RAYUS QUALITY INSTITUTE

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Lung Cancer AUC

Appropriateness of advanced imaging procedures* in patients with cancer of the lung (primary or metastatic, suspected or confirmed):

05/17/2022

*Including MRI, CT, Nuclear medicine scanning, FDG-PET/CT, and SPECT

Abbreviation list:

ACCP	American College of Chest Physicians
ACR	American College of Radiology
ACS	American Cancer Society
ASCO	American Society of Clinical Oncology, Inc.
AUC	Appropriate Use Criteria
BTS	British Thoracic Society
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
ESMO	European Society for Medical Oncology
FDG	Fluorodeoxyglucose
GGN	Ground-glass nodule
LDCT	Low-dose computed tomography
Lung-RADS	Lung CT Screening Reporting & Data System
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
PET	Positron emission tomography
PLE	Provider Led Entity
SCLC	Small cell lung cancer
SNMMI	Society for Nuclear Medicine and Molecular Imaging
SPECT	Single-photon emission computed tomography
SPN	Solitary pulmonary nodule
STR	Society of Thoracic Radiology
TNM	Primary tumor (T) / regional lymph nodes (N) / distant metastasis (M)
UKLS	UK lung cancer screening trial
USPSTF	United States Preventive Services Task Force

Appropriate Use Criteria: How to Use this Document

The RAYUS Quality Institute follows the recommendation framework defined by the Appraisal of Guidelines for Research & Evaluation (AGREE II), AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) and a modified version of the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) to evaluate the strength of recommendations concerning advanced imaging. Considerations used to determine a recommendation are listed below.

Primary recommendation (green): Strong recommendation for imaging. There is confidence that the desirable effects of imaging outweigh its undesirable effects.

Alternative recommendation (yellow): Conditional recommendation for imaging. The desirable effects of imaging likely outweigh its undesirable effects, although some uncertainty may exist. Alternative imaging recommendations may be indicated with a contraindication to the primary recommendation, in specific clinical scenarios, or when the primary recommendation results are inconclusive or incongruent with the patient's clinical diagnosis.

Recommendation against imaging (red): The test may not be accurate, may not be reliable, or the undesirable effects of imaging outweigh any desirable effects. Additionally, the recommendation may be impractical or not feasible in the targeted population and/or practice setting(s).

Lung Cancer AUC summary:

For patients with incidentally discovered pulmonary nodule(s), follow-up intervals for advanced imaging can vary according to size and density of the nodule. If the nodule(s) is smaller than 6 mm, no routine imaging is typically indicated. For nodules ≥ 6 mm, a range of times rather than a specific interval is provided for follow-up low dose CT, and imaging should be based on clinical decision making and multidisciplinary evaluation (defined as at least including a thoracic surgeon, a thoracic and/or interventional radiologist, and a pulmonologist; Ettinger et al [*NCCN*] 2021). In general, longer-term follow-up is recommended for subsolid nodules. PET/CT is preferred for further evaluation of larger pulmonary nodules (> 8mm).

Lung cancer screening with low-dose CT is recommended in select high-risk smokers and former smokers who are asymptomatic. Specifically, these individuals are age 50-77 years, have a smoking history of ≥ 20 pack years, and either currently smoke or have quit within the last 15 years. Surveillance of nodules detected on initial screening can vary according to the size and density of the nodule, and whether it is growing or unchanged.

For patients who present with suspicious symptoms, the clinical presentation and findings on CT and/or PET/CT usually allow the physician to presumptively make a diagnosis of lung cancer and differentiate between non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Chest CT (extending through the adrenal glands) is the modality of choice for evaluating the size and location of the primary tumor, while PET/CT can help to evaluate the extent of disease, including bone metastasis. Brain imaging is recommended for initial evaluation of SCLC, for NSCLC patients who exhibit neurologic symptoms, and for asymptomatic NSCLC patients with stage IB [optional], II, II, and IV disease.

Further imaging may be necessary for restaging and treatment response assessment. If there is no evidence of disease after completion of definitive therapy, surveillance imaging should be completed, with timing of CT scans (and brain imaging for SCLC patients) based on clinical decision making.

PICO 1: Evaluation of a pulmonary nodule* or mass incidentally discovered on previous imaging:

*Excluding nodules with classically benign imaging features (e.g., diffuse, central, laminated, or popcorn calcification (ACR *Lung-RADS® Version 1.1, 2019;* McWilliams et al 2013)).

Note: Multidisciplinary evaluation is recommended to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy (Ettinger et al [*NCCN*] 2021). These guidelines are not intended to preclude either shorter- or longer-term follow-up in individual subjects, when deemed clinically appropriate (MacMahon et al 2017).

Solid nodule(s), low-risk (< 5% malignancy) based on standard risk assessment criteria

Single or multiple solid nodules < 6 mm

- **Red –** No routine follow-up imaging recommended

Single solid nodule 6-8 mm

- **Green** – Follow-up low-dose CT chest without IV contrast (at 6-12 mo)
- **Yellow** – Follow-up low-dose CT chest without IV contrast (at 18-24 mo)

Multiple solid nodules 6-8 mm

- **Green** – Follow-up low-dose CT chest without IV contrast (at 3-12 mo)
- **Yellow** – Follow-up low-dose CT chest without IV contrast (at 18-24 mo)

Single solid nodule > 8mm

- **Green** – Follow-up low-dose CT chest without IV contrast (at ~3 mo)
- **Green** – FDG-PET/CT

Multiple solid nodules > 8 mm

- **Green** – Follow-up low-dose CT chest without IV contrast (at 3-6 mo)
- **Green** – FDG-PET/CT
- **Yellow** – Follow-up low-dose CT chest without IV contrast (at 18-24 mo)

Solid nodule(s), high-risk (≥ 5% malignancy) based on standard risk assessment criteria

Single or multiple solid nodule(s) < 6 mm

- **Yellow** – Follow-up low-dose CT chest without IV contrast (at ~12 mo)

Single solid nodule 6-8 mm

- **Green** – Follow-up low-dose CT chest without IV contrast (at 6-12 mo)
- **Yellow** – Follow-up low-dose CT chest without IV contrast (at 18-24 mo)

Multiple solid nodules 6-8 mm

- **Green** – Follow-up low-dose CT chest without IV contrast (at 3-12 mo)

- **Yellow** – Follow-up low-dose CT chest without IV contrast (at 18-24 mo)

Single or multiple solid nodule(s) > 8 mm

- **Green** – FDG-PET/CT
- **Green** – Follow-up low-dose CT chest without IV contrast (at ~3 mo)
- **Yellow –** Follow-up low-dose CT chest without IV contrast (at 12-24 mo)
- **Yellow –** CT chest with IV contrast or CT chest without IV contrast

Subsolid nodule(s), low-risk or high-risk based on standard risk assessment criteria

Single ground glass or part-solid nodule ≤ 6 mm

- **Red** – Routine follow-up imaging

Single ground glass nodule > 6 mm

- **Green** – Follow-up low-dose CT chest without IV contrast (at 6-12 mo)
- **Green** – Follow-up low-dose CT chest without IV contrast (at ~3 years and ~5 years)

Single part-solid nodule ≥ 6 mm, solid component < 6 mm

- **Yellow** – Follow-up low-dose CT chest without IV contrast (at 3-6 mo)
- **Yellow** – Follow-up low-dose CT chest without IV contrast (annually for at least 5 years)

Multiple part-solid nodules, solid component < 6 mm

- **Green** – Follow-up low-dose CT chest without IV contrast (at 3-6 mo)
- **Yellow** – Follow-up low-dose CT chest without IV contrast (at ~2 years and ~4 years)

Single or multiple part-solid nodule(s), solid component > 6 mm

- **Green** – Follow-up low-dose CT chest without IV contrast (at 3-6 mo)
- **Green** – Follow-up low-dose CT chest without IV contrast (annually for at least 5 years)
- **Yellow** – FDG-PET/CT
- **Yellow** – CT chest with IV contrast or CT chest without IV contrast

Level of Evidence: Low-dose CT chest: moderate; CT chest: low, PET/CT: very low for small nodules, moderate for larger nodules; MRI: insufficient

Notes concerning applicability and/or patient preferences:
Patients should have the opportunity to discuss concerns about lung cancer and surveillance regimens (Callister et al [*BTS*] 2015). Some patients may be uncomfortable with the prospect of waiting up to 12 months for follow-up examinations and sooner follow-up may be warranted (MacMahon et al 2017). Most nodules smaller than 1 cm will not be visible on chest radiographs; however, for larger solid nodules that are clearly visualized and are considered low risk, follow-up with radiography rather than CT may be appropriate to take advantage of the lower radiation exposure (MacMahon et al 2017).

Guideline and PLE expert panel consensus opinion summary:
In an individual with an indeterminate nodule identified by chest radiography, it is recommended that a

thin section CT of the chest be performed to help characterize the nodule (Gould et al [*ACCP*] 2013: grade 1C recommendation; PLE expert panel consensus opinion). In the case of a large or very suspicious nodule(s), it is recommended to proceed with a complete thoracic CT examination for further evaluation (MacMahon et al 2017). A chest CT scan can provide specific information about the location, shape, margins, and attenuation characteristics of nodules, and also may identify unsuspected lymphadenopathy, synchronous parenchymal lesions, or invasion of the chest wall or mediastinum (Gould et al [*ACCP*] 2013). All CT scans of the thorax in adults should be reconstructed and archived with contiguous thin sections ($\leq$ 1.5 mm, typically 1.0 mm) to enable accurate characterization and measurement of small nodules, and routine acquisition and archiving of off-axis (coronal and sagittal) reconstructed series is strongly recommended (MacMahon et al 2017: grade 1A; strong recommendation, high-quality evidence; Callister et al [*BTS*] 2015). Prior imaging studies should always be reviewed if they are available to determine possible growth or stability (MacMahon et al 2017: grade 1A; strong recommendation, high-quality evidence).

The accurate assessment of risk before additional imaging and volumetric analysis has an important place in lung cancer screening (McWilliams et al 2013). Predictive tools based on patient and nodule characteristics can be used to accurately estimate the probability that lung nodules detected on baseline screening low-dose CT scans are malignant (McWilliams et al 2013). Since risk is determined by multiple factors, and patient preference for either more aggressive or conservative treatment plays an important role, a range of times rather than a specific interval is provided for follow-up CT (MacMahon et al 2017). Follow-up intervals may also vary according to size of nodule (MacMahon et al 2017). Patients with solid nodules that show stability (e.g., < 25% change in volume) on CT after one year may not require further surveillance, with 18- to 24-month surveillance considered on an individual basis (MacMahon et al 2017; Callister et al [*BTS*] 2015: grade C recommendation). Given the frequency with which follow-up CT examinations of the thorax are performed, a low-radiation technique should be used (MacMahon et al 2017: grade 1A; strong recommendation, high quality evidence; Callister et al [*BTS*] 2015).

