National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Lung Cancer Screening

Version 2.2016

NCCN.org

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NCCN Guidelines Panel Disclosures

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

Updates in Version 2.2016 of the NCCN Guidelines for Lung Cancer Screening from Version 1.2016 include:

LCS-6
- Suspected infection/inflammation; Follow-up modified: ~~Radiologic follow-up~~ Chest CT without contrast in 3-6 mo to resolution or stability.

Updates in Version 1.2016 of the NCCN Guidelines for Lung Cancer Screening from Version 2.2015 include:

LCS-1
- Risk Assessment
  - Bullet 1, Smoking history: "present or past" removed and content elaborated in footnote "c."
  - Footnote "c" modified with the addition of the following sentence: "Smoking history should document both extent of exposure in pack-years and the amount of time since smoking cessation in former smokers."
  - Footnote "d" modified: "Documented *sustained and substantially elevated* ~~high~~ radon exposure."
  - Bullet 5: Family history of lung cancer clarified as "in first-degree relatives."
  - Footnote "h" added: "Although randomized trial evidence supports screening to age 74 years, there is uncertainty about the upper age limit to initiate or continue screening. One can consider screening beyond age 74 years as long as patient functional status and comorbidity allow consideration for curative intent therapy."
- Risk Status
  - Moderate risk and Low risk: "Routine" removed before "lung cancer screening not recommended."
  - High-risk group: ~~For patients eligible~~ "*In candidates* for screening, shared patient/physician decision making is ~~required~~ *recommended*, including a discussion of benefits/risks."
  - Footnote "i" added: Risk calculators may assist with decision making to determine if screening should be performed. Tammemägi MC, Church TR, Hocking WG, et al. Evaluation of the lung cancer risks at which to screen ever- and never-smokers: screening rules applied to the PLCO and NLST cohorts. PLOS Med 2014;11(12)e1001764 http://www.ncbi.nlm.nih.gov/pubmed/25460915.

LCS-2 through LCS-5
- Follow-up of Screening Findings
  "Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient *is* no longer ~~eligible~~ *a candidate* for definitive treatment."

LCS-2
- Footnote "k" modified: "Strongly recommend standardized reporting (http://www.acr.org/Quality-Safety/Resources/LungRADS). *Pinsky PF, Gierada DS, Black W, et al. Performance of Lung-RADS in the National Lung Screening Trial: A Retrospective Assessment. Ann Intern Med 2015;162:485-491.*"

LCS-3
- Footnote "p" modified: "PET has a low sensitivity for nodules with less than 8 mm of solid component *and for small nodules near the diaphragm. PET/CT is only one consideration of multiple criteria for determining whether a nodule has a high risk of being lung cancer. If a patient has granulomatous disease, PET/CT is less specific.*"
- Footnote "u" added: "If biopsy is non-diagnostic and a strong suspicion for cancer persists, suggest repeat biopsy or surgical excision or short interval follow-up (3 months)."

LCS-4 and LCS-5
- Follow-up of Screening Findings
  "Stable" changed to "Stable, resolving, or resolved"

LCS-B
- Benefits, last bullet added: "Discovery of other significant occult health risks (eg, thyroid nodule, severe but silent coronary artery disease, early renal cancer in upper pole of kidney, aortic aneurysm, breast cancer)."
- Reference 1 added.

RISK ASSESSMENT[a,b]

- Smoking history[c]
- Radon exposure[d]
- Occupational exposure[e]
- Cancer history[f]
- Family history of lung cancer in first-degree relatives
- Disease history (COPD or pulmonary fibrosis)
- Smoking exposure[g] (second-hand smoke)
- Absence of symptoms or signs of lung cancer (if symptoms, see appropriate NCCN Guidelines)

RISK STATUS

High risk:[h]
- Age 55–74 y and
- ≥30 pack-year history of smoking and
- Smoking cessation <15 y

(category 1)

or
- Age ≥50 y and
- ≥20 pack-year history of smoking and
- One additional risk factor (other than second-hand smoke)

→ In candidates for screening, shared patient/physician decision making is recommended, including a discussion of benefits/risks[i] → See Screening Findings (LCS-2)

Moderate risk:
- Age ≥50 y and
- ≥20 pack-year history of smoking or second-hand smoke exposure[g]
- No additional risk factors

→ Lung cancer screening not recommended

Low risk:
- Age <50 y and/or
- <20 pack-year history of smoking

→ Lung cancer screening not recommended

[a]It is recommended that institutions performing lung cancer screening use a multidisciplinary approach that includes the specialties of thoracic radiology, pulmonary medicine, and thoracic surgery.

[b]Lung cancer screening is appropriate to consider for high-risk patients who are potential candidates for definitive treatment. Chest x-ray is not recommended for lung cancer screening.

[c]All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking (http://www.surgeongeneral.gov/initiatives/tobacco/index.html). For additional cessation support and resources, smokers can be referred to http://www.smokefree.gov. Lung cancer screening should not be considered a substitute for smoking cessation. Smoking history should document both extent of exposure in pack-years and the amount of time since smoking cessation in former smokers. See also the NCCN Guidelines for Smoking Cessation.

[d]Documented sustained and substantially elevated radon exposure.

[e]Agents that are identified specifically as carcinogens targeting the lungs: silica, cadmium, asbestos, arsenic, beryllium, chromium, diesel fumes, nickel, coal smoke, and soot.

[f]There 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.

[g]Individuals exposed to second-hand smoke have a highly variable exposure to the carcinogens, with varying evidence for increased risk after this variable exposure. Therefore, second-hand smoke is not independently considered a risk factor for lung cancer screening.

[h]Although randomized trial evidence supports screening to age 74 years, there is uncertainty about the upper age limit to initiate or continue screening. One can consider screening beyond age 74 years as long as patient functional status and comorbidity allow consideration for curative intent therapy.

[i]Risk calculators may assist with decision making to determine if screening should be performed. Tammemägi MC, Church TR, Hocking WG, et al. Evaluation of the lung cancer risks at which to screen ever- and never-smokers: screening rules applied to the PLCO and NLST cohorts. PLOS Med 2014;11(12)e1001764. http://www.ncbi.nlm.nih.gov/pubmed/25460915.

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SCREENING MODALITY / SCREENING FINDINGS

Baseline low-dose CT (LDCT)[j]

- **Lung nodule(s) on LDCT[k]**
  - **Solid or part-solid nodule[l]** → See Evaluation of Screening Findings (LCS-3)
  - **Ground-glass opacity (GGO)[l]; Ground-glass nodule (GGN)[l]; Nonsolid nodule (NS)[l]** → See Evaluation of Screening Findings (LCS-4)
  - **Multiple GGOs/GGNs/NSs[l]** → See Evaluation of Screening Findings (LCS-5)
- **No lung nodule(s) on LDCT** → **Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient is no longer a candidate for definitive treatment[j,m,n]**
- **Findings requiring follow-up for diseases other than lung cancer (eg, suspicious for other cancers, COPD, coronary artery calcifications)**

[j]All 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, where standard-dose CT with IV contrast might be appropriate (See LCS-A). There should be a systematic process for appropriate follow-up.

[k]Strongly recommend standardized reporting (http://www.acr.org/Quality-Safety/Resources/LungRADS). Pinsky PF, Gierada DS, Black W, et al. Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment. Ann Intern Med 2015;162:485-491.

[l]Without 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 LDCT 1–2 months later.

[m]If new nodule at annual or follow-up LDCT, see LCS-6. New nodule is defined as ≥3 mm in mean diameter.

[n]There is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.

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EVALUATION OF SCREENING FINDINGS / FOLLOW-UP OF SCREENING FINDINGS

Solid or part-solid nodule[l]

- **<6 mm[o]** → Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient is no longer a candidate for definitive treatment[j,m,n]
- **6–8 mm[o]** → LDCT in 3 mo[j,m] → If no increase[r,s] in size, LDCT in 6 mo[k,n]
  - → Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient is no longer a candidate for definitive treatment[j,m,n]
  - → If increase in size[p,q] → Surgical excision (see below)
- **>8 mm[o]** → Consider PET/CT[p]
  - → Low suspicion of lung cancer → LDCT in 3 mo[j,m]
    - → If no increase[r,s] in size, LDCT in 6 mo[k,n]
    - → If increase in size[p,q] → Surgical excision (see below)
  - → Suspicion of lung cancer[q] → Biopsy[t,u] or Surgical excision
    - → No cancer → Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient is no longer a candidate for definitive treatment[j,m,n]
    - → Cancer confirmed → See appropriate NCCN Guidelines
- **Solid endobronchial nodule** → LDCT[j,m] in 1 mo (immediately after vigorous coughing) → If no resolution → Bronchoscopy

[j]All 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, where standard-dose CT with IV contrast might be appropriate. (See LCS-A). There should be a systematic process for appropriate follow-up.

