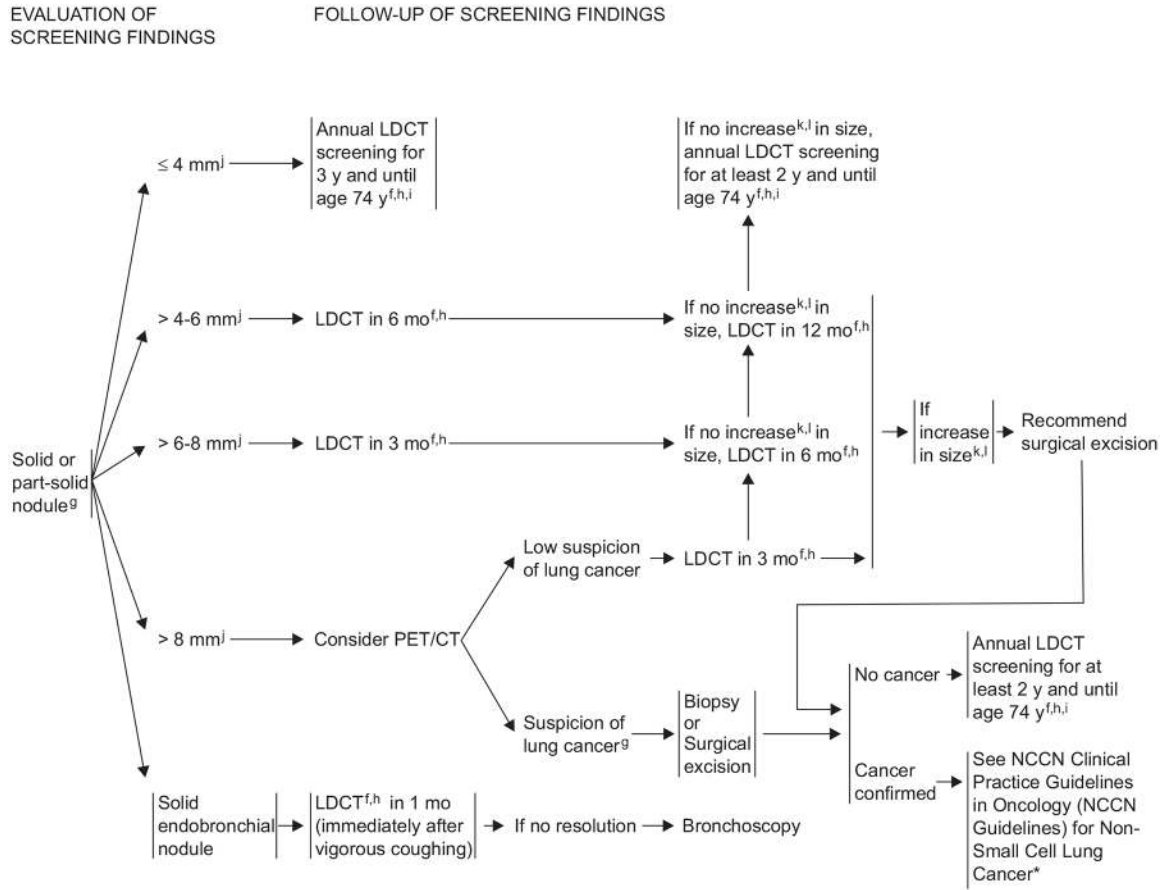


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