PET/CT is preferred for further evaluation of larger pulmonary nodules, as no alternative shows superiority (Callister et al [*BTS*] 2015). In particular, if a nodule is > 8mm or the initial risk of malignancy is > 10%, PET/CT should be considered, as PET has good sensitivity and moderate specificity for determining a malignant nodule (Ettinger et al [*NCCN*] 2021; Callister et al [*BTS*] 2015: evidence level 1 – supported by 2++; Callister et al [*BTS*] 2015: grade B recommendation; Gould et al [*ACCP*] 2013: grade 2C recommendation). Large part-solid nodules (measuring $\geq$ 15 mm in diameter) should proceed directly to further evaluation with PET, nonsurgical biopsy, and/or surgical resection (Gould et al [*ACCP*] 2013). Contrarily, ground glass opacities and an otherwise normal chest CT do not require a PET scan for staging (Silvestri et al [*ACCP*] 2013). In high-risk populations, a positive PET/CT scan warrants progression to more invasive diagnostic tests to confirm or refute malignancy, while a negative scan has a lower exclusion value for malignancy and requires continued surveillance with CT (Callister et al [*BTS*] 2015).

FDG-PET is limited in its inability to accurately characterize smaller (< 8mm) lesions (Kanne et al [*ACR*] 2013; Ettinger et al [*NCCN*] 2021). PET also has lower sensitivity and a higher false-negative rate in subsolid nodules, and in general should not be used to characterize those with a solid component $\leq$ 8mm (Callister et al [*BTS*] 2015: evidence level 2++ and 3; Gould et al [*ACCP*] 2013).

Use of MRI in evaluating pulmonary nodules is relatively limited (Kanne et al [*ACR*] 2013; Callister et al [*BTS*] 2015: grade D recommendation), and MRI generally does not have a routine place in assessing pulmonary nodules outside of research studies (Callister et al [*BTS*] 2015: evidence level 2++ and 3).

In general, SPECT should not be used to determine whether a nodule is malignant when PET/CT is an available alternative (Callister et al [*BTS*] 2015: grade D recommendation), as it does not show any advantage over PET/CT in the assessment of pulmonary nodules (Callister et al [*BTS*] 2015: evidence level 2++ and 3).

Solid nodules
"Low risk" corresponds to an estimated risk of cancer of less than 5%, and is generally associated with younger age, less smoking, no other risk factors (e.g., family history of lung cancer or occupational exposure), smaller nodule size, regular margins, and locations other than the upper lobes (MacMahon et al 2017; PLE expert panel consensus opinion). In general, when a solid nodule(s) is detected on chest CT in those with low risk for lung cancer:

- If the nodule(s) is smaller than 6 mm, no routine imaging is typically indicated (Ettinger et al [*NCCN*] 2021; MacMahon et al 2017: grade 1C; strong recommendation, low- or very-low quality evidence; Gould et al [*ACCP*] 2013: grade 2C recommendation), but the patient should be informed about the potential benefits and harms of this approach (Gould et al [*ACCP*] 2013).
- If the nodule is between 6 and 8 mm, follow-up CT at 6-12 months is recommended, dependent upon size, morphology, and patient preference (MacMahon et al 2017: grade 1C; strong recommendation, low- or very-low-quality evidence; Ettinger et al [*NCCN*] 2021; Gould et al [*ACCP*] 2013: grade 2C recommendation). One follow-up examination should suffice in most instances; if morphology is suspicious or stability is uncertain, additional study after a further 6-12 months can be considered (MacMahon et al 2017). The risk of malignancy is very low in this category, and not all solid nodules require traditional 2-year follow-up (MacMahon et al 2017).
- For solitary solid noncalcified nodules larger than 8 mm in diameter, 3-month follow-up can be considered along with PET/CT, tissue sampling, or a combination thereof; any of these options may be appropriate depending on size, morphology, comorbidity, and other factors (MacMahon et al 2017: grade 1A; strong recommendation, high-quality evidence; Ettinger et al [*NCCN*] 2021). While the average risk is approximately 3% depending on morphology and location, a considerably higher risk can be inferred in certain patients (MacMahon et al 2017). It is suggested that clinicians estimate the pretest probability of malignancy in these nodules either qualitatively by using clinical judgment and/or quantitatively with a validated model (Gould et al [*ACCP*] 2013: grade 2C recommendation; Callister et al [*BTS*] 2015).

To estimate "high risk", the *Fleischner Society* recommends combining previously established intermediate-risk (5%-65% risk) and high-risk (>65% risk) categories (MacMahon et al 2017). In general, when a solid nodule(s) is detected on chest CT in a patient with high risk for lung cancer, or with one or more risk factors:

- Solid nodules smaller than 6 mm do not require routine follow-up in all patients with high clinical risk; however, some nodules smaller than 6 mm with suspicious morphology, upper lobe location, or both may warrant follow-up at 12 months (MacMahon et al 2017: grade 2A; weak recommendation, high-quality evidence; Ettinger et al [*NCCN*] 2021; Gould et al [*ACCP*] 2013: grade 2C recommendation; *ACR Lung-RADS* 2019). Earlier follow-up is not typically recommended in such instances, as experience has shown that such small nodules, if malignant, rarely advance in stage over 12 months, whereas a short-term follow-up examination showing no apparent change may provide false reassurance (MacMahon et al 2017).
- If the nodule(s) is between 6 and 8 mm, follow-up CT at 6-12 months and again at 18-24 months is recommended (MacMahon et al 2017: grade 1B; strong recommendation, moderate quality evidence; Ettinger et al [*NCCN*] 2021; *ACR Lung-RADS® Version 1.1,* 2019). The average risk of malignancy in this group is estimated to be 0.5%-2.0% (MacMahon et al 2017).

- If a nodule is larger than 8 mm, CT at 3-month follow-up should be considered (MacMahon et al 2017; Ettinger et al [*NCCN*] 2021; Gould et al [*ACCP*] 2013: grade 2C recommendation; *ACR Lung RADS* 2019). PET/CT, tissue sampling, or a combination thereof may also be appropriate depending on size, morphology, comorbidity, and other factors (MacMahon et al 2017: grade 1A; strong recommendation, high-quality evidence; *ACR Lung-RADS* 2019). For very large nodules (≥ 15 mm) chest CT with or without IV contrast can be considered to evaluate mediastinal abnormalities or lymph nodes (Wood et al [*NCCN*] 2021; *ACR Lung-RADS® Version 1.1,* 2019).

For multiple solid noncalcified nodules smaller than 6 mm in diameter, no routine follow-up is typically recommended, however, follow-up at 12-months may be considered in patients who are at high risk, with active infection, or immunocompromised (MacMahon et al 2017: grade 2B; weak recommendation, moderate-quality evidence). Small nodules in this size range are frequently encountered in routine clinical practice and usually benign in origin (MacMahon et al 2017). For multiple solid nodules with at least one nodule 6 mm or larger in diameter, follow-up is recommended at 3-6 months with another optional scan at 18-24 months (MacMahon et al 2017: grade 1B; strong recommendation, moderate-quality evidence).

Follow-up of well-defined solid nodules with benign morphology can optionally be discontinued at 12-18 months if the nodule is accurately measurable and unequivocally stable (MacMahon et al 2017). Solid nodules that decrease in size but do not disappear completely should be followed to resolution or lack of growth over 2 years (Gould et al [*ACCP*] 2013).

Subsolid nodules (part-solid or nonsolid/pure ground glass)
In general, longer-term follow-up is recommended for subsolid nodules (MacMahon et al 2017). For solitary pure ground-glass nodules or part-solid nodules smaller than 6 mm in diameter, no routine follow-up is recommended (Ettinger et al [*NCCN*] 2021; Gould et al [*ACCP*] 2013: grade 2C recommendation; MacMahon et al 2017: grade 1B; strong recommendation, moderate-quality evidence; MacMahon et al 2017: grade 1C; strong recommendation, low- or very-low-quality evidence). However, selected higher risk patients can have optional follow-up at 2 and 4 years (MacMahon et al 2017).

For pure ground-glass nodules 6 mm or larger, follow-up scanning is recommended at 6-12 months and then every 2 years thereafter for 5 years (MacMahon et al 2017: grade 1B; strong recommendation, moderate-quality evidence; Gould et al [*ACCP*] 2013: grade 2C recommendation). For solitary part-solid nodules 6 mm or larger with a solid component less than 6 mm in diameter, follow-up at 3-6 months is recommended, and then annually for a minimum of 5 years (Ettinger et al [*NCCN*] 2021; MacMahon et al 2017; *ACR Lung-RADS* 2019). CT follow-up studies have shown that incidental non-calcified non-solid lung lesions do not need shorter repeat CT examinations before 1-2 years and are less aggressive than solid or part-solid lesions (Postmus et al [*ESMO*] 2017).

For solitary part-solid nodules with a solid component 6 mm or larger, a short-term follow-up CT at 3-6 months should be considered (MacMahon et al 2017; *ACR Lung-RADS® Version 1.1,* 2019). If the nodule persists, annual CT is recommended for a total of 5 years. For nodules with particularly suspicious morphology, a growing solid component, or a solid component larger than 8 mm, PET/CT, biopsy, or resection are recommended (MacMahon et al 2017: grade 1B; strong recommendation, moderate-quality evidence; Gould et al [*ACCP*] 2013: grade 2C recommendation; *ACR Lung-RADS® Version 1.1,* 2019). Chest CT with or without IV contrast can also be considered, especially if the solid component is 8

mm or larger (Wood et al [*NCCN*] 2021; *ACR Lung-RADS® Version 1.1,* 2019).

If multiple subsolid nodules of any size are seen, repeat CT in 3-6 months is recommended, particularly when the diagnosis is uncertain and the differential diagnosis includes nonneoplastic causes (MacMahon et al 2017; Ettinger et al [*NCCN*] 2021). If the multiple nodules are smaller than 6 mm, infectious causes should be considered (MacMahon et al 2017). If these lesions remain persistent after an initial follow-up scan at 3-6 months, consider follow-up at approximately 2 and 4 years to confirm stability (MacMahon et al 2017: grade 1C; strong recommendation, low- or very-low-quality evidence). In patients with multiple subsolid nodules, with at least one that is 6 mm or larger, management should be based on the most suspicious (but not necessarily largest) nodule; if persistent after 3-6 months, multiple primary adenocarcinomas should be considered (MacMahon et al 2017: grade 1C; strong recommendation, low- or very-low-quality evidence).