[l]Without 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 LDCT 1–2 months later.

[m]If new nodule at annual or follow-up LDCT, see LCS-6. New nodule is defined as ≥3 mm in mean diameter.

[n]There is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.

[o]Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter.

[p]PET has a low sensitivity for nodules with less than 8 mm of solid component and for small nodules near the diaphragm. PET/CT is only one consideration of multiple criteria for determining whether a nodule has a high risk of being lung cancer. If a patient has granulomatous disease, PET/CT is less specific.

[q]Criteria for suspicion of malignancy: hypermetabolism higher than the background of surrounding lung parenchyma, regardless of absolute SUV.

[r]For nodules <15 mm: increase in mean diameter ≥2 mm in any nodule or in the solid portion of a part-solid nodule compared to baseline scan. For nodules ≥15 mm: increase in mean diameter of ≥15% compared to baseline scan.

[s]Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than non-small cell lung cancer. (see LCS-6)

[t]Tissue samples need to be adequate for both histology and molecular testing. Travis WD, et al. Diagnosis of lung cancer in small biopsies and cytology: Implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. Arch Pathol Lab Med 2013;137:668-684.

[u]If biopsy is non-diagnostic and a strong suspicion for cancer persists, suggest repeat biopsy or surgical excision or short-interval follow-up (3 months).

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EVALUATION OF SCREENING FINDINGS / FOLLOW-UP OF SCREENING FINDINGS

GGO GGN NS[v]

- **≤5 mm[o]** → **LDCT in 12 mo[j,m]**
  - **Stable, resolving, or resolved** → **Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient is no longer a candidate for definitive treatment[j,m,n]**
  - **Increase in size[r,s] and/or becomes solid or part solid[l]** → **LDCT 3–6 mo[j,m]** or **Consider surgical excision** →
- **>5–10 mm[o]** → **LDCT in 6 mo[j,m]**
  - **Stable, resolving, or resolved** → **Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient is no longer a candidate for definitive treatment[j,m,n]**
  - **Increase in size[r,s] and/or becomes solid or part solid[l]** → **Surgical excision** →
- **>10 mm[o]** → **LDCT in 3–6 mo[j,m]**
  - **Stable, resolving, or resolved** → **LDCT for 6–12 mo[j,m]** or **Biopsy[t]** → or **Consider surgical excision** →
  - **Increase in size[r,s] and/or becomes solid or part solid[l]** → **Surgical excision** →

(Surgical excision/biopsy) →
- **No cancer** → **Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient is no longer a candidate for definitive treatment[j,m,n]**
- **Cancer confirmed** → **See appropriate NCCN Guidelines**

[j]All 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, where standard dose CT with IV contrast might be appropriate. (See LCS-A). There should be a systematic process for appropriate follow-up.
[l]Without 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 LDCT 1–2 months later.
[m]If new nodule at annual or follow-up LDCT, see LCS-6. New nodule is defined as ≥3 mm in mean diameter.
[n]There is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.
[o]Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter.
[r]For nodules <15 mm: increase in mean diameter ≥2 mm in any nodule or in the solid portion of a part-solid nodule compared to baseline scan. For nodules ≥15 mm: increase in mean diameter of ≥15% compared to baseline scan.
[s]Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than non-small cell lung cancer. (see LCS-6).
[t]Tissue samples need to be adequate for both histology and molecular testing. Travis WD, et al. Diagnosis of lung cancer in small biopsies and cytology: Implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. Arch Pathol Lab Med 2013;137:668-684.
[v]It is crucial that all GGOs/GGNs/nonsolid lesions be reviewed at thin (<1.5 mm) slices to exclude any solid components. Any solid component in the nodule requires management of the lesion with the part-solid recommendations (see LCS-3).

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EVALUATION OF SCREENING FINDINGS — FOLLOW-UP OF SCREENING FINDINGS

Multiple GGOs GGNs NSs[l,v]

- **Pure GGNs ≤5 mm[o]** → **LDCT in 12 mo[j,m]**
  - **Stable, resolving, or resolved** → **Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient is no longer a candidate for definitive treatment[j,m,n]**
  - **Increase in size[r,s] and/or becomes solid or part solid[l]** → **LDCT 3–6 mo[j,m] or Consider surgical excision** →
    - **No cancer** → **Consider annual LDCT until patient is no longer a candidate for definitive treatment[j,m,n]**
    - **Cancer confirmed** → **See appropriate NCCN Guidelines**
- **Pure GGNs >5 mm[o] without a dominant lesion** → **LDCT in 6 mo[j,m]**
  - **Stable, resolving, or resolved** → **Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient is no longer a candidate for definitive treatment[j,m,n]**
  - **Increase in size[r,s] and/or becomes solid or part solid[l]** → **Consider surgical excision** →
    - **No cancer** → **Consider annual LDCT until patient is no longer a candidate for definitive treatment[j,m,n]**
    - **Cancer confirmed** → **See appropriate NCCN Guidelines**
- **Dominant nodule(s) with part-solid or solid component[o]** → **LDCT in 3–6 mo[j,m,v]**
  - **Resolved** → **Annual LDCT screening[j,n] (see LCS-1)**
  - **Persistent or increase in size[r,s]** → **See LCS-3**

[j]All 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, where standard dose CT with IV contrast might be appropriate. (See LCS-A). There should be a systematic process for appropriate follow-up.
[l]Without 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 LDCT 1–2 months later.
[m]If new nodule at annual or follow-up LDCT, see LCS-6. New nodule is defined as ≥3 mm in mean diameter.
[n]There is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.
[o]Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter.
[r]For nodules <15 mm: increase in mean diameter ≥2 mm in any nodule or in the solid portion of a part-solid nodule compared to baseline scan. For nodules ≥15 mm: increase in mean diameter of ≥15% compared to baseline scan.
[s]Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than non-small cell lung cancer. (see LCS-6)
[v]It is crucial that all GGOs/GGNs/nonsolid lesions be reviewed at thin (<1.5 mm) slices to exclude any solid components. Any solid component in the nodule requires management of the lesion with the part-solid recommendations (see LCS-3).

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EVALUATION OF SCREENING FINDINGS

FOLLOW-UP OF SCREENING FINDINGS

New nodule[l,s,w] at annual or follow-up LDCT

- **Suspected infection/ inflammation** → • Consider treatment with antimicrobials • Repeat LDCT in 1–2 mo[j]
  - **Resolving** → Chest CT without contrast in 3-6 mo to resolution or stability → Annual LDCT screening[j,n] (see LCS-1)
  - **Resolved** → Annual LDCT screening[j,n] (see LCS-1)
  - **Persistent or enlarging** → PET/CT[x]
    - **Low suspicion of lung cancer** → LDCT in 3 mo[j] (See LCS-3 or LCS-4)
    - **Suspicion of lung cancer[q]** → Biopsy[t,u] or Surgical excision
      - **No lung cancer** → LDCT in 3 mo[j] (See LCS-3 or LCS-4)
      - **Lung cancer confirmed** → See appropriate NCCN Guidelines
      - **No lung cancer** → Annual LDCT screening[j,n] (see LCS-1)
- **No suspected infection/ inflammation**
  - **Solid or part-solid nodule[l]** → See Evaluation of Screening Findings (LCS-3)
  - **GGOs/GGNs/NSs[l]** → See Evaluation of Screening Findings (LCS-4)
  - **Multiple GGOs/GGNs/NSs[l]** → See Evaluation of Screening Findings (LCS-5)

[j]All 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, where standard dose CT with IV contrast might be appropriate. (See LCS-A). There should be a systematic process for appropriate follow-up.
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[n]There is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.
[q]Criteria for suspicion of malignancy: hypermetabolism higher than the background of surrounding lung parenchyma, regardless of absolute SUV.
[s]Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than non-small cell lung cancer.
[t]Tissue samples need to be adequate for both histology and molecular testing. Travis WD, et al. Diagnosis of lung cancer in small biopsies and cytology: Implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. Arch Pathol Lab Med 2013;137:668-684.
[u]If biopsy is non-diagnostic and a strong suspicion for cancer persists, suggest repeat biopsy or surgical excision or short-interval follow-up (3 months).
[w]New nodule is defined as ≥3 mm in mean diameter.
[x]PET-CT for lesions >8 mm.