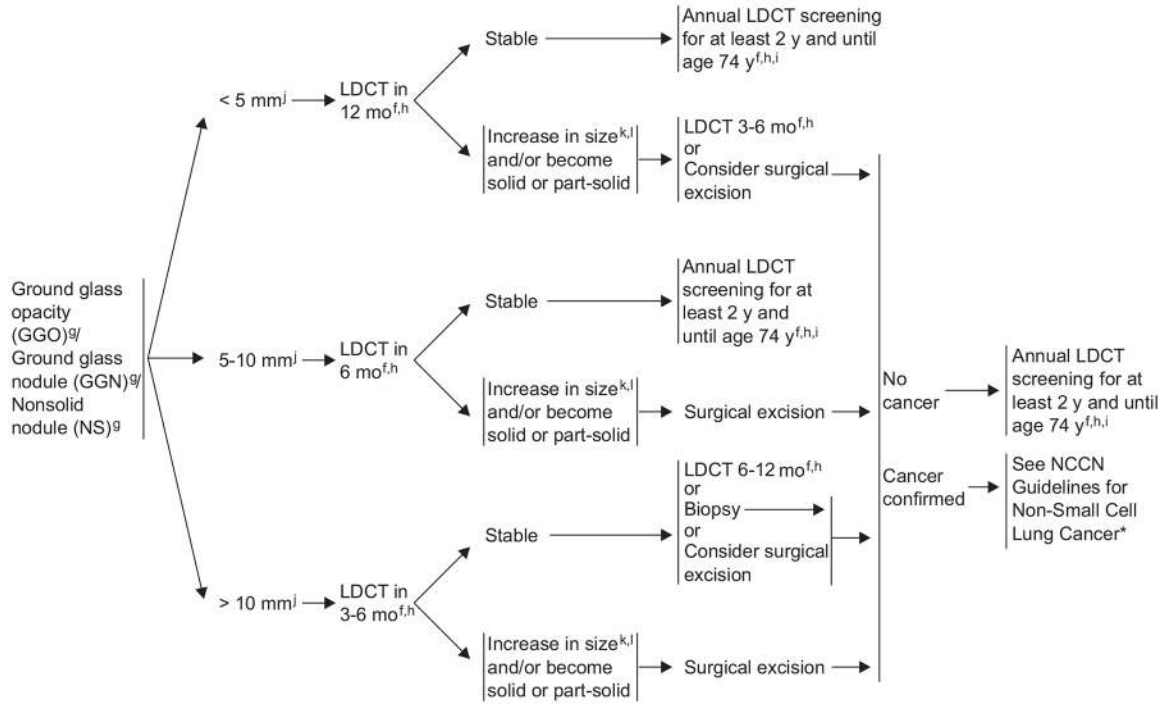
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EVALUATION OF SCREENING FINDINGS