<u>Clinical and imaging notes:</u>

- Initial evaluation should always begin with a comparison with previous exams (MacMahon et al 2017).
- Pulmonary nodule risk factors for malignancy include (MacMahon et al 2017):
    - Nodule size, which is a dominant factor in management approach;
    - Marginal spiculation, however the threshold for determining its presence has not been defined;
    - Nodule location, with lung cancers occurring more frequently in the upper lobes and a tendency to occur in the right lung;
    - Nodule multiplicity, with an increased risk as nodules increase from 1-4, but decreased risk in those with 5 or more;
    - Nodule growth rate, with a wide range observed depending on morphology and histologic findings;
    - Presence of emphysema or pulmonary fibrosis;
    - Age, with risk increasing steadily following each additional decade of life after 40; and
    - Cigarette use, with a 10- to 35-fold increased risk when compared to non-smokers.
- CT examinations performed for evaluation or follow-up on pulmonary nodules should be performed using contiguous ≤ 1.5mm sections to enable accurate characterization and measurement. Routine acquisition and archiving of coronal and sagittal reconstructions is recommended, as is the use of low-dose techniques (MacMahon et al 2017).
- Nodule diameter is based on the average of the long and short axes obtained on the same axial, sagittal or coronal slice, and rounded to the nearest mm (MacMahon et al 2017).
- Nonsolid nodules that grow or develop a solid component are often malignant, prompting further evaluation and/or consideration of resection (Gould et al [*ACCP*] 2013).
- Nodules with diffuse, central, laminated, or popcorn pattern of calcification or macroscopic fat can be considered benign (Callister et al [*BTS*] 2015; Gould et al [*ACCP*] 2013).
- The CT component of the FDG-PET/CT examination improves anatomical localization and can provide additional growth/morphological information that may strengthen a diagnosis of lung malignancy or raise the possibility of alternative benign diagnoses (Callister et al [*BTS*] 2015).
- On the basis of expert consensus and insights from lung cancer screening experience, the *American College of Radiology* developed the *Lung-RADS* as a framework to follow-up and manage pulmonary nodules (*ACR Lung-RADS® Version 1.1,* 2019; Hammer et al; 2019). Other groups advocate the use of volumetric measurements and volume doubling time, while several risk calculators have also been developed to stratify pulmonary nodules (e.g., the *Brock*

University Calculator) (Hammer et al 2019).

Evidence update (2016-present):

Low Level of Evidence

Liu et al (2021), in a meta-analysis, compared the diagnostic accuracy of MRI versus CT for detecting pulmonary nodules. Two independent reviewers conducted a literature search and studies were evaluated using the *Quality Assessment of Diagnostic Accuracy Studies* (*QUADAS*). A total of 8 studies (n = 653 individuals) were included and pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and area under the curve (AUC) were calculated. Results found pooled sensitivity, specificity, PLR, NLR, and AUC of 0.91 (95%CI: 0.80–0.96), 0.76 (95%CI: 0.58–0.87), 3.72 (95%CI: 2.05–6.76), 0.12 (95%CI: 0.06–0.27), and 0.91 (95%CI: 0.88–0.93) for MRI respectively, while the pooled sensitivity, specificity, PLR, NLR, and AUC for CT were 1.00 (95% CI: 0.95–1.00), 0.99 (95%CI: 0.78–1.00), 79.35 (95%CI: 3.68–1711.06), 0.00 (95%CI: 0.00–0.06), and 1.00 (95%CI: 0.99–1.00), respectively. A comparison of the diagnostic accuracy of CT versus MRI found that compared with MRI, CT showed statistically higher sensitivity (odds ratio [OR] for MRI vs CT: 0.91; 95%CI: 0.85–0.98; P value .010), specificity (OR: 0.82; 95%CI: 0.69–0.97; P value .019), PLR (OR: 0.29; 95%CI: 0.10–0.83; P value 0.02), AUC (OR: 0.91; 95%CI: 0.89–0.94; P value<.001), and lower NLR (OR: 8.72; 95%CI: 1.57–48.56; P value .013). The authors conclude that while both CT and MRI have a high diagnostic accuracy for diagnosing pulmonary nodules, CT was superior to MRI in the current existing evidence.

Hammer et al (2019), in a retrospective study, tested which methodology performs best when assessing subsolid nodule malignancy risk in lung cancer screening CT examinations: a linear measurement-based scheme (*Lung-RADS*), volumetric measures (*NELSON trial*), or the *Brock University model*, which includes patient and nodule characteristics. Subsets of ground-glass nodules (GGNs) and part-solid nodules were selected from the *National Lung Screening Trial*. A total of 622 nodules were evaluated by a thoracic radiologist, of which 434 nodules were subsolid. The primary outcome was development of malignancy within the follow-up period (median, 6.5 years). At baseline, 304 nodules were classified as Lung-RADS category 2, with a malignancy rate of 3%, and 67 nodules were classified as Lung-RADS category 3, with a malignancy rate of 14%. The malignancy rate for GGNs < 10mm (1.3%) was smaller than that for GGNs measuring 10-19mm (6%; P value = 0.01). The *Brock model* was found to predict malignancy better than *Lung-RADS* and the *NELSON trial* scheme, with area under the receiver operating characteristic curve = 0.78, 0.70, and 0.67, respectively; P value = 0.02). The authors conclude that subsolid nodules classified as *Lung-RADS* categories 2 and 3 have a higher risk of malignancy than previously reported, while the *Brock* risk calculator performed better than measurement-based classification schemes, such as *Lung-RADS*.

Taralli et al (2019), in a retrospective study, evaluated the ^{18}F-FDG PET/CT diagnostic performance in [large] pulmonary nodules detected during follow-up in oncological patients and the relationship between malignancy and nodules' characteristics. A total of 182 pulmonary nodules (121 solitary nodules, mean size 16.5mm, median size 15mm) in 148 patients (mean age = 69.5) were included. Final diagnosis was established by histology or radiological follow-up. Among all nodules, the prevalence of malignancy was 75.8%: malignancy prevalence was 87.6% among solitary nodules and 52.5% among multiple nodules. Overall, PET/CT provided sensitivity = 79%, specificity = 81.8%, accuracy = 79.7%, PPV = 93.1%, and NPV = 55.4%. Malignant nodules were prevalent in males, in solitary pattern and in upper lobes, and had significantly greater size and metabolic activity than benign ones. The authors conclude that ^{18}F-FDG PET/CT provides good diagnostic performance for ruling in the malignancy in pulmonary nodules detected during follow-up.

Li et al (2018), in a meta-analysis, investigated the value of ^{18}F-FDG-PET/CT in the diagnosis of malignant solitary pulmonary nodules (SPNs). Two independent reviewers assessed study eligibility, and a total of 21 studies were included (n = 1557 patients with SPNs; 918 malignant and 639 benign). All SPNs were < 3 cm and diagnosed based on either histology or follow-up. Pooled results indicated ^{18}F-FDG-PET/CT showed a diagnostic sensitivity of 0.89 (95% CI 0.87-0.91) and a specificity of 0.70 (95% CI 0.66-0.73). The positive likelihood ratio was 3.33 (95% CI 2.35-4.71) and the negative likelihood ratio was 0.18 (95% CI 0.13-0.25). The diagnostic odds ratio was 22.43 (95% CI 12.55-40.07). The authors conclude that ^{18}F-FDG-PET/CT showed insufficient sensitivity and specificity for diagnosing [small] malignant SPNs, and cannot replace the “gold standard” pathology by resection or percutaneous biopsy.

PICO 2: Screening and surveillance in an asymptomatic active smoker or former smoker that has quit within the past 15 years:

Note: Multidisciplinary evaluation is recommended to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy (Ettinger et al [*NCCN*] 2021; *ACR-STR* 2019). These guidelines are not intended to preclude either shorter- or longer-term follow-up in individual subjects, when deemed clinically appropriate (MacMahon et al 2017).

Screening of patient age > 50 years and ≤ 77 years, AND with either a 20 pack-year smoking history or established occupational-related lung disease (CMS 2022):

- **Green** – Low-dose CT chest without IV contrast (every 12 mo)

Screening of patient with any of the following:

Age < 50 years,
Age > 77 years,
< 20 pack-year smoking history,
Quit date > 15 years ago,
Health problem that limits life expectancy,
Unwilling to have curative lung surgery,
Symptoms of lung cancer or previous lung cancer (*follow appropriate guidelines for work up and surveillance*):

- **Red –** No screening CT recommended

Surveillance of "definitely benign" or "benign-appearing" (< 1% risk of malignancy) nodule(s) detected on initial screening, including any of the following:

Nodule(s) with specific calcifications (complete, central, popcorn, concentric rings and fat containing nodules)
Solid nodule(s) < 6 mm at baseline,
New solid nodule(s) < 4mm,
Part-solid nodule(s) < 6 mm at baseline,
New non solid (ground glass) nodule(s) ≤ 30mm,
Non solid (ground glass) nodule(s) > 30 mm that are unchanged

- **Red** – No screening CT recommended

Surveillance of "probably benign" (1-2% risk of malignancy) nodule(s) detected on initial screening, including any of the following:

Solid nodule(s) ≥ 6 to < 8mm at baseline,
New solid nodule(s) 4mm to 6mm,
Part-solid nodule(s) ≥ 6mm with solid component < 6mm,

New part-solid nodule(s) < 6mm total diameter,
Non solid (ground glass) nodule(s) > 30mm,
New non solid (ground glass) nodule(s) of any size

- **Green** – Follow-up low-dose CT chest without IV contrast (at 6 mo; *then continue with annual screening if no change*)

Surveillance of "suspicious" (5-15% risk of malignancy) nodule(s) detected on initial screening, including any of the following:

Solid nodule(s) ≥ 8 to < 15mm at baseline,
Growing* solid nodule(s) < 8mm,
New solid nodule(s) 6mm to < 8mm,
Part-solid nodule(s) ≥ 6mm with solid component ≥ 6mm to < 8mm,
Part-solid nodules(s) with new or growing* solid component < 4mm ,
Endobronchial nodule(s) of any size

- **Green** – Follow-up low-dose CT chest without IV contrast (at 3 mo; *then continue with annual screening if no change*)
- **Yellow** – PET/CT (when solid component ≥ 8mm)

Surveillance of "very suspicious" (> 15% risk of malignancy) nodule(s) detected on initial screening, including any of the following:

Solid nodule(s) ≥ 15mm,
New or growing* solid nodule(s) ≥ 8mm,
Part-solid nodule(s) with solid component ≥ 8mm,
Part-solid nodules(s) with new or growing* solid component ≥ 4mm,
Nodule(s) with additional features or imaging findings that increases the suspicion of malignancy (e.g., spiculation or enlarged lymph nodes)

- **Green** – CT chest with IV contrast or CT chest without IV contrast
- **Yellow** – PET/CT (when solid component ≥ 8mm)
- **Yellow** – Follow-up low-dose CT chest without IV contrast (at 1 mo *to rule out infection or inflammation*)

*Growing refers to an increase in size of > 1.5mm

Level of Evidence: Low-dose CT: moderate-to-high; CT chest: low (surveillance), PET/CT: very low for small nodules, moderate for larger nodules (surveillance); MRI: insufficient

Notes concerning applicability and/or patient preferences:
Patients should have the opportunity to discuss concerns about lung cancer and surveillance regimens (Callister et al [*BTS*] 2015). In candidates for screening, shared patient/physician decision-making is recommended, including a discussion of the potential benefits, limitations, and harms (*USPSTF* 2021; Wood et al [*NCCN*] 2021; *ACR-STR* 2019; Wender et al [*ACS*] 2013). Those who are projected to have a high net benefit from lung cancer screening (based on the results of validated clinical risk prediction

calculations and life expectancy estimates, or based on life-year gained calculations) may be offered annual screening with low-dose CT (Mazzone et al [*ACCP*] 2021: weak recommendation, moderate-quality evidence). Some individuals eligible for this recommendation may have a low net-benefit from screening (e.g., those with comorbidities that substantially limit life expectancy and adversely influence ability to tolerate the evaluation or treatment) and may therefore choose not to undergo screening (Mazzone et al [*ACCP*] 2021: strong recommendation, low-quality evidence).