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Low-Dose Computed Tomography Acquisition, Storage, Interpretation, and Nodule Reporting

Acquisition	**Small Patient (BMI ≤30)**	**Large Patient (BMI >30)**
Total radiation exposure	≤3 mSv	≤5 mSv
kVp	100–120	120
mAs	≤40	≤60
	All Patients	
Gantry rotation speed	≤0.5	
Detector collimation	≤1.5 mm	
Slice width	≤2.5 mm; ≤1.0 mm preferred	
Slice interval	≤slice width; 50% overlap preferred for 3D and CAD applications	
Scan acquisition time	≤10 seconds (single breath hold)	
Breathing	Maximum inspiration	
Contrast	No oral or intravenous contrast	
CT scanner detectors	≥16	
Storage	All acquired images, including thin sections; MIPs and CAD renderings if used	
Interpretation Tools		
Platform	Computer workstation review	
Image type	Standard and MIP images	
Comparison studies	Comparison with prior chest CT images (not reports) is essential to evaluate change in size, morphology, and density of nodules; review of serial chest CT exams is important to detect slow growth	
Nodule Parameters		
Size	Largest mean diameter on a single image*	
Density	Solid, ground-glass, or mixed†	
Calcification	Present/absent; if present: solid, central vs. eccentric, concentric rings, popcorn, stippled, amorphous	
Fat	Report if present	
Shape	Round/ovoid, triangular	
Margin	Smooth, lobulated, spiculated	
Lung location	By lobe of the lung, preferably by segment, and if subpleural	
Location in dataset	Specify series and image number for future comparison	
Temporal comparison	If unchanged, include the longest duration of no change as directly viewed by the interpreter on the images (not by report); if changed, report current and prior size	

BMI = body mass index; CAD = computer-aided diagnosis; CT = computed tomography; MIP = maximum intensity projection.
*Mean of the longest diameter of the nodule and its perpendicular diameter, when compared to the baseline scan.
†Mixed; otherwise referred to as part solid.

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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 and procedures**
- **Radiation exposure**
- **Cost**
- **Incidental lesions**

BENEFITS
- **Decreased lung cancer mortality[1]**
- **Quality of life**
  - **Reduction in disease-related morbidity**
  - **Reduction in treatment-related morbidity**
  - **Improvement in healthy lifestyles**
  - **Reduction in anxiety/psychosocial burden**
- **Discovery of other significant occult health risks (eg, thyroid nodule, severe but silent coronary artery disease, early renal cancer in upper pole of kidney, aortic aneurysm, breast cancer)**

*See Discussion for more detailed information.

[1]National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 03/17/15

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.

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Overview

Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide.[1-4] In 2015, it is estimated that 158,040 deaths (86,380 in men, 71,660 in women) from lung cancer will occur in the United States.[5] Five-year survival rates for lung cancer are only 16.8%, partly because most patients have advanced-stage lung cancer at initial diagnosis.[6] 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.[7,8] 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.[9] Currently, most lung cancer is diagnosed clinically when patients present with symptoms such as persistent cough, pain, and 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 low-dose computed tomography (LDCT) of the chest to screen select patients who are at high risk for lung cancer.[9-13] Chest x-ray is not recommended for lung cancer screening.[9,14]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Lung Cancer Screening were developed in 2011 and have been subsequently updated at least once every year.[9,15,16] These NCCN Guidelines®: 1) describe risk factors for lung cancer; 2) recommend criteria for selecting individuals with high-risk factors 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. The *Summary of the Guidelines Updates* section in the algorithm briefly describes the new changes for 2015. For example, the NCCN Panel revised the recommendation to category 2A (previously category 2B) for one of the high-risk groups eligible for lung cancer screening. For LDCT of the lung, the recommended slice width was revised as shown in the table on *Low-Dose Computed Tomography Acquisition, Storage, Interpretation, and Nodule Reporting*.

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. Adenocarcinoma is the most common type of NSCLC.[17] Thus, these NCCN Guidelines for Lung Cancer Screening mainly refer to detection of adenocarcinoma. Other types of cancer can metastasize to the lungs, such as breast cancer. There are also less common cancers of the lung or chest, such as malignant pleural mesothelioma and thymic carcinoma. Lung screening may also detect noncancerous conditions of the thorax (eg, aortic aneurysm, coronary artery calcification), tumors or benign disease outside of the chest (eg, renal cell carcinoma, adrenal adenoma), and infections (eg, tuberculosis, sarcoidosis).[18,19]

The goal of screening is to detect disease at a stage when it is not causing symptoms and when treatment will be 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 (eg, 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*.[20] 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.[21-24]

LDCT as Part of a Screening Program

Lung cancer screening with LDCT should be part of a program of care and should not be performed in isolation as a free-standing test.[25,26] Trained personnel and an organized administrative system to contact patients to achieve compliance with recommended follow-up studies are required for an effective lung screening program.[25] The NCCN-recommended follow-up intervals assume compliance with follow-up recommendations. To help ensure good image quality, all LDCT screening programs should use CT scanners that meet the standards of the American College of Radiology (ACR). The ACR has developed the Lung Imaging Reporting and Data System (Lung-RADS) to standardize the reporting and management from LDCT lung examinations.[27] The Lung-RADS protocol has been shown to improve the detection of lung cancer and to decrease the false-positive rate.[25,27-29]

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.[22,23,30,31] Shared patient/physician decision making may be the best approach before deciding whether to do LDCT lung screening, especially for patients with comorbid conditions.[32-34] It is recommended that institutions performing lung cancer screening use a multidisciplinary approach that may include specialties such as chest radiology, pulmonary medicine, and thoracic surgery.[35] Guidelines from the American College of Chest Physicians (ACCP) and ASCO state that only centers with considerable expertise in lung cancer screening should do LDCT.[36]

Randomized Trials

Disease-specific mortality, which is the number of cancer deaths relative to the number of individuals screened, is considered the ultimate test of screening effectiveness and is the only test that is without bias.[37] 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 (eg, lead-time bias, length-time bias).[38]

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 are 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.[8] For further discussion of randomized and nonrandomized screening trials, see *Benefits of Lung Cancer Screening* in this Discussion.

Several randomized trials have assessed whether screening with chest radiography could improve lung cancer survival. Many of these studies were flawed in their design or power, and all were negative.[23,39-42] A phase III randomized trial (The Prostate, Lung, Colorectal, and Ovarian [PLCO]) reported that annual screening with chest radiography is not useful for lung cancer screening in individuals at low risk for lung cancer.[43] More recently, studies have focused on the more sensitive modality of LDCT–based lung cancer screening (see *Benefits of Lung Cancer Screening* in this Discussion). However, analyses of some lung cancer screening studies using LDCT scans suggest that overdiagnosis (ie, diagnosis of cancer that would never be life-threatening) and false-positive screening tests are significant concerns.[24,44,45] Thus, although LDCT scanning may be a better screening test for lung cancer, it also has limitations (see *Benefits of Lung Cancer Screening* and *Risks of Lung Cancer Screening* in this Discussion).[23]

Multiple randomized trials are assessing LDCT screening for lung cancer among high-risk groups, including: 1) the National Lung Screening Trial (NLST), sponsored by the NCI;[8] 2) the Dutch-Belgian randomized lung cancer screening trial (NELSON); and the UK Lung Screen (UKLS).[10,46-55] The published results from the NLST show that LDCT decreased the relative risk (RR) of death from lung cancer by 20% (95% CI, 6.8–26.7; *P* = .004) when compared with chest radiography alone.[9] Although the NLST also reported a significant decrease in all-cause mortality of 7%, the apparent decrease is not significant after lung cancer mortality has been subtracted.