FOLLOW-UP OF SCREENING FINDINGS

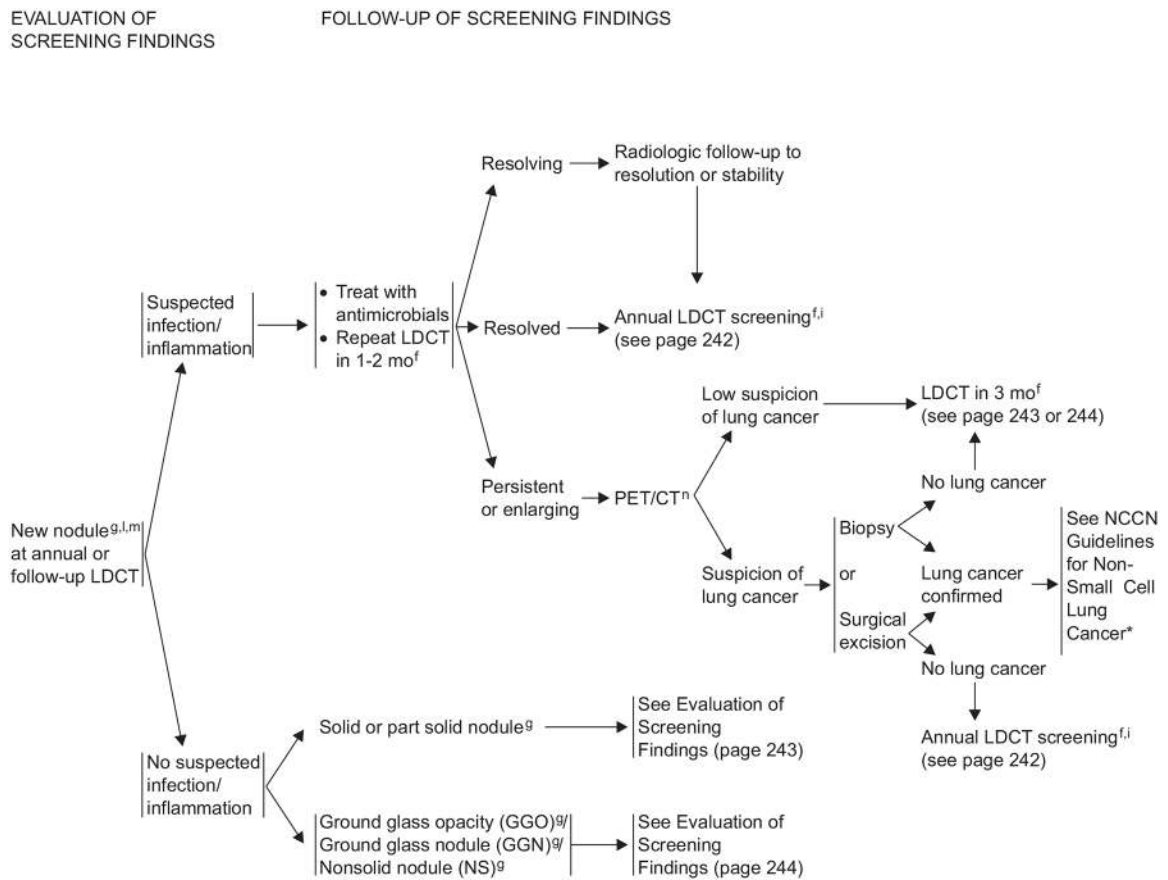


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^aSmokers should always be encouraged to quit smoking (<http://www.smokefree.gov/>).

^bDocumented high radon exposure.

^cAgents that are identified specifically as carcinogens targeting the lungs: silica, cadmium, asbestos, arsenic, beryllium, chromium, diesel fumes, and nickel.

^dThere is increased risk of developing new primary lung cancer among survivors of lung cancer, lymphomas, cancers of the head and neck, or smoking-related cancers.

^eIndividuals exposed to secondhand smoke have a highly variable exposure to the carcinogens, with varying evidence for increased risk after this variable exposure. Therefore, secondhand smoke is not independently considered a risk factor for lung cancer screening.

^fAll screening and follow-up CT scans should be performed at low dose (100–120 kVp and 40–60 mAs or less), unless evaluating mediastinal abnormalities or lymph nodes, for which standard-dose CT with IV contrast might be appropriate.

^gWithout benign pattern of calcification, fat in nodule as in hamartoma, or features suggesting inflammatory etiology. When multiple nodules are present and occult infection or inflammation is a possibility, an added option is a course of a broad-spectrum antibiotic with anaerobic coverage, followed by low-dose CT 1–2 mo later.

^hIf new nodule at annual or follow-up LDCT, see page 245. New nodule is defined as ≥ 3 mm in mean diameter

ⁱThere is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.

^jMean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter when compared with the baseline scan.

^kFor nodules ≤ 15 mm: increase in mean diameter ≥ 2 mm in any nodule or in the solid portion of a part solid nodule compared with baseline scan. For nodules ≥ 15 mm: increase in mean diameter of $\geq 15\%$ compared with baseline scan.

^lRapid increase in size should raise suspicion of inflammatory etiology or malignancy other than NSCLC.

^mNew nodule is defined as ≥ 3 mm in mean diameter.

ⁿPET-CT for lesions ≥ 8 mm.

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

RISKS/BENEFITS OF LUNG CANCER SCREENING

RISKS

- Futile detection of small aggressive tumors or indolent disease
- Quality of life
 - Anxiety of test findings
- Physical complications from diagnostic workup
- False-positive results
- False-negative results
- Unnecessary testing
- Radiation exposure
- Cost

BENEFITS

- Decreased lung cancer mortality
- Quality of life
 - Reduction in disease-related morbidity
 - Reduction in treatment-related morbidity
 - Improvement in healthy lifestyles
 - Reduction in anxiety/psychosocial burden
- Cost-effectiveness

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