Guideline and PLE expert panel consensus opinion summary:

Annual screening

Low-dose CT

Lung cancer screening using low-dose CT (LDCT) is recommended in select high-risk smokers and former smokers [who are asymptomatic] (Ettinger et al [*NCCN*] 2021). The *USPSTF* recommends annual screening for lung cancer with LDCT in adults aged 50 to 80 years who have a 20 pack-year smoking history and who currently smoke or have quit within the past 15 years (*USPSTF* 2021). Taking the *USPSTF* recommendation into consideration, the *CMS national coverage determination* for lung cancer screening has been updated, with "evidence sufficient to expand the eligibility criteria" for Medicare beneficiaries receiving LDCT and: age 50-77 years; asymptomatic; tobacco smoking history of $\geq$ 20 pack years, and current smoker or one who has quit within the last 15 years (*CMS* 2022). The *NCCN*, *ACR*, *ACCP*, and *American Cancer Society* also agree that LDCT screening for higher risk patients is appropriate (Wood et al [*NCCN*] 2021; Mazzone et al [*ACCP*] 2021: weak recommendation, moderate-quality evidence; Donnelly et al [*ACR*] 2018; Wender et al [*ACS*] 2013).

Although no studies have implemented a population-based CT screening and surveillance program specifically for occupational lung disease, several recent studies have found adequate detection of parenchymal changes with reduced-dose CT in at-risk workers (Cox et al [*ACR*] 2020). The *NCCN* notes a calculated mean relative risk for development of lung cancer of 1.59 among individuals with a known occupational exposure to carcinogenic agents compared to non-exposed individuals, with smokers likely at higher risk than nonsmokers (Wood et al [*NCCN*] 2021).

Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery (*USPSTF* 2021: B recommendation; Wood et al [*NCCN*] 2021; Mazzone et al [*ACCP*] 2021: strong recommendation, moderate-quality evidence). Lung cancer screening is generally not recommended for individuals considered to be at low risk for lung cancer with no additional risk factors (Wood et al [*NCCN*] 202; Donnelly et al [*ACR*] 2018).

CT chest with IV contrast

There is no relevant literature regarding the use of CT with IV contrast for lung cancer screening (Donnelly et al [*ACR*] 2018; Cox et al [*ACR*] 2020).

MRI

The role of MRI as a lung cancer screening modality has not been adequately studied, and there is no direct evidence to support its use in population-based screening (Donnelly et al [*ACR*] 2018; Cox et al [*ACR*] 2020).

FDG-PET/CT

Though FDG PET has a high sensitivity and specificity for lung cancer, its role as a screening modality has not been adequately studied, and there is no direct evidence to support its use in population-based

screening (Donnelly et al [*ACR*] 2018; Cox et al [*ACR*] 2020).

Surveillance of nodule(s) detected on screening

Lung-RADS® Version 1.1 – American College of Radiology. Release date: 2019

Category	Lung-RADS Score	Findings	Management	Risk of Malignancy
Incomplete	0	Prior chest CT examination(s) being located for comparison Part or all of lungs cannot be evaluated	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed	n/a
Negative No nodules and definitely benign nodules	1	No lung nodules Nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat containing nodules	Continue annual screening with LDCT in 12 months	< 1%
Benign Appearance or Behavior Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	**Perifissural nodule(s)** < 10mm **Solid nodule(s):** < 6mm new < 4mm **Part-solid nodule(s):** < 6mm on baseline screening **Non solid nodule(s) (GGN):** < 30mm OR ≥ 30mm and unchanged or growing slowly **Category 3 or 4 nodules unchanged for ≥ 3 months**		
Probably Benign Probably benign finding(s) – short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	**Solid nodule(s):** ≥ 6mm to < 8mm at baseline OR new 4mm to < 6mm **Part-solid nodule(s)** ≥ 6mm with solid component < 6mm OR new < 6mm **Non solid nodule(s)** (GGN) > 30mm on baseline CT or new	6 month LDCT	1-2%

Suspicious Findings for which additional diagnostic testing is recommended	4A	**Solid nodule(s):** ≥ 8 to < 15mm at baseline OR growing < 8mm OR new 6 to < 8mm **Part-solid nodule(s):** > 6mm with solid component > 6mm to < 8mm OR with a new or growing < 4mm solid component **Endobronchial nodule**	3 month LDCT; PET/CT may be used when there is a ≥ 8mm solid component	5-15%
Very Suspicious Findings for which additional diagnostic testing and/or tissue sampling is recommended	4B	**Solid nodule(s):** ≥ 15mm OR new or growing, and ≥ 8mm **Part-solid nodule(s) with:** a solid component > 8mm OR a new or growing ≥ 4mm solid component	Chest CT with or without contrast, PET/CT and/or tissue sampling depending on the probability of malignancy and comorbidities. PET/CT may be used when there is a ≥ 8mm solid component. For new large nodules that develop on an annual repeat CT screening CT, a 1 month LDCT may be recommended to address potentially infectious or inflammatory conditions	≥ 15%
	4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy		
Other Clinically significant or potentially clinically significant findings (non lung cancer)	S	**Modifier – may add on to category 0-4 coding**	As appropriate to the specific finding	n/a

Solid nodule detected on baseline LDCT *(Wood et al [NCCN] 2021):*

Type	Size	Imaging Recommendation
Solid nodule(s)	< 6mm in diameter	Low-dose CT chest in 12 months
Solid nodule(s)	≥ 6mm to ≤ 7mm in diameter	Low-dose CT chest in 6 months
Solid nodule(s)	≥ 8mm to ≤ 14mm in diameter	Low-dose CT chest in 3 months (or consider PET/CT)
Solid nodule(s)	≥ 15mm in diameter	Chest CT with IV contrast and/or PET/CT
Part-solid nodule(s)	< 6mm in diameter	Low-dose CT chest in 12 months
Part-solid nodule(s)	≥ 6mm in diameter with solid component of ≤ 5mm	Low-dose CT chest in 6 months

Part-solid nodule(s)	≥ 6mm in diameter with solid component of ≥ 6mm and ≤ 7mm	Low-dose CT chest in 3 months (or consider PET/CT)
Part-solid nodule(s)	Solid component of ≥ 8mm in diameter	Chest CT with IV contrast and/or PET/CT
Nonsolid nodule(s)	≤ 19mm in diameter	Low-dose CT chest in 12 months
Nonsolid nodule(s)	≥ 20mm in diameter	Low-dose CT chest in 6 months

Follow-up of solid lung nodule identified on previous lung cancer screening *(Wood et al [NCCN] 2021)*:

Type	Size	Imaging Recommendation
New lung nodule detected and possible infection or inflammation suspected	Any	Low-dose CT chest in 1-3 months
No change on follow-up LDCT	≤ 7mm in diameter	Low-dose CT chest in 12 months
No change on follow-up LDCT	≥ 8 and ≤ 14mm in diameter	Low-dose CT chest in 6 months
No change on follow-up LDCT	≥ 15mm in diameter	Low-dose CT chest in 6 months (or consider PET/CT)
No change on yearly LDCT	Any	Low-dose CT chest in 12 months
New nodule detected	≤ 3mm in diameter	Low-dose CT chest in 12 months
New nodule detected	≥ 4mm and ≤ 5mm in diameter	Low-dose CT chest in 6 months
New nodule detected	≥ 6mm and ≤ 7mm in diameter	Low-dose CT chest in 3 months
New nodule detected	≥ 8mm in diameter	Chest CT with IV contrast and/or PET/CT
Growing nodule (>1.5mm)	≤ 7mm in diameter	Low-dose CT chest in 3 months
Growing nodule (>1.5mm)	≥ 8mm in diameter	Chest CT with IV contrast and/or PET/CT

Follow-up of part-solid nodule identified on previous lung cancer screening *(Wood et al [NCCN] 2021):*

Type	Size	Imaging Recommendation
New lung nodule detected and possible infection or inflammation suspected	Any	Low-dose CT chest in 1-3 months
No change on follow-up LDCT	≤ 5 mm in diameter	Low-dose CT chest in 12 months
No change on follow-up LDCT	≥ 6mm in diameter with solid component ≥ 6mm and ≤ 7mm	Low-dose CT chest in 6 months
No change on follow-up LDCT	≥ 6mm in diameter with solid component ≥ 8mm	Low-dose CT chest without IV contrast in 6 months or consider PET/CT
No change on yearly LDCT	Any	Low-dose CT chest without IV contrast in 12 months
New nodule detected	≤ 5mm in diameter	Low-dose CT chest without IV contrast in 6 months
New nodule detected OR growing nodule with solid part > 1.5mm	≥ 6mm in diameter with growing solid component ≤ 3mm	Low-dose CT chest without IV contrast in 3 months

New nodule detected OR growing nodule with solid part > 1.5mm	Solid component ≥ 4mm	CT chest with IV contrast and/or PET/CT

Follow-up of nonsolid nodule identified on previous lung cancer screening *(Wood et al [NCCN] 2021):*

Type	Size	Imaging Recommendation
New nodule or stable nodule	≤ 19mm in diameter	Low-dose CT chest in 12 months
New nodule or stable nodule	≥ 20mm in diameter or growing (> 1.5mm)	Low-dose CT chest in 6 months

Clinical and imaging notes:

- The goal of lung cancer screening is to detect early-stage disease before it becomes clinically evident and when appropriate treatment can lead to improved survival (Donnelly et al [*ACR*] 2018).
- Only a minority of lung cancers are diagnosed while the patient is asymptomatic (Ost et al [*ACCP*] 2013).
- If a person decides to be screened, they should ideally be referred to a center with experience and expertise in lung cancer screening (*USPSTF* 2021; Wender et al [*ACS*] 2013).
- A pack-year is a way of calculating how much a person has smoked in their lifetime. One pack-year is the equivalent of smoking an average of 20 cigarettes – 1 pack – per day for a year (*USPSTF* 2021).
- Second-hand smoke is not independently considered a risk factor sufficient for recommending lung cancer screening (Wood et al [*NCCN*] 2021).
- Distinguishing incidentally detected lung nodules found on examinations performed for reasons other than lung cancer screening from nodules detected in the setting of lung cancer screening is key (Martin et al 2017). *Lung-RADS* was developed specifically for use in lung cancer screening CT reporting. The recently published updated guidelines of the *Fleischner Society* (MacMahon et al 2017) for the management of incidentally detected lung nodules specifically state that the updated guidelines do not apply to lung cancer screening (Martin et al 2017).
- One of the exclusion criteria for lung cancer screening CT is signs or symptoms that can be attributed to lung cancer. Thus, for patients in whom lung cancer is suspected, lung cancer screening CT should not be performed, and patients should instead undergo a diagnostic chest CT examination (Martin et al 2017).
- As part of the shared decision-making process, patients should be asked about signs and symptoms of any recent respiratory tract infection. In general, patients with a recent respiratory tract infection should delay lung cancer screening for approximately 3 months to ensure that any residual lung inflammation has resolved (Martin et al 2017).
- In a screening population, the presence of multiple pulmonary nodules has been found to indicate a lower risk of malignancy (Callister et al [*BTS*] 2015: evidence level 2+). That being said, evidence has demonstrated that effective management of subjects with multiple nodules was achieved as determined by the management of the largest nodule (Callister et al [*BTS*] 2015: evidence level 2+).
- A typical lung cancer screening CT of the thorax is performed with multidetector helical (spiral) technique in a single-breath hold (*ACR-STR* 2019). The study must include axial images from the lung apices to the costophrenic sulci acquired and viewed at 2.5-mm slice thickness or smaller, with reconstruction intervals equal to or less than the slice thickness (*ACR-STR* 2019).

- Scans must be obtained through the entire lungs, from apices to bases, and the field of view must be optimized for each patient to include the entire transverse and anteroposterior diameter of the lungs (*ACR-STR* 2019).

Evidence update (2016-present):

High Level of Evidence

Jonas et al (2021), in a large systematic review, conducted an analysis of the evidence on screening for lung cancer with low-dose CT (LDCT) to inform the *US Preventive Services Task Force*. All studies of screening with LDCT, accuracy of LDCT, risk prediction models, or treatment for early-stage lung cancer were selected. Data were not pooled because of heterogeneity of populations and screening protocols. Included were a total of 223 publications. Seven randomized clinical trials (RCTs) (N = 86 486) evaluated lung cancer screening with LDCT; the *National Lung Screening Trial* (*NLST*, N = 53 454) and *Nederlands-Leuvens Longkanker Screenings Onderzoek* (*NELSON*, N = 15 792) were the largest RCTs. The *NLST* found a reduction in lung cancer mortality (incidence rate ratio [IRR], 0.85 [95%CI, 0.75-0.96]; number needed to screen [NNS] to prevent 1 lung cancer death, 323 over 6.5 years of follow-up) with 3 rounds of annual LDCT screening compared with chest radiograph for high-risk current and former smokers aged 55 to 74 years. *NELSON* found a reduction in lung cancer mortality (IRR, 0.75 [95%CI, 0.61-0.90]; NNS to prevent 1 lung cancer death of 130 over 10 years of follow-up) with 4 rounds of LDCT screening with increasing intervals compared with no screening for high-risk current and former smokers aged 50 to 74 years. Harms of screening included radiation-induced cancer, false-positive results leading to unnecessary tests and invasive procedures, overdiagnosis, incidental findings, and increases in distress. For every 1000 persons screened in the *NLST*, false-positive results led to 17 invasive procedures (number needed to harm, 59) and fewer than 1 person having a major complication. Overdiagnosis estimates varied greatly. The authors conclude that screening high-risk persons with LDCT can reduce lung cancer mortality, but can also cause false-positive results. Of note, the authors found that most studies reviewed did not use current nodule evaluation protocols, which might reduce false-positive results and affiliated invasive procedures.

de Koning et al (2020), in a randomized trial, reported lung cancer incidence, mortality, and the performance of the four screening rounds in the *NELSON* trial among 13,195 male participants (main analysis) and 2,594 female participants (subgroup analysis). A total of 99.5% of included participants had smoked for > 25 years. All participants were between ages 50-74, and were randomly assigned to undergo CT screening at T0 (baseline), year 1, year 3, and year 5.5, or no screening. A minimum follow-up of 10 years was completed for all participants. At 10 years of follow-up, among men, the incidence of lung cancer was 5.58 cases per 1000 person-years in the screening group and 4.91 cases per 1000 person-years in the control group. Lung cancer mortality was 2.5 deaths per 1000 person-years and 3.30 deaths per person-years, respectively. Screening-detected lung cancers were substantially more often diagnosed in stage IA or IB (58.6%), compared to only 13.5% of the control group. Stage IV cancer was diagnosed in 45.7% of the control group, whereas only 9.4% of the screening-detected lung cancers were diagnosed in stage IV. The authors conclude that the *NELSON* trial showed that volume CT lung cancer screening resulted in substantially lower lung cancer mortality than no screening among high-risk persons.

Moderate Level of Evidence

Field et al (2021), presented data from the randomized *UK lung cancer screening trial* (*UKLS*) for incidence and mortality outcomes, and also conducted a meta-analysis of randomized, controlled LDCT screening trials which have reported lung cancer mortality with at least a median of three years' follow-up. A total of 4,055 participants (75% male, 64% aged 60-69, 34% aged 70-76, 39% current smokers, 61%

ex-smokers, 94% with 20+ pack years, 38% with asbestos exposure, 51% with history of respiratory disease) were randomly allocated to either a single invitation of screening with LDCT or to no screening (usual care). A total of 1,987 participants in the intervention and 1,981 in the usual care arms were followed for a median 7.3 years. A total of 86 cancers were diagnosed in the LDCT arm and 75 in the control arm, with 30 lung cancer deaths in the screening arm and 46 in the control arm (relative rate 0.65 [95%CI 0.41-1.02]; p value = 0.062). The primary analysis showed that these differences were not statistically significant. The meta-analysis, including UKLS results, indicated a significant reduction in lung cancer mortality with a pooled overall relative rate of 0.84 (95%CI 0.76-0.92) from nine eligible trials (n = 94,834). The authors conclude that, while the *UKLS* results are not statistically significant, largely due to the number of individuals recruited, there is sufficient follow-up to include in a larger meta-analysis which provides unequivocal support (16% relative reduction in lung cancer mortality) for lung cancer screening in identified risk groups.

Passiglia et al (2021), in a systematic review and meta-analysis, examined all the available randomized clinical trials comparing CT lung screening (CTLS) versus either no screening (NS) or chest x-ray (CXR) among tobacco-exposed populations. Two authors independently screened articles, extracted data, and assessed risk of bias. A total of nine trials (n = 88,497 patients) were included. Pooled analysis showed that CTLS was associated with: a significant reduction of lung cancer–related mortality (overall RR, 0.87; 95% CI, 0.78 to 0.98; NS RR, 0.80; 95% CI, 0.69 to 0.92); a significant increase of early-stage tumors diagnosis (overall RR, 2.84; 95% CI 1.76 to 4.58; NS RR, 3.33; 95% CI, 2.27 to 4.89; CXR RR, 1.52; 95% CI, 1.04 to 2.23); a significant decrease of late-stage tumors diagnosis (overall RR, 0.75; 95% CI, 0.68 to 0.83; NS RR, 0.67; 95% CI, 0.56 to 0.80); a significant increase of resectability rate (NS RR, 2.57; 95% CI, 1.76 to 3.74); a nonsignificant reduction of all-cause mortality (overall RR, 0.99; 95% CI, 0.94 to 1.05); and a significant increase of overdiagnosis rate (NS, 38%; 95% CI, 14 to 63). The authors conclude that, despite there still being uncertainty about overdiagnosis, this meta-analysis suggested that the CTLS benefits outweigh harms in subjects with cigarette smoking history, ultimately supporting the systematic implementation lung cancer screening worldwide.

Hoffman et al (2020), in a meta-analysis, evaluated the association of low-dose CT (LDCT) lung cancer screening with early-stage diagnosis, mortality, and screening harms, such as false positive results and complications. A minimum two reviewers were involved in decisions regarding article retrieval, and four authors independently assessed for risk of bias among selected studies. A total of nine studies (n = 96,559 subjects) were included. The risk of bias across studies was judged to be low. Results found that LDCT screening significantly increased the detection of stage I lung cancer (relative rate = 2.93; 95%CI 2.16-3.98) and reduced lung cancer mortality (relative rate 0.84 (95%CI 0.75-0.93). The pooled false positive rate was 8% (95% CI 4-18); subjects with false positive results had < 1 in 1,000 risk of major complications following invasive diagnostic procedures. The authors conclude that LDCT screening significantly reduced lung cancer mortality, while the estimated risks were low.

Sadate et al (2020), in a systematic review and meta-analysis, evaluated the efficacy of screening by low-dose CT (LDCT) compared with any other intervention in populations reporting tobacco consumption for more than 15 years. Primary outcomes were lung cancer mortality and overall mortality, and inclusion criteria was a randomized controlled trial (RCT) study design. Two double-blind reviewers selected the publications, critically appraised each eligible RCT, and extracted data for the meta-analysis. A total of seven RCTs were included in the meta-analysis (n = 84,558 participants). Results observed a significant reduction of lung cancer-specific mortality of 17% (risk ratio = 0.83, 95%CI 0.76-0.91) and a relative reduction of overall mortality of 4% (risk ratio = 0.96, 95%CI 0.92-1.00) in the screening group compared with the control group. The authors conclude that, in populations highly exposed to tobacco, screening

by LDCT reduces lung cancer mortality.

Kato et al (2018), in a prospective, multicenter, cross-sectional study, examined the prevalence of lung cancer (LC) and malignant pleural mesothelioma (MPM) in subjects with past asbestos exposure (AE). A total of 2,132 subjects (96.2% male, mean age 76.1 years, 78.8% former or current smokers) were enrolled. All subjects were screened using low-dose CT, and evaluated findings included subpleural curvilinear shadow/subpleural dots, ground glass opacity or interlobular reticular opacity, traction bronchiectasia, honeycombing change, parenchymal band, emphysema changes, pleural effusion, diffuse pleural thickening, rounded atelectasis, pleural plaques, and tumor formation. Results found that pleural plaques were detected in most subjects (89/4%) and emphysema changes were seen in 46%. A pathological diagnosis of lung cancer was confirmed in 45 cases (2.1%) and MPM in 7 cases (0.3%). The prevalence of lung cancer was 2.5% in those with a smoking history, which was significantly higher than in never smokers (0.7%, p = 0.027). Logistic regression analysis revealed smoking history, fibrotic plus emphysema changes, and pleural effusion as significant explanatory variables.