Lung Cancer Screening Guidelines

NCCN was the first major organization to develop lung cancer screening guidelines using LDCT based on the NLST data.[15] The International Association for the Study of Lung Cancer (IASLC) supports the NCCN Guidelines by emphasizing the need for guidelines, a multidisciplinary team approach, and integrated smoking cessation programs.[35] The U.S. Preventive Services Task Force (USPSTF) recently recommended lung screening; their B recommendation means that lung screening will now be covered under the Affordable Care Act for individuals with high-risk factors who are 55 to 80 years of age.[32] In February 2015, the Centers for Medicare & Medicaid Services (CMS) agreed to cover annual LDCT screening for appropriate Medicare beneficiaries at high risk for lung cancer (ie, smokers and former smokers ages 55–77 years with a 30 pack-year smoking history) if they also receive counseling and participate in shared decision making before screening. ACCP and ASCO also recommend lung cancer screening for individuals at high risk if they meet the criteria of the NLST (ie, smokers and former smokers ages 55–74 years with a 30 pack-year smoking history);[36] this recommendation has also been approved by the American Thoracic Society. The ACCP and ASCO Guidelines also emphasize the need for a multidisciplinary team approach and smoking cessation. The American Cancer Society, American Association for Thoracic Surgery, and USPSTF have also developed guidelines for lung cancer screening.[32,56-58]

Risk Factors for Lung Cancer

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.[27,59-62] This section reviews the currently known risk factors for the development of lung cancer to identify populations with high-risk factors that should be targeted for screening. Note that individuals with high-risk factors who are candidates for screening should not have any symptoms suggestive of lung cancer (eg, cough, 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.[1,7] Smoking tobacco is also associated with other cancers and diseases. It is estimated that about 443,000 U.S. adults die from smoking-related illnesses each year.[63] Globally, it is estimated that deaths from smoking tobacco will increase to 10 million by 2020.[64] 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 7000 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.[65-67] The FDA has recently defined a list of 93 chemicals that are considered harmful and potentially harmful constituents (HPHCs) in tobacco products or tobacco smoke.

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. The RR for lung cancer is approximately 20-fold higher[1,68] for smokers than for nonsmokers. Cessation of tobacco smoking decreases the risk for lung cancer.[69-72] However, even former smokers have a higher risk for lung cancer compared with never-smokers. 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 NCCN Guidelines, 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.[8,9] Individuals with a 30 pack-year smoking history who quit smoking fewer than 15 years ago are still in this highest-risk group. *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. Note that the data for determining whether patients are at high risk for cancer are based on cigarette smoking and not on other kinds of tobacco products, which may also put patients at risk for cancer. For those who smoke cigars, information is available that may be useful for determining the risk for cancer.[73]

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.[74] Since then, several studies and pooled RR estimates have suggested that second-hand smoke causally increases the risk for lung cancer among nonsmokers.[75] However, the NCCN Panel does not feel that second-hand smoke is 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 candidates for lung cancer screening in the NCCN 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.[76] 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.[75] The pooled estimate for 6 studies suggests a dose–response relationship between number of years of second-hand smoke exposure and lung cancer risk.[75] 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.[75]

Occupational Exposure to Carcinogens

Approximately 150 agents are classified as known or probable human carcinogens (IARC 2002). Agents that are identified specifically as carcinogens targeting the lungs include arsenic, chromium, asbestos, nickel, cadmium, beryllium, silica, diesel fumes, coal smoke, and soot.[60,77-81] 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.[60,81] Among those who are exposed to these carcinogens, smokers have a greater risk for lung cancer than nonsmokers.[82]

Residential Radon Exposure

Radon (a gaseous decay product of uranium-238 and radium-226) has been implicated in the development of lung cancer.[83] The risk for lung cancer from occupational exposure among uranium miners is well established.[84] 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).[85] However, a 2005 meta-analysis of 13 studies (using individual data from patients) reported a linear relationship between the amount of radon detected in a home and the risk of developing lung cancer.[86] Among those exposed to radon, smokers have a greater risk for lung cancer than nonsmokers.[86]

History of Cancer

Evidence shows an increased risk for new primary cancers among patients who survive lung cancer, lymphomas, cancers of the head and neck, or smoking-related cancers such as 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.[87] Risk for second cancers is increased if survivors continue smoking.[88]

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.[89]

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. In patients with laryngeal or hypopharyngeal cancer, the lung is the most common site of second primary cancers.[90] However, data do not suggest that previous treatment for head and neck cancers increases the risk for subsequent new primary lung cancer independent of tobacco exposure.[91,92] Evidence suggests that patients who are successfully treated (ie, cured) for an initial smoking-related lung cancer and who stop smoking will have a decreased risk for a subsequent smoking-related cancer compared with those who continue smoking.[93]

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.[94,95] 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.[96] 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.[97] 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.[98] 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 for lung cancer, nicotine dependence, and peripheral artery disease.[99-101] It was noted that subunits of the nicotinic acetylcholine receptor genes are localized to this area (*CHRNA5*, *CHRNA3*, and *CHRNB4*). Other investigators recently found that a variant at 15q24-25 is associated with spirometric bronchial obstruction and emphysema as assessed with CT.[102,103] Patients with classic familial cancer susceptibility syndromes (such as retinoblastoma and Li-Fraumeni syndrome) have a substantially increased risk for lung cancer if they also smoke tobacco.[104-106]

History of Lung Disease

Chronic Obstructive Pulmonary Disease

A history of chronic obstructive pulmonary disease (COPD) is associated with lung cancer risk,[107-113] and this association may be largely caused by smoking.[97] Yang et al[114] 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.[115-117] For example, 1) family history of chronic bronchitis and emphysema is associated with increased risk for lung cancer, and 2) COPD is associated with lung cancer among never-smokers.[114,117,118] Yang et al[114] found that COPD accounts for 10% of lung cancer cases among never-smokers. Koshiol et al[117] 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 for 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).[119,120] 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.[121]

Hormone Replacement Therapy

Whether use of hormone replacement therapy (HRT) affects the risk for 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,[122] 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 Individuals for Lung Screening

Well-known risk factors exist for the development of lung cancer, especially smoking tobacco.[7] Results from the NLST support screening select individuals who are at high risk for lung cancer.[9] The NCCN Panel recommends that individuals at high risk for lung cancer should be screened using LDCT; however, individuals at moderate or low risk should not be screened. Patients are selected for the different risk categories using the NLST inclusion criteria, nonrandomized studies, and/or observational studies. However, screening with LDCT should only be recommended for select individuals at high risk if they are potential candidates for definitive treatment (ie, curative intent therapy). Chest radiography is not recommended for lung cancer screening.[9,14]

Based on the available data, the NCCN Panel recommends using the following criteria to determine whether individuals are at high, moderate, or low risk for lung cancer.

Individuals with High-Risk Factors

The NCCN Panel recommends lung cancer screening using LDCT for individuals with high-risk factors. There are 2 groups of individuals who qualify as high risk:

- Group 1: Individuals age 55 to 74 years with a 30 or more pack-year history of smoking tobacco who currently smoke or, if former smoker, have quit within 15 years (category 1).[8,9] This is a category 1 recommendation, because these individuals are selected based on the NLST inclusion criteria.[8,9] An NCCN category 1 recommendation is based on high-level evidence (ie, randomized controlled trial) and uniform consensus among panel members. Annual screening is recommended for these individuals with high-risk factors for 2 years (category 1) based on the NLST.[9] Annual screening is suggested for those with negative LDCT scans or for those whose nodules do not meet the size cutoff for more frequent scanning or other intervention until individuals are no longer eligible for definitive treatment. However, uncertainty exists about the appropriate duration of screening and the age at which screening is no longer appropriate.
- Group 2: Individuals age 50 years or older with a 20 or more pack-year history of smoking tobacco and with one additional risk factor (category 2A). For the 2015 update, the NCCN Panel revised this recommendation from category 2B to 2A because panel members feel it is important to expand screening beyond the NLST criteria to a larger group of individuals at risk for lung cancer, which is described in greater detail in this section. This category 2A recommendation is based on lower level evidence (eg, nonrandomized studies, observational data, ongoing randomized trials). These additional risk factors were previously described and include cancer history, lung disease history, family history of lung cancer, radon exposure, and occupational exposure to carcinogens.[59,60,62,86,89,96,117] Note that the NCCN 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* in this Discussion).

In the NCCN Guidelines, the age range for LDCT was extended for individuals in group 2 (ie, ≥50 years and >74 years) for several reasons. NCCN Panel Members feel that individuals in group 2 are also at high risk for lung cancer based on data from the NLST and other studies as discussed later. Panel members feel that limitation to the NLST criteria alone is arbitrary and naïve, because the NLST only used age and smoking history for inclusion criteria and did not consider other well-known risk factors for lung cancer. Others share this opinion.[57,123] Three ongoing phase III randomized trials are also screening younger patients ages 50 to 55 years of age. The NELSON screening and UKLS trials are assessing LDCT in individuals 50 to 75 years of age.[46,47,49,50,52,55] The Danish Lung Cancer Screening Trial (DLCST) is screening individuals 50 to 70 years of age.[124,125] Several studies have assessed LDCT using an extended age range of 50 to 85 years.[126-128]

For the 2015 update, the NCCN Panel voted to revise the recommendation from category 2B to 2A for individuals in group 2 of the NCCN high-risk categories (ie, those ≥50 years with a ≥20 pack-year smoking history and one additional risk factor, other than second-hand smoke).[129,130] In earlier versions of the NCCN Guidelines, the panel recommended screening for this group but without uniform consensus.[15] The NCCN Panel feels that it is important to expand screening beyond the NLST criteria to a larger group of individuals at risk for lung cancer.[130,131] Using just the narrow NLST criteria---shown in group 1 of the NCCN high-risk categories (eg, individuals age 55–74 years with a 30 or more pack-year smoking history)---only 27% of patients currently being diagnosed with lung cancer will be covered.[131] A study reported that expanding the groups at high risk who are eligible for screening---for example, including individuals age 50 or more years with a 20 or more pack-year smoking history and one additional risk factor (other than second-hand smoke)---may save thousands of additional lives.[130]

It is uncertain what the age cutoff should be, where screening is no longer appropriate.[36] The NCCN Guidelines acknowledge that select individuals with high-risk factors who are older than 74 years are also eligible for LDCT. At diagnosis of lung cancer, the median age of patients is 70 years.[6] Approximately 53% of lung cancer is diagnosed in patients aged 55 to 74 years; however, about 28% of lung cancer is diagnosed in older patients aged 75 to 84 years.[6] Screening may benefit older patients who are 75 to 84 years.[132] Recent recommendations from USPSTF recommend LDCT for individuals aged 55 to 80 years with high-risk factors.[32] Similarly, recommendations from the American Association for Thoracic Surgery recommend LDCT for individuals aged 55 to 79 years with high-risk factors.[57] In addition, data from modeling studies suggest that the most advantageous age range for screening is 55 to 80 years.[23] Thus, annual LDCT seems reasonable for select individuals with high-risk factors older than 74 years who are eligible for definitive treatment, generally defined as curative intent therapy (eg, surgery, chemoradiation, stereotactic body radiation therapy [SBRT]).

For individuals with negative LDCT scans or those whose nodules do not meet the size cutoff for more frequent scanning or other intervention, the NCCN Guidelines suggest annual LDCT until individuals are no longer eligible for definitive treatment. The appropriate duration of screening is uncertain.[36] After the 3 rounds of LDCT in the NLST, new cases (367 cases) of lung cancer were frequently diagnosed during the 3.5 years of follow-up (median of 6.5 years).[9,133] The NLST data show that lung cancer continues to occur over time in individuals with high-risk factors. In addition, the incidence of lung cancer and the death rate from lung cancer did not change during the 7 years of the NLST.[134] Thus, the NLST data support annual LDCT for at least 2 years but do not define a time limit on efficacy.

Individuals with Moderate-Risk Factors

NCCN defines individuals with moderate-risk factors as those aged 50 years or older and with a 20 or more pack-year history of smoking tobacco or second-hand smoke exposure but no additional lung cancer risk factors. The NCCN Panel does not recommend lung cancer screening for these individuals at moderate risk for lung cancer. This is a category 2A recommendation based on nonrandomized studies and observational data.[36,135]

Individuals with Low-Risk Factors

NCCN defines individuals with low-risk factors as those younger than 50 years and/or with a smoking history of fewer than 20 pack-years. The NCCN Panel does not recommend lung cancer screening for these individuals at low risk for lung cancer. This is a category 2A recommendation based on nonrandomized studies and observational data.[36,135]

Accuracy of LDCT Protocols and Imaging Modalities

As shown in the NCCN algorithm, LDCT is recommended for detecting noncalcified nodules that may be suspicious for lung cancer depending on their type and size (eg, solid, part-solid, and ground-glass nodules [GGNs]). Most noncalcified nodules are solid.[38] Solid and subsolid nodules are the 2 main types of pulmonary nodules. Subsolid nodules include: 1) nonsolid nodules, also known as ground-glass opacities (GGOs) or GGNs; and 2) part-solid nodules, which contain both ground-glass and solid components.[136-139] Nonsolid nodules are mainly adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA), formerly known as bronchioloalveolar carcinomas (BAC); patients have 5-year disease-free survival of 100% if these nonsolid nodules are completely resected.[17,136-138,140,141] Data also suggest that many GGOs can resolve.[38] 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.[18,142-144]

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.[145-155] The use of thinner images has also improved the characterization of small lung nodules.[156]

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 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.[157,158] However, LDCT seems to be less sensitive for detecting very low-density nonsolid nodules or GGOs.[159] Decreasing the radiation dose does not significantly affect the measurement of nodule size when using 1-mm thick slices.[160] These low-dose scans require radiologists to assess images that are much noisier than typical scans.[161] Studies suggest that some variation occurs in interpretation of LDCT scans among radiologists.[162-165]

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.[9,166] However, studies using multidetector LDCT screening for lung cancer in individuals with high-risk factors have applied various different protocol algorithms for detection and follow-up of pulmonary nodules/lesions.[8,125,126,167-171] 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 (ie, doubling time).[172-179] Most of these protocols recommend that 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.[19,180-186] PET has low sensitivity for nodules with less than 8 mm of solid component. If lung nodules have higher uptake on PET compared to surrounding lung parenchyma (ie, hypermetabolism in the lung nodules), then the nodules are suspicious for lung cancer, regardless of the standardized uptake value (SUV) analysis.[184,187] 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.[188,189]

Optimally, these lung cancer screening methods will increase detection of early-stage lung cancer and decrease 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.[190] Strict adherence to a screening protocol may also significantly reduce unnecessary biopsies.[191] When a biopsy is recommended, tissue samples need to be adequate for both histology and molecular testing.[140,192,193]

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.[49,170,186] The I-ELCAP (International Early Lung Cancer Action Program) and NLST are the largest recent series examining lung cancer detection using LDCT in individuals with high-risk factors (see *Benefits of Lung Cancer Screening* in this Discussion).[8,174] Differences in screening algorithms or recommended diagnostic pathways between these studies are summarized in Table 1.[8,174] To help ensure good image quality, all LDCT screening programs should use CT scanners that meet quality standards equivalent to or exceeding the accreditation standards of the ACR.

In 2005, the Fleischner Society published guidelines for the management of small pulmonary nodules detected on LDCT scans.[144] Most radiologists in the United States are aware of these guidelines and/or work in a practice that uses them.[194] The Fleischner Society recently published guidelines for the management of part-solid or nonsolid pulmonary nodules.[137] 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 for solid and subsolid nodules, NLST data, and the I-ELCAP protocol guidelines.[137,144] Studies suggested that the definition of a positive result from an LDCT scan should be revised, because the original definition from the NLST was associated with a high percentage of false-positive results.[9,46,195,196] Thus, the cutoff sizes for assessing lung nodules currently recommended by NCCN and the ACR were recently increased to 6 mm rather than the 4 mm originally used in the NLST and in earlier versions of the NCCN Guidelines for Lung Cancer Screening.[15,129]

The NCCN-recommended cutoff sizes for solid and subsolid nodules detected on LDCT scans are shown in the algorithm. For nodules that are immediately suspicious for malignancy, diagnostic procedures and/or surgical excision is recommended. For nodules of borderline concern, assessment with interval LDCT scans is often recommended to determine if the nodule is changing to a suspicious form by increasing in size and/or by having a new or growing solid component.