Heuvelmans et al (2017), in a subgroup analysis of the *NELSON* trial containing all participants with non-calcified baseline nodules on LDCT screening, explored the relationship between nodule count and lung cancer probability. A total of 3,392 participants (7,258 nodules) were included, and lung cancer probabilities per nodule count category were compared. Malignancy was confirmed by histology. A total of 1,746 (51.5%) participants had one nodule, 800 (23.6%) had two nodules, 354 (10.4%) had three nodules, 191 (5.6%) had four nodules, and 301 (8.9%) had > 4 nodules. The analysis found lung cancer probabilities 3.6% in those with one nodule, 4.1% for two nodules, 4.8% for three nodules, 6.3% for four nodules, and 3.3% for > 4 nodules. The authors conclude that half of participants with lung nodules had more than one nodule, and that probability did not significantly change with the number of nodules. Therefore, each nodule found in lung cancer screening should be assessed separately in the presence of other nodules.

Low Level of Evidence

Su et al (2021), in a retrospective study using *National Lung Screening Trial* data, investigated the impact of low-dose CT (LDCT) screening for primary lung cancer (PLC) on the risk of developing brain metastasis (BM) after PLC diagnosis. A total of 1,502 participants (mean age 65.9 years) who were diagnosed with PLC and had follow-up data for BM were included. Overall, 41.4% of participants had PLC detected through LDCT screening versus 58.6% detected through other methods, such as chest radiograph or incidental detection. Those whose PLC was detected with LDCT screening had a significantly lower 3-year incidence of BM (6.5%) versus those without (11.9%) with an adjusted cause-specific hazard ratio of 0.53 (p value = 0.001). The significant reduction in BM risk among PLCs detected through LDCT screening persisted in subgroups of those with early-stage PLC and those who underwent surgery. The authors conclude that early detection of PLC using LDCT is associated with lower risk of BM after PLC diagnosis.

Aggarwal et al (2019), in a prospective cohort study, sought to determine how to best prioritize participants for rescreening with low-dose CT (LDCT) after a long interval between LDCT scans that were originally negative. Out of a total 1,261 eligible participants, 359 were able to return for a rescreening scan (mean 7.6 years between scans; mean age 62.8 at baseline). Participants were divided into low (< 2%), moderate ($\underline{\geq}$ 2 to < 3.5%), and high baseline risk ($\underline{\geq}$ 3.5%) cohorts. The primary outcomes were the proportion of biopsy-proven lung cancer in the participants who returned for a LDCT scan within each risk cohort and the overall proportion of lung cancer cases. Those in the high-risk cohort compared to moderate- or low-risk were older (66 years vs. 62 and 59 years) and had a greater smoking history (54 pack-years vs. 47 and 29 pack-years). Results found the incidence of cancer in the high-risk cohort was

significantly higher than in the moderate-risk cohort (11% vs. 1.7%, p value = 0.002).

Kavanagh et al (2018), in a prospective cohort study, assessed the incidence of lung cancer in patients with negative findings at previous lung cancer screening. First, a total of 4,782 individuals who had negative screening results as part of the *International Early Lung Cancer Action Program* were identified. Subjects were then assigned a lung cancer risk score using a validated risk model. Subjects were interviewed by phone and invited to undergo low-dose CT. In all, a total of 327 participants were contacted and 200 participated in the study. The average age was 74 years (range, 57-88 years) and median time since previous CT was 7 years. The incidence rate of developing lung cancer during the next 6 years was estimated at 5.6%, and the period prevalence of lung cancer was 20.8%. The detection rate of low-dose CT was 7% (14 of 200 subjects), and of the 14 screening-detected cancers, 12 were stage I or II. The authors conclude that high-risk individuals have a high incidence of lung cancer after previous negative lung cancer screening, and that early-stage lung cancer can be successfully detected in older high-risk individuals.

PICO 3: Evaluation of patients presenting with signs or symptoms suggestive of lung cancer:

Note: Multidisciplinary evaluation is recommended to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy (Ettinger et al [*NCCN*] 2021).

- **Green** – CT chest (including adrenals) with IV contrast
- **Yellow** – FDG-PET/CT
- **Yellow** – CT chest without IV contrast
- **Red** – CT chest without and with IV contrast
- **Red** – MRI chest

Level of Evidence: CT chest: moderate; PET/CT: low-to-moderate, MRI: insufficient

Notes concerning applicability and/or patient preferences:
Practices may vary from institution to institution, likely because of varying prevalence of lung disease in different parts of the country, varying skill levels of operators, and varying availability of equipment (Kanne et al [*ACR*] 2013).

Guideline and PLE expert panel consensus opinion summary:
CT is considered the gold standard test for the diagnosis of lung cancer, while the use of PET/CT can also be an important tool (Alvarez et al [*SEPAR*] 2016). The clinical presentation and the findings on CT and/or PET/CT usually allow the physician to presumptively make a diagnosis of lung cancer and to differentiate between non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (Rivera et al [*ACCP*] 2013).

A CT scan with contrast is recommended for patients with suspected lung cancer who are eligible for treatment (*NICE* 2019; de Groot et al [*ACR*] 2019; Silvestri et al [*ACCP*] 2013: grade 1B recommendation; Cox et al [*ACR*] 2020). It is also the established imaging modality to determine the etiology of hemoptysis (Olsen et al [*ACR*] 2020). At a minimum, the initial CT scan should include the chest and upper abdomen, including the adrenals (Ettinger et al [*NCCN*] 2021; *NICE* 2019). If there is contraindication to contrast, such as known renal impairment or allergy, a chest CT without IV contrast may be utilized (de Groot et al [*ACR*] 2019; *NICE* 2019; Olsen et al [*ACR*] 2020; Cox et al [*ACR*] 2020). There are no data to support any added value of CT chest without IV contrast prior to the administration of IV contrast in the diagnosis of hemoptysis (Olsen et al [*ACR*] 2020).

In patients with suspected lung cancer who have an abnormal clinical evaluation and no suspicious extrathoracic abnormalities on chest CT, additional imaging for metastases is recommended (Silvestri et al [*ACCP*] 2013: grade 1B recommendation). PET/CT imaging can be useful before selecting a biopsy site, as it is better to biopsy the site that will confer the highest stage (Ettinger et al [*NCCN*] 2021). While PET/CT poorly differentiates benign from malignant changes in progressive massive fibrosis, it can also provide benefit in the diagnosis of pleural and lung malignancies among patients with asbestos exposure (Cox et al [*ACR*] 2020).

While beyond the scope of this guideline, a variety of tests (sputum cytology, biopsy, etc) are available to establish a definitive diagnosis and confirm lung cancer type (Rivera et al [*ACCP*] 2013).

Clinical notes:

- Common symptoms of lung cancer include fatigue, loss of appetite, weight loss, breathlessness, cough, hemoptysis, hoarseness, chest pain, bone pain, spinal cord compression, brain metastases, and superior vena cava obstruction (*NICE* 2019).
- Lung cancer symptoms typically occur late in the disease, so the majority of patients with lung cancer present with advanced disease (Postmus et al [*ESMO*] 2017; Ost et al [*ACCP*] 2013).
- Compared to small pulmonary nodules, which are usually asymptomatic, larger pulmonary lesions, central tumors, or tumors with an endobronchial component are more likely to result in pulmonary symptoms, including cough, dyspnea, chest pain, and hemoptysis. Of these, cough is the most common presentation (Ost et al [*ACCP*] 2013).
    - Recurrent pneumonia in the same anatomic distribution or relapsing acute exacerbations of COPD should raise concern for neoplasm. Dyspnea may accompany these scenarios (Ost et al [*ACCP*] 2013).
    - Hemoptysis accompanying lung cancer is rarely massive. Patients may dismiss small amounts of blood; however, hemoptysis may be the presenting symptom of lung cancer even in the setting of a normal or nonlocalizing chest radiograph (Ost et al [*ACCP*] 2013).
    - Persistent hemoptysis, even in small amounts, in patients with a history of smoking and COPD should raise concern about possible endobronchial tumor (Ost et al [*ACCP*] 2013).

Evidence update (2016-present):

Low Level of Evidence:

Bradley et al (2021), in a prospective cohort study, sought to determine the sensitivity and specificity of chest x-ray (CXR) for lung cancer in patients with symptoms aged > 50 years, and also to estimate the positive predictive values (PPVs) of being diagnosed with lung cancer within 1 year and 2 years following a negative CXR. In total, 114 of 8,996 (1.3%) patients who requested a CXR were diagnosed with lung cancer within 1 year. Sensitivity was 75.4% and specificity was 90.2%. The PPV of all symptoms for a diagnosis of lung cancer within 1 year of CXR was <1% for all individual symptoms except for hemoptysis, which had a PPV of 2.9%. PPVs for a diagnosis of lung cancer within 2 years of CXR was <1.5% for all single symptoms except for hemoptysis, which had a PPV of 3.9%. Observed cancer incidence for patients with a negative SR-CXR for 1 year and 2 years following SR-CXR was 0.35% (95% CI 0.22-0.48) and 0.71% (95% CI 0.53-0.89), respectively. The authors note however, that even in patients who appear to be at low risk, a negative CXR does not fully eliminate the possibility of lung cancer and, in some cases, further investigation should be considered if symptoms persist or evolve. Additionally, findings support guidance that unexplained hemoptysis warrants urgent referral, regardless of CXR result.

PICO 4: Staging, management, and surveillance of non-small cell lung cancer (NSCLC):

Note: Multidisciplinary evaluation is recommended to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy (Ettinger et al [*NCCN*] 2021).

Staging and management/restaging

- **Green** – CT chest (including adrenals) with IV contrast
- **Green** – FDG-PET/CT
- **Yellow** – CT chest without IV contrast
- **Yellow** – MRI brain without and with IV contrast or MRI brain without IV contrast
- **Yellow** – CT head without and with IV contrast or CT head with IV contrast
- **Yellow** – CT abdomen and pelvis with IV contrast
- **Yellow** – CT abdomen and pelvis without IV contrast
- **Yellow** – MRI chest without and with IV contrast or MRI chest without IV contrast
- **Yellow** – MRI abdomen without and with IV contrast or MRI abdomen without IV contrast
- **Yellow –** Whole body bone scan

Surveillance (in patient without symptoms)

- **Green** – CT chest (including adrenals) with IV contrast
- **Green** – Low-dose CT chest without IV contrast (annually)
- **Yellow** – CT chest (including adrenals) without IV contrast
- **Yellow** – CT abdomen and pelvis with or without IV contrast
- **Red** – FDG-PET/CT
- **Red** – MRI
- **Red** - Bone Scan

Level of Evidence: CT chest, PET/CT: moderate-to-high; MRI brain: moderate; bone scan: insufficient

Notes concerning applicability and/or patient preferences:
Practices differ from institution to institution, likely because of varying prevalence of lung disease in different parts of the country, varying skill levels of operators, and varying availability of equipment (Kanne et al [*ACR*] 2013). Chosen investigations should give the most information about diagnosis and staging with the least risk to the person (*NICE* 2019).