For solid or part-solid nodules, the NCCN definition of a positive scan is a nodule measuring *6 mm;* nodules of this size require a short-term follow-up LDCT scan in 3 months to assess for malignancy.[10,18,49,197] For nonsolid lesions, the NCCN-recommended cutoff for nonsolid lesions is *greater than 5 mm;* nodules of this size (>5 mm and ≤10 mm) require a short-term follow-up LDCT scan in 6 months to assess for malignancy. The NCCN Guidelines emphasize that nonsolid lesions must be evaluated using thin slices (<1.5 mm) to increase the sensitivity for a solid component and to detect subtle changes over time.[136,137,146,147,156] The ACR has developed Lung-RADS to standardize LDCT lung examinations.[27,198] Lung-RADS has been shown to improve the detection of lung cancer and to decrease the false-positive rate to approximately 1 in 10 screened individuals compared with more than 1 in 4 in NLST.[25,27-29] The NCCN Panel is working to harmonize Lung-RADS with the NCCN Guidelines for Lung Cancer Screening.

The NCCN definition of *nodule growth* is as follows*:* 1) for nodules 15 mm or smaller: *an increase in mean diameter of 2 mm or more in any nodule or in the solid portion of a part-solid nodule when compared with the baseline scan*; or 2) for nodules 15 mm or larger: *an increase of 15% in mean diameter when compared with the baseline scan.*[16] *Mean diameter* is the mean of the longest diameter of the nodule and its perpendicular diameter. 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).[199] This definition of nodule growth is simplified compared with the formula used by I-ELCAP (see Table 1 in this Discussion), 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 (≥10% increase in nodule diameter).[9]

Currently, the NCCN recommendations for lung screening do not include other possibly relevant nodule features, such as proximity to the pleura or fissure.[200-203] The topics of nodule volumetric analysis and/or calculations of tumor doubling time have not been addressed either.[123,204] The NELSON trial is using volumetric analysis, which has decreased the false-positive rate to 64%; the NLST had a false-positive rate of 96%.[35,49,52,167] Only 2.6% of individuals had a positive initial test result in the NELSON trial compared with 24% in the NLST. 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. Note that if endobronchial nodules are suspected, then LDCT is recommended after 1 month. The technician should ask the patient to cough vigorously, then the LDCT should be immediately done. If infection or inflammation is suspected, then treatment with antimicrobials should be considered with a repeat LDCT in 1 to 2 months.

For the 2015 update, the table on recommended LDCT acquisition parameters was moved from the Discussion text to the algorithm to increase awareness of this important information. 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.[156] 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.

For the 2015 update, the preferred slice width was revised to 1 mm or less (from ≤1.5 mm), and the acceptable slice width was revised to 2.5 mm or less (from ≤3 mm) based on Lung-RADS.[27,29,137,146] Nonsolid lesions must be evaluated at thin slices (<1.5 mm) to exclude solid components.[137] Part-solid nodules have higher malignancy rates than either solid nodules or pure nonsolid nodules and, therefore, require rigorous evaluation.[137] Because slice thickness, reconstruction algorithms, and postprocessing filters affect nodule size measurement, the same technical parameters should be used for each screening LDCT (eg, the same window/width and window/level settings).[161,205] Ultra-low-dose chest CT currently produces lower sensitivity for nodule detection, especially in larger patients.[158] However, new LDCT technologies may soon make it possible to significantly decrease the radiation dose without compromising nodule detection and evaluation.[206-209] Some organizations, including the ACR, recommend using CT dose tracking for all CT screening programs to ensure that screening facilities are adhering to acceptable radiation limits (eg, reporting the dose-length product [DLP] for each CT).[210]

Multiple GGOs/GGNs/Nonsolid Nodules

As previously mentioned, subsolid nodules include 1) nonsolid nodules, also known as GGOs or GGNs; and 2) part-solid nodules, which contain both ground-glass and solid components.[136-139] Subsolid nodules may contain part-solid or solid components, which increase the possibility of malignancy. When multiple subsolid nodules occur, the dominant lesion should be assessed.[18] Careful assessment is needed to determine whether patients have: 1) a malignant nodule and several benign nodules; 2) several synchronous lung cancers; or 3) dominant malignant nodule with metastases.[211] Multiple nodules may also be due to inflammation or infection, especially if they are rapidly expanding in size.[18]

The following increase the degree of suspicion that nonsolid or part-solid nodules may be malignant: 1) part-solid GGOs/GGNs, especially those with solid components larger than 5 mm; 2) pure GGOs/GGNs larger than 10 mm; 3) atypical subsolid nodules with spiculated contours, *bubbly* appearance, or reticulation; 4) pure GGOs/GGNs or part-solid nodules with solid components smaller than 5 mm that show interval change in size or attenuation; or 5) solid lesions with characteristics that are suspicious for invasive carcinoma.[137,142,212] All GGOs should be reviewed at thin (<1.5 mm) slices to exclude any solid components.[137] If the nodule contains any solid components, then the nodule should be managed using the recommendations from the NCCN Panel for part-solid nodules.[180,213]

Benefits and Risks of Lung Cancer Screening

The goal of screening is to identify disease at an early stage while it is still treatable and curable. The potential huge benefits of lung cancer screening include a reduction in mortality and improvement in quality of life.[22,214] The risks of lung screening include false-negative and false-positive results, radiation exposure, overdiagnosis of incidental findings, futile detection of aggressive disease, anxiety, unnecessary testing, complications from diagnostic workup, and financial costs.[21,214-218] Most lung nodules found on LDCT are benign; if possible, these nodules should be assessed using noninvasive procedures to avoid the morbidity of invasive procedures in patients who may not have cancer.[216,219] The risks and benefits of lung cancer screening should be discussed with the individual before an LDCT scan is done (see *Shared Decision Making* in this Discussion).

Benefits of Lung Cancer Screening

This section summarizes current information about the possible or projected benefits of screening for lung cancer using 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); and 3) detection of disease, other than lung cancer, that requires treatment.[12,23,31,36,134] Effective lung screening may prevent more than 12,000 premature lung cancer deaths per year.[220]

Oncology Outcomes

After a clinical diagnosis of NSCLC, survival is directly related to stage at diagnosis.[221] 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 (eg, 5-year survival is 71% for stage IB; 58% for IIA; 49% for IIB; and <25% for stages III and IV).[222] Note that staging for NSCLC uses the 2010 AJCC staging system.[223]

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[224,225] 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.[9]

Nonrandomized Trials

Of the single-armed screening studies (ie, nonrandomized), the I-ELCAP study is the largest.[40] It included 31,567 individuals with high-risk factors from around the world, all of whom were to be screened with baseline and annual LDCT scans analyzed centrally in New York.[174] In the I-ELCAP study, Henschke et al[174] 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 3 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.[226,227] They concluded that annual 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[228] 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).[9,17,133] A recent analysis of the NLST data stated that 18% of all lung cancers detected by LDCT seemed to be indolent.[24] Data suggest that baseline CT scans find more indolent cancers, and subsequent annual scans find more rapidly growing cancers.[10,11,229]

Randomized Trials

To address the concerns of bias and overdiagnosis from nonrandomized studies, the NCI launched the NLST in 2002.[8] The NLST was a prospective, randomized lung cancer screening trial comparing annual LDCT scan with annual chest radiograph for 2 years; this trial was designed to have 90% power to detect a 21% decrease in the primary endpoint of lung cancer–specific mortality in the screened group. The investigators enrolled 53,454 individuals 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. The NLST results showed that annual LDCT decreased the RR of death from lung cancer by 20%.[9] 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 rounds of screening, positive LDCT scan screens were determined to be actual lung cancer cases (ie, true-positive) 4%, 2%, and 5% of the time, compared with 6%, 4%, and 7% of the time 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.[9] Thus, annual LDCT decreased the RR of death by 20%. These results are impressive, and the NLST represents the first randomized study showing an improvement in disease-specific mortality when using a lung cancer screening program.[10] The NLST results indicate that to prevent one death from lung cancer, 320 individuals with high-risk factors must be screened with LDCT. The NLST results will likely change medical practice in the United States. Results of the NELSON and UKLS trials may confirm the NLST findings in separate cohorts.[49,50]