Guideline and PLE expert panel consensus opinion summary:
Patients are confirmed to have NSCLC based on a pathologic evaluation (Ettinger et al [*NCCN*] 2021). Pathologic evaluation is also used to determine the extent of invasion, whether the margins are involved, whether lymph nodes are involved, or whether certain gene variants or biomarkers are present (Ettiger et al [*NCCN*] 2021). After the pathologic diagnosis has been established, clinical staging is performed. The clinical stage is typically determined by the patient's symptoms, the disease history, and physical examination together with a limited battery of tests (Ettinger et al [*NCCN*] 2021).

Staging
Clinical noninvasive staging by radiologic imaging is the first step in determining the appropriate

management for patients with lung cancer (de Groot et al [*ACR*] 2019). Site specific symptoms warrant directed evaluation of that site with the most appropriate study (Silvestri et al [*ACCP*] 2013).

Chest CT

Chest CT is the modality of choice for evaluating the size and location of the primary tumor (T) (de Groot et al [*ACR*] 2019) or suspected multiple lung cancers (based on presence of biopsy-proven synchronous lesions or history of lung cancer) (Ettinger et al [*NCCN*] 2021). For NSCLC, the chest CT should include the upper abdomen, including the adrenals (*NICE* 2019; de Groot et al [*ACR*] 2019; Ettinger et al [*NCCN*] 2021; Silvestri et al [*ACCP*] 2013: grade 1B recommendation), while initial evaluation of combined NSCLC/SCLC should include CT of chest/abdomen/pelvis with contrast (Ganti et al [*NCCN*] 2021). For those with contraindication to contrast, a chest CT without IV contrast may be obtained (de Groot et al [*ACR*] 2019; *NICE* 2019). A chest CT without IV contrast may be able to better characterize adrenal nodules than chest CT with contrast, but its benefit for this purpose may be obviated by performance of PET/CT (de Groot et al [*ACR*] 2019).

CT staging of nodal (N) disease in the mediastinum is inadequate because of low sensitivity and specificity (de Groot et al [*ACR*] 2019). However, findings on chest CT of enlarged mediastinal nodes aids in guiding the biopsy, as invasive staging of the mediastinum is recommended over imaging alone (de Groot et al [*ACR*] 2019).

Chest CT is adequate for the identification of contralateral lung nodules constituting metastasized (M) disease and extrathoracic metastases of the adrenal glands (de Groot et al [*ACR*] 2019). Chest CT with IV contrast can aid in identifying mediastinal or chest wall invasion by tumor, evaluation of hilar lymph nodes, assessment for liver metastases, and distinguishing central obstructing tumor from surrounding atelectasis (de Groot et al [*ACR*] 2019). For patients with metastatic NSCLC, the scan should include complete assessment of the liver, kidneys, and adrenal glands (Planchard et al [*ESMO*] 2020: level IV evidence, grade A recommendation; Silvestri et al [*ACCP*] 2013). For those with a known lung cancer who have an abnormal clinical evaluation and no suspicious extrathoracic abnormalities on chest CT, additional imaging for metastases is recommended (Silvestri et al [*ACCP*] 2013: grade 1B recommendation).

FDG-PET/CT

FDG-PET/CT is usually appropriate to evaluate for extrathoracic metastases in patients with NSCLC, however, is not required for patients with stage 0 adenocarcinoma in situ with an otherwise normal chest CT examination (de Groot et al [*ACR*] 2019).

PET/CT can help evaluate the extent of disease and potentially avoid inappropriate surgery (Ettinger et al [*NCCN*] 2021). Patients with NSCLC who could potentially have treatment with curative intent should be offered FDG-PET/CT, if not previously done (*NICE* 2019; Ettinger et al [*NCCN*] 2021; Silvestri et al [*ACCP*] 2013: grade 1B recommendation; Kozower et al [*ACCP*] 2013: grade 1B/2C recommendation). Evaluation of the mediastinal nodes is a key step in the further staging of the patient, and FDG PET/CT scans can be used as an initial assessment of both the mediastinal and hilar nodes (Ettinger et al [*NCCN*] 2021). FDG-PET/CT has high sensitivity for the evaluation of solitary pulmonary nodules, intra-thoracic pathological lymph nodes, and distant metastatic disease (Planchard et al [*ESMO*] 2020). While PET scans can play a role in the evaluation staging of NSCLC, integrated FDG-PET/CT is even more sensitive and is the recommended modality, as it is more accurate for staging of the N and M descriptors than independent FDG-PET or CT (Ettinger et al [*NCCN*] 2021; de Groot et al [*ACR*] 2019). PET is useful to differentiate malignant neoplasms from radiation fibrosis, atelectasis, or other benign conditions in

patients with abnormal CT scans (Ettinger et al [*NCCN*] 2021). Positive PET/CT scan findings for mediastinal or distant disease need pathologic or other radiologic (e.g., MRI) confirmation (Ettinger et al [*NCCN*] 2021).

If bone metastases are clinically suspected, bone imaging is required (Planchard et al [*ESMO*] 2020: level IV evidence, grade B recommendation). FDG-PET/CT is the most sensitive modality in detecting bone metastasis, with a higher sensitivity and specificity than bone scintigraphy (Planchard et al [*ESMO*] 2020: level II evidence, grade B recommendation).

PET scans are not recommended for assessing whether brain metastases are present (Ettinger et al [*NCCN*] 2021).

MRI Brain (or CT head)
MRI brain without and with IV contrast is recommended in all NSCLC patients exhibiting neurologic symptoms, regardless of stage (Ettinger et al [*NCCN*] 2021; de Groot et al [*ACR*] 2019; Planchard et al [*ESMO*] 2020: level IV evidence, grade A recommendation). Brain MRI with IV contrast is also recommended to rule out asymptomatic brain metastases in patients with stage II, III, and IV disease if aggressive combined-modality therapy is being considered (*NICE* 2019; Ettinger et al [*NCCN*] 2021; de Groot et al [*ACR*] 2019; Postmus et al [*ESMO*] 2017: level III evidence, grade A recommendation; Silvestri et al [*ACCP*] 2013: grade 2C recommendation; Kozower et al [*ACCP*] 2013: grade 1C recommendation). Patients with stage IB NSCLC are less likely to have brain metastases; brain MRI is optional in this setting (Ettinger et al [*NCCN*] 2021; de Groot et al [*ACR*] 2019). Those with clinical stage I A NSCLC who have no neurological symptoms and are having treatment with curative intent do not require brain imaging (*NICE* 2019).

If MRI is not possible, CT of the head with contrast can be performed (Ettinger et al [*NCCN*] 2021; de Groot et al [*ACR*] 2019; Postmus et al [*ESMO*] 2017: level III evidence, grade B recommendation; Silvestri et al [*ACCP*] 2013: grade 2C recommendation). However, MRI brain is the preferred imaging modality for evaluating intracranial metastases, as it is more sensitive than CT (de Groot et al [*ACR*] 2019; Planchard et al [*ESMO*] 2020: level III evidence, grade B recommendation).

CT abdomen and pelvis (or MRI abdomen)
CT abdomen and pelvis with IV contrast may be an alternative imaging modality for extrathoracic metastasis in lung cancer patients being considered for curative therapy if FDG-PET or PET/CT is not performed (de Groot et al [*ACR*] 2019). It is also recommended in NSCLC patients with abnormal clinical evaluation (e.g., signs or symptoms referable to the abdomen/pelvis) and no suspicious extrathoracic findings on chest CT (de Groot et al [*ACR*] 2019). Additionally, if PET is unavailable, abdominal CT (with bone scan) is a reasonable alternative to evaluate for extrathoracic disease (Silvestri et al [*ACCP*] 2013).

MRI abdomen may be used to characterize adrenal nodules when findings on CT are equivocal and FDG-PET/CT is not performed, as it has high sensitivity for detecting and characterizing small liver lesions (de Groot et al [*ACR*] 2019). It can also be considered in patients with intolerance or other contraindication to CT contrast (PLE expert panel consensus opinion).

MRI chest
MRI can be used when necessary to assess the extent of disease for people with superior sulcus tumors (*NICE* 2019). MRI should not be routinely used to assess the stage of the primary tumor (T) in non-small-cell lung cancer (*NICE* 2019). However, MRI chest without and with IV contrast may be indicated in

specific clinical circumstances in NSCLC patients with equivocal findings on chest CT, and may also be useful for assessing chest wall or spinal invasion and tumor involvement of mediastinal structures (de Groot et al [*ACR*] 2019). MRI may also complement or improve the diagnostic staging accuracy of FDG-PET/CT imaging, particularly in assessing local chest wall, vascular or vertebra invasion and is also effective for identification of nodal and distant metastatic disease (Planchard et al [*ESMO*] 2020).

Whole body bone scan
If bone metastases are clinically suspected, bone imaging is required (Planchard et al [*ESMO*] 2020: level IV evidence, grade B recommendation). Bone scan can be used for detection of bone metastasis (Planchard et al [*ESMO*] 2020: level IV evidence, grade B recommendation), but its routine use is not recommended (Ettinger et al [*NCCN*] 2021). Rather, FDG-PET/CT is the more sensitive modality in detecting bone metastasis, with a higher sensitivity and specificity than bone scanning (Planchard et al [*ESMO*] 2020: level II evidence, grade B recommendation). If PET is not available, bone scan can be a reasonable alternative (Silvestri et al [*ACCP*] 2013).

Management/Restaging
Restaging is performed to exclude disease progression or interval development of metastatic disease (Ettinger et al [*NCCN*] 2021). Surgical reevaluation is performed to determine whether the tumor is resectable after treatment (Ettinger et al [*NCCN*] 2021). Assessment of treatment response is generally recommended after two cycles of systemic therapy, then after every two to four cycles of therapy or when clinically indicated (Ettinger et al [*NCCN*] 2021). Initial assessment typically consists of CT with (or without) contrast (Ettinger et al [*NCCN*] 2021). FDG-PET/CT has also been shown to be useful in restaging after neoadjuvant therapy (Ettinger et al [*NCCN*] 2021). The selective use of FDG-PET may also be recommended when recurrence after radiation therapy or stereotactic ablative radiotherapy is suspected based on previous serial chest CT scan, or to evaluate previous imaging findings indeterminate for recurrent lung cancer (Postmus et al [*ESMO*] 2017: level III evidence, grade B recommendation; Ettinger et al [*NCCN*] 2021; PLE expert panel consensus opinion). PET/CT significantly improves the targeting accuracy of radiation therapy, especially for patients with significant atelectasis and when IV contrast is contraindicated (Ettinger et al [*NCCN*] 2021). The *Society of Nuclear Medicine and Molecular Imaging* (Jadvar et al [*SNMMI*] 2017) has assigned a score of 7 (appropriate) to the use of FDG-PET/CT in restaging and treatment response assessment of malignant lung cancer, including:

- restaging for detection of local recurrence,
- restaging for detection of metastases, and/or
- treatment response evaluation.