Some feel that the 20% reduction in mortality from LDCT screening (compared with chest radiography) may actually be greater in clinical practice, because the observed mortality reduction underestimates the true reduction and because chest radiographs are not currently recommended for lung cancer screening as standard practice.[230-232] In stop screening trials, such as the NLST, deaths during prolonged follow-up may have been prevented if screening had been continued.[230] Thus, if annual lung screening is continued for more than 2 years, this increased screening may yield mortality reductions of more than 20% (which was reported by the NLST after annual lung screening for only 2 years). Findings suggest that showing the benefit of breast cancer screening requires follow-up of at least 20 years.[233] However, others feel that the mortality benefit from screening for lung cancer with LDCT will vary substantially across patients who differ in their baseline risk of developing lung cancer.[234] Smaller randomized trials, such as the MILD and DLSCT trials, have not reported that LDCT screening decreases mortality.[124,235] However, the MILD trial was underpowered to detect a difference in mortality.[38,235]

Quality of Life

The NLST assessed quality of life among participants at the time of each annual screening study.[236] 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.[8] 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. In addition, lung cancer screening may identify other clinical conditions unrelated to lung cancer that require follow-up (eg, coronary artery calcification, COPD, other cancers); presumably, treatment of these other conditions will decrease the overall disease burden.[9,18,237-240]

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.[241,242] 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.[243] 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 (or SBRT, also known as stereotactic ablative radiotherapy [SABR]) probably has less treatment-related morbidity than a patient with stage III lung cancer requiring combined-modality therapy (ie, chemotherapy, radiation, possible lung resection).[244,245] 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.[9] 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. Data from the NELSON trial also suggest that CT screening detects more early-stage lung cancer.[49] 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.[246-249]

Patients with early-stage lung cancer may be eligible for treatment that would not be appropriate for those with advanced stage disease. Video-assisted thoracoscopic surgery (VATS) is an option for patients with early-stage NSCLC (eg, those who may not tolerate or may refuse an open lobectomy).[250-253] VATS lobectomy is associated with less morbidity than open lobectomy. Recent data suggest that SBRT is also a reasonable option for patients with early-stage lung cancer who are not eligible for surgery.[244,254,255]

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.[256] Neither hypothesis has been supported by any substantial evidence.[257,258] 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.[259] 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.[260]

Smokers, including those undergoing lung cancer screening, should always be encouraged to quit smoking tobacco.[261,262] Likewise, former smokers should be encouraged to remain abstinent. Lung cancer screening is not a substitute for smoking cessation.[263] Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful in helping individuals to quit smoking.[263-265]

Reduction in Anxiety and Psychological Burden

Whether lung cancer screening causes anxiety or improves overall quality of life has been assessed in the NLST and NELSON trials. In the NLST trial, patients with either a false-positive result or significant incidental finding did not report increased anxiety or differences in quality of life at 1 or 6 months after screening.[236] In the NELSON trial, recipients of an indeterminate result from the LDCT scan experienced increased distress in the short term, whereas relief was experienced after a negative baseline screening examination.[266] After 2 years of follow-up, data from the NELSON trial suggest that lung screening did not adversely affect quality of life.[267] 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.[268] Little definitive research is available to support or refute effects on quality of life from lung cancer screening.

Risks of Lung Cancer Screening

Lung cancer screening with LDCT has inherent risks and benefits.[22,23,36,133,269] 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 (ie, 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%.[127,248,270-273] In the NLST, the false-positive rate was 96.4% for the CT screening group.[9] The cumulative risk of a false-positive result was 33% for a person undergoing lung cancer screening with 2 sequential annual examinations.[270] Thus, LDCT had a high rate of sensitivity but a low rate of specificity in the NLST. These false-positive results in the NLST were probably due to benign intrapulmonary lymph nodes and noncalcified granulomas.[9,19] Data from the NELSON trial show that using volumetric analysis decreases the false-positive rate.[52,167]

False-positive and indeterminate results 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.[274] Approximately 7% of individuals with a false-positive result will undergo an invasive procedure (typically bronchoscopy).[270] 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.[9]

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. The NCCN protocol uses the NLST and I-ELCAP protocols/recommendations (see Table 1 in this Discussion) and the Fleischner Society guidelines and is based on expert opinion from the NCCN Panel Members.[9,137,144,275] 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.[30,276]

Bach et al[228] 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 represents 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%.[277] These potential harms associated with thoracic surgery[277-279] mandate that the effectiveness of LDCT screening be accurately assessed. Methods of decreasing potential harms with thoracic surgery include using treatment with less morbidity (eg, sublobar resection, VATS lobectomy), using minimally invasive diagnostics (endobronchial ultrasound and navigational bronchoscopy), and utilizing experienced, dedicated, multidisciplinary teams to minimize unnecessary testing and procedures and the morbidity of those procedures.

False-Negative Results

Sone et al[280] published 2 reports on lung cancers missed at screening.[281,282] 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.[231]

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 within 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. A database of lung nodules on CT scans has been published to provide an imaging resource for radiologists, which may help to decrease false-negative and false-positive results.[283]

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.[284] 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.[285]

However, the NLST trial results show that lung cancer screening is effective in select individuals with high-risk factors.[9] 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,[286] 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, studies of some low-grade lung cancers (ie, BAC) show a potential for prolonged survival in some patients with NSCLC, even without therapy.[287,288] The current lung adenocarcinoma classification states that the term *BAC* should not be used anymore. Newly defined entities of AIS and MIA, which are likely to present as GGNs, should have a 100% 5-year disease-free survival rate if completely resected.[17,287] 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.[17,287,288]

Furthermore, experience in lung cancer screening has raised the question of increased identification of indolent tumors in the screened population, which is termed *overdiagnosis*.[228,289] 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.[17]

Overdiagnosis is difficult to measure; initial estimates from the NLST suggested that it was 13%, but others suggested it may have been as high as 25%.[38,290] A recent analysis of the NLST data reported that 18% of all lung cancers detected by LDCT seemed to be indolent.[24] Bach et al[228] found an increase in the number of patients with lung cancer detected through screening, yet found 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.[9]

Quality of Life

The effect of lung cancer screening on the quality of life (see *Benefits of Lung Cancer Screening* in this Discussion) is not fully known. A study by van den Bergh et al[291] found no measured adverse effects, although approximately half of the participants reported discomfort while waiting for the results. Several studies (including the NLST and NELSON trial) will be measuring quality-of-life issues.[266,267] Recent data from the NLST and NELSON trials suggest that lung screening did not adversely affect quality of life.[236,267] False-positive and indeterminate results may decrease quality of life because of mental anguish and additional testing.[21]

During the NLST, 3 rounds of LDCT screening were done (ie, baseline, year 1, year 2) and then individuals were followed for an additional 3.5 years. Lung cancer was diagnosed between annual screens in some patients (ie, interval cancers); lung cancer was also diagnosed during follow-up.[9] Thus, individuals should be cautioned that LDCT may not identify all lung cancers or prevent death from lung cancer.[9] In addition, they should be informed that a positive test result does not mean they have lung cancer because many false-positive results occur with LDCT.[30]

Unnecessary Testing

Any lung cancer screening program will result in additional testing. In a report by Croswell et al[292] (from the PLCO 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 was a carefully supervised randomized controlled trial. In a less-controlled environment, the rate of additive studies may be higher. Sistrom et al[293] 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.[294]

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 1.5 mSv (SD, 0.5 mSv) compared with an average of 7 mSv for conventional CT.[9,12,38,295] 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. Brenner[296] 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.[297,298] The risk of radiation exposure over long periods will have to be taken into account when screening guidelines are developed, especially when recommending how frequently the scans should be performed.[276]

Increased Cost

Many are concerned about the effect of lung cancer screening on medical resources, including the cost of LDCT screening and additional testing. The cost of an LDCT scan was estimated to be about $527 (in 2011 U.S. dollars).[299] It is estimated that about 19% of the U.S. population (about 45 million people) are active smokers.[63,300] The number of individuals at high risk for lung cancer screening is approximately 7 million (using NLST data).[9] Depending on the screening rate (50% or 75%), the annual cost in the United States is estimated to be about $1.3 to $2 billion.[299] If 75% of the eligible population has screening, it is estimated that it will cost $240,000 to prevent one lung cancer death.[31] About $12.1 billion is spent each year on lung cancer care in the United States.[299]

LDCT screening will lead to false-positive results, detection of indeterminate nodules, and detection of potential disease other than lung cancer.[236] In the NLST, although 24.2% of the LDCT scans were positive, most of these were false-positive (96.4%).[9] Follow-up for positive nodules typically involves further imaging.[9] Assuming a 50% screening rate, a conservative estimate of the annual cost of working up false-positive nodules is about $800 million (3.5 million × 23% × $1000). Since efforts are underway to decrease the false-positive rate, the cost may decrease. 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).[270] Limiting screening to only individuals with high-risk factors not only helps avoid unnecessary risks in individuals with a lower risk for cancer but also is important for decreasing the costs of the screening program. *Pre-screening* based on age, smoking history, appropriate medical history, family history, and occupational history is important to determine which patients are at 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 screening studies using 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; COPD; and renal, adrenal, and liver lesions.[18,231,238-240,301,302] Although detection of other diseases may frequently provide a clinical benefit to the patient, costs will be further increased with additional testing and treatment. It is important to rule out infection; however, antimicrobials are not indicated for chronic lesions.[231] Inappropriate use of antimicrobials may cause adverse side effects and will increase cost. Incidental lesions may also be detected, which may require further testing (eg, intrapulmonary lymph nodes, noncalcified granulomas, thyroid incidentalomas, upper abdominal lesions).[9]

Cost-Effectiveness and Cost-Benefit Analyses

The cost-effectiveness of lung cancer screening is also important to take into account.[303] LDCT imaging is more expensive than many other screening programs, and therefore it is important to validate the effectiveness of screening.[304] Currently, Medicare reimburses $285 for a CT scan.[299,303] Note that cost-benefit analysis provides dollar values for the outcomes, whereas cost-effectiveness analysis provides cost per health outcome (eg, cost per life-year gained). The cost-effectiveness of lung screening with LDCT was calculated for the NLST study.[303] Estimates are that lung screening with LDCT will cost $81,000 per quality-adjusted life-years (QALYs) gained and $52,000 per life-year gained, which is less than a threshold level of $100,000 per QALY gained that some experts consider to be a reasonable value in the United States.

A fundamental flaw with cost–benefit analyses for lung cancer screening is that the true benefit of screening requires more years of follow-up and more years of screening to realize the full potential; therefore, this crucial factor has been arbitrarily assigned or assumed in prior analyses.[233] 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%.[270] The cost of false-positive cancer screening results has been estimated to be at least $1000 per incident.[305]

The ELCAP 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.[306] 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.[307] The emerging NLST 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.

Shared Decision Making

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.[22,23,30,31,195,308] Individuals should be cautioned that LDCT may not identify all lung cancers or prevent death from lung cancer.[9] In addition, they should be informed that a positive test result does not mean they have lung cancer because false-positive results occur with LDCT.[30] Shared patient/physician decision making may be the best approach before deciding whether to do LDCT lung screening, especially for elderly patients with comorbid conditions.[32-34] Smoking cessation counseling is recommended.[309] Lung screening is not recommended for patients who are not able or willing to have curative therapy, because of health problems or other major concerns.[32] It is recommended that institutions performing lung cancer screening use a multidisciplinary approach that may include specialties such as chest radiology, pulmonary medicine, and thoracic surgery.[35] Guidelines from the ACCP and ASCO state that only centers with considerable expertise in lung cancer screening should do LDCT.[25,36]

Summary

Lung cancer screening with LDCT is a complex and controversial topic, with inherent risks and benefits. Results from the large, prospective, randomized NLST showed that screening with LDCT decreased the RR of death from lung cancer by 20% in a select group of individuals with high-risk factors.[9] The NLST results indicate that to prevent one death from lung cancer, 320 individuals at high risk must be screened with LDCT. However, the NLST findings have not yet been replicated in a separate cohort. Further analysis of the NLST is underway, including comparative effectiveness modeling. The cost-effectiveness of lung screening with LDCT was calculated for the NLST study.[303] Estimates are that lung screening with LDCT will cost $81,000 per QALY gained and $52,000 per life-year gained, which is less than a threshold level of $100,000 per QALY gained that some experts consider to be a reasonable value in the United States. At some point, an acceptable level of risk will have to be deemed appropriate for the benefits of screening.

The NCCN Panel recommends LDCT screening for select individuals at high risk for lung cancer based on the NLST results, nonrandomized studies, and observational data. These NCCN 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 (eg, solid and part-solid nodules). The cutoffs for assessing suspicious nodules were recently revised to decrease the false-positive rate. For solid or part-solid nodules, the NCCN definition of a positive scan is a solid nodule measuring 6 mm. For nonsolid lesions, the NCCN-recommended cutoff is greater than 5 mm. The ACR has developed Lung-RADS to standardize the reporting and management from LDCT lung examinations.[27,198] Lung-RADS has been reported to improve the detection of lung cancer and to decrease the false-positive rate.[25,27-29]

For the 2015 update, the recommendation was revised from category 2B to 2A for group 2 of the high-risk groups eligible for lung cancer screening (those ≥50 years with a ≥20 pack-year smoking history and one additional risk factor other than second-hand smoke). The NCCN Panel revised this recommendation, because the panel feels it is important to expand screening beyond the narrow NLST criteria to a larger group of individuals at high risk.[130] Using just the narrow NLST criteria, only 27% of patients currently being diagnosed with lung cancer will be covered. For LDCT of the lung, the preferred slice width was revised to 1.0 mm or less (from ≤1.5 mm) and the acceptable slice width was revised to 2.5 mm or less (from ≤3.0 mm) based on Lung-RADS.

Before recommending lung cancer screening, shared patient/physician decision making is recommended so that patients have a full understanding of all risks and benefits related to screening with LDCT.[130] Smokers should always be advised to quit smoking tobacco. Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful. Former smokers should be encouraged to remain abstinent. As policies for implementing lung screening programs are designed, a focus on multidisciplinary programs (incorporating chest radiology, pulmonary medicine, and thoracic surgery) will be helpful to optimize decision-making and minimize interventions for patients with benign lung disease.

The USPSTF recently recommended lung screening; their B recommendation means that lung screening will now be covered under the Affordable Care Act for individuals with high-risk factors who are 55 to 80 years of age. In February 2015, CMS agreed to cover annual LDCT screening for appropriate Medicare beneficiaries at high risk for lung cancer based on the NLST criteria if they also receive counseling and shared decision making before screening.

Table 1: Comparison of the I-ELCAP and NLST Lung Screening Protocols

Definition of Positive Nodule*	**I-ELCAP**	**NLST†**
Baseline	Solid and PS nodule ≥5 mm‡	Nodule ≥4 mm
	NS nodule ≥8 mm‡	
Annual	New solid or PS nodule	Same as Baseline
	New NS nodule ≥8 mm‡	
Recommendations for Positive Nodule		
Baseline	LDCT in 3 mo, then resume annual LDCT if stable. Consider PET if solid component >10 mm. Biopsy if PET positive; annual LDCT if PET negative. If nodule ≥15 mm, treat with antibiotics and LDCT at 1 mo, or biopsy. LDCT in 1 mo for solid endobronchial nodule.	Solid or PS nodule 4–10 mm, then LDCT 3–6 mo. NS nodule 4–10 mm, then LDCT 6–12 mo. If growth but nodule <7 mm, then LDCT in 3–6 mo. If growth and nodule ≥7 mm, then follow recommendations of nodules >10 mm. Any nodule >10 mm consider biopsy, CECT, PET/CT; or LDCT in 3–6 mo if low suspicion.
Annual	Annual LDCT if NS nodule <8 mm. LDCT in 6 mo if new solid/PS nodule. Antibiotics and 1 mo LDCT if solid/PS nodule ≥5 mm or NS nodule ≥8 mm, then LDCT at 3 mo if nodule stable.	Same as Baseline
Definition of Nodule Growth	≥50% increase in mean diameter if nodule <5 mm	≥10% increase in nodule diameter
	≥30% increase in mean diameter if nodule 5–9 mm	
	≥20% increase in mean diameter if nodule >10 mm	

CECT = contrast-enhanced CT; CT = computed tomography; I-ELCAP = International Early Lung Cancer Action Program; LDCT = low-dose CT;

NLST = National Lung Screening Trial; NS = nonsolid; PET = positron emission tomography; PS = part solid.

I-ELCAP protocol. Available at (http://www.ielcap.org/protocols). Accessed April 14, 2016.

NLST protocol. Available at (http://www.acrin.org/TabID/145/Default.aspx). Accessed April 14, 2016.

*Requiring imaging or workup in addition to annual LDCT. †Guidelines rather than a strict study regimen. ‡Mean diameter of nodule.

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