Brain MRI with contrast is recommended if there is recurrence after the completion of definitive therapy; if MRI is not possible, CT of head with contrast can be used (Ettinger et al [*NCCN*] 2021).

Surveillance imaging
CT chest
If there is no evidence of clinical radiographic disease after completion of definitive therapy (Ettinger et al [*NCCN*] 2021; Postmus et al [*ESMO*] 2017: level III evidence, grade B recommendation; Colt et al [*ACCP*] 2013: grade 2C recommendation):

- For stage I-II patients whose primary treatment included surgery with or without chemotherapy, chest CT should be completed every 6 months for 2-3 years, then LDCT without contrast annually.
- For stage I-II patients whose primary treatment included radiation therapy, or stage III-IV patients, chest CT should be completed every 3-6 months for 3 years, then chest CT every 6

months for 2 years, then LDCT without contrast annually.

Timing of follow-up/surveillance CT scans within the recommended parameters should be based on clinical decision making (Ettinger et al [*NCCN*] 2021). It is recommended that clinicians use a diagnostic chest CT that includes the adrenals, with contrast (preferred) or without contrast when conducting surveillance for recurrence during the first 2 years post treatment (Schneider et al [*ASCO*] 2020: informal consensus, low evidence quality, moderate strength of recommendation; Ettinger et al [*NCCN*] 2021). There is no evidence of added benefit for a CT of the abdomen and pelvis over a chest CT (through the adrenals) as a surveillance imaging modality for recurrence (Schneider et al [*ASCO*] 2020). Low-dose screening chest CT should be used when conducting surveillance for new lung primaries after the first 2-3 years post treatment (Schneider et al [*ASCO*] 2020: evidence based, low evidence quality, moderate strength of recommendation; Ettinger et al [*NCCN*] 2021).

For curatively treated stage I-III NSCLC, surveillance imaging may be omitted in patients who are clinically unsuitable for or unwilling to accept further treatment; consideration of overall health status, chronic medical conditions, and patient preferences is recommended (Schneider et al [*ASCO*] 2020: informal consensus, low evidence quality, weak strength of recommendation).

FDG-PET/CT

FDG PET/CT is not typically recommended for the routine surveillance of NSCLC patients without symptoms (Ettinger et al [*NCCN*] 2021; Schneider et al [*ASCO*] 2020: informal consensus, low evidence quality, moderate strength of recommendation; Colt et al [*ACCP*] 2013: grade 1C recommendation).

MRI brain (or CT head)

Brain MRI is not typically recommended for the routine surveillance of NSCLC patients without symptoms (Ettinger et al [*NCCN*] 2021 (Schneider et al [*ASCO*] 2020: informal consensus, low evidence quality, moderate strength of recommendation; Ettinger et al [*NCCN*] 2021) Some sub groups of patients, especially those with EGFR- or ALK-mutated lung cancer have a higher risk of developing brain metastases and may benefit from surveillance imaging to allow for early intervention with focused radiation and other treatment modalities (e.g., Mitra et al 2019; Rangachari et al 2015).

<u>Clinical and imaging notes:</u>

- Non-small-cell lung cancer (NSCLC), including adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma, comprises approximately 85% of lung cancer cases (de Groot et al [*ACR*] 2019).
- The *TNM system* is the most widely used cancer staging system. In the *TNM system* (*National Cancer Institute* 2015):
    - T refers to the size and extent of the main (primary) tumor);
    - N refers to the number of nearby lymph nodes that have cancer; and
    - M refers to whether the cancer has metastasized from the primary tumor to other parts of the body.

T (primary tumor)	
Tx	Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence primary tumor
Tis	Carcinoma in situ
T1	Tumor <u>≤</u> 3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1mi	Minimally invasive adenocarcinoma
T1a	Tumor <u>≤</u> 1 cm in greatest dimension

T1b	Tumor > 1 but ≤ 2 cm in greatest dimension
T1c	Tumor > 2 but ≤ 3 cm in greatest dimension
T2	Tumor > 3 but ≤ 5 cm or with any of the following features: involves main bronchus regardless of distance from the carina but without involvement of the carina; invades visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
T2a	Tumor > 3 but ≤ 4 cm in greatest dimension
T2b	Tumor > 4 but ≤ 5 cm in greatest dimension
T3	Tumor > 5 but ≤ 7cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium)
T4	Tumor > 7cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina
N (regional lymph nodes)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal nodes
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M (distant metastasis)	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with plural or pericardial nodule(s) or malignant pleural or pericardial effusion
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases in one or more organs

(Goldstraw et al 2016)

- CT and FDG-PET/CT for staging should ideally be performed within 60 days of any planned resection and within 30 days before radiation therapy, as sensitivity and accuracy for nodal staging diminishes over time (de Groot et al [*ACR*] 2019; Ettinger et al [*NCCN*] 2021).
- PET/CT should be performed skull base to knees or whole body (Ettinger et al [*NCCN*] 2021).
- The CT component of the FDG-PET/CT examination improves anatomical localization and can provide additional growth/morphological information that may strengthen a diagnosis of lung malignancy or raise the possibility of alternative benign diagnoses (Callister et al [*BTS*] 2015).

Evidence update (2016-present):

Moderate Level of Evidence:

Vella et al (2019), in a retrospective cohort study, examined the association of PET/CT use with non-small cell lung cancer (NSCLC) mortality in the *US Department of Veterans Affairs* (*VA*) health care system from 2000 to 2013. The cohort study included 64,103 veterans (98% male) receiving care who were diagnosed with incident NSCLC. Primary outcome was all-cause and NSCLC-specific 5-year mortality, with secondary outcome of receipt of stage-appropriate treatment. A total of 51,844 (80.9%) patients had a PET/CT performed: 25,735 (40.1%) in the 12 months before diagnosis and 41,242 (64.3%) in the 5 years after diagnosis. Increased PET/CT use (59.2% in 2000 vs. 93.2% in 2013) and decreased NSCLC-specific 5-year mortality (89.9% in 2000 vs. 82.4% in 2013) were found over time. Increased use of stage-appropriate therapy was also seen over time (35.4% in 2000 to 52.7% in 2013). Use of PET-CT before diagnosis was associated with increased likelihood of stage-appropriate treatment for all stages of NSCLC and decreased mortality in a risk-adjusted model among all participants and among veterans undergoing stage-appropriate treatment (all-cause mortality: hazard ratio [HR], 0.78; 95%CI, 0.77-0.79;

NSCLC-specific mortality: HR, 0.78; 95%CI, 0.76-0.80). Findings suggest that use of PET/CT before diagnosis is associated with a higher level of care for veterans along with decreased mortality.

Low Level of Evidence:
Kim et al (2021), in a retrospective study, estimated the cumulative incidence and risk factors for brain metastasis development in patients with NSCLC without brain metastases at initial presentation. A total of 1,495 patients with NSCLC (mean age 65) that received brain MRI at initial presentation were included. Follow-up brain MRI was ordered at physician discretion, and MRIs were reviewed in combination with clinical records. A total of 258 patients (17.3%) underwent follow-up brain MRI, and 72 (4.8%) had brain metastases develop at a median 12.3 months after NSCLC diagnosis. The cumulative incidence of brain metastases at 6, 12, 18, and 24 months after initial evaluation was 0.6%, 2.1%, 4.2%, and 6.8%, respectively. Cumulative incidence at 6, 12, 18, and 24 months was higher ($p < .001$) in patients with clinical stage III–IV disease (1.3%, 3.9%, 7.7%, and 10.9%, respectively) than in those with clinical stage I–II disease (0.0%, 0.8%, 1.2%, and 2.6%, respectively). The authors note that, for those with clinical stage III-IV disease, brain MRI performed 12 months after initial evaluation may be warranted.

Toba et al (2021), in a retrospective study, examined the diagnostic capability of FDG-PET/CT for detecting recurrence among postoperative NSCLC patients, and evaluated the results of surveillance using FDG-PET/CT in asymptomatic patients. A total of 496 FDG-PET/CT exams were performed to detect recurrence for 187 NSCLC patients who had undergone potentially curative operations at a single institution. Among those (n = 47) who had recurrence, FDG-PET/CT correctly diagnosed recurrence in 46 (97.9%) and 68 of 69 (98.6%) recurrent sites. FDG-PET/CT had 97.9% sensitivity, 97.1% specificity, 92% positive predictive value, 99.3% negative predictive value, and 97.3% accuracy. In asymptomatic patients, the detection rate of recurrence in stage III patients was significantly higher than the detection rates in the stage I and II patients, and FDG-PET/CT performed ≤ 3 years following resection was able to detect significantly more FDG-positive lesions compared to that performed after 4 years. The authors conclude that FDG-PET/CT is very useful for detecting recurrence in NSCLC patients after operation, and that it might be sufficient to perform follow-up FDG-PET/CT until 3 years after resection for advanced-stage patients.

Kim et al (2020), in a retrospective study, evaluated the diagnostic yield of staging brain MRI in the initial evaluation of lung cancer. A total of 1,712 patients (mean age 64 years) who underwent staging chest CT and staging brain MRI were included. The diagnostic yield of staging brain MRI in newly diagnosed NSCLC was 11.9% (203/1,712, 95% CI 10.4%-13.4%). In clinical stage IA, IB, and II disease, the diagnostic yields were 0.3% (2/615; 95% CI 0.0%-1.2%), 3.8% (7/186; 95% CI 1.5%-7.6%), and 4.7% (8/171; 95% CI 2.0%-9.0%), respectively. The diagnostic yield was higher in patients with adenocarcinoma (13.6%; 176/1297; 95% CI 11.8%-15.6%) than squamous cell carcinoma (5.9%; 21/354; 95% CI 3.7%-8.9%) and in patients with EGFR mutation–positive adenocarcinoma (17.5%; 85/487; 95% CI 14.2%-21.1%) than with EGFR mutation–negative adenocarcinoma (10.6%; 68/639; 95% CI 8.4%-13.3%) (p .001 for both). The authors conclude that the diagnostic yield of staging brain MRI in stage IA NSCLC was low but higher diagnostic yield was found in stage IB and also in epidermal growth factor receptor mutation-positive adenocarcinoma.

Suh et al (2020), in a retrospective study, investigated the utility of FDG PET/CT for preoperative staging of subsolid NSCLCs with a solid portion size of 3cm or smaller. A total of 855 patients with pathologically proven NSCLCs manifesting as subsolid nodules were included. The diagnostic performance of FDG PET/CT and chest CT were compared for detection of lymph node, intrathoracic, or distant metastases.

In total, there were lymph node metastases in 25 of 765 (3.3%) patients who underwent surgical lymph node dissection or biopsy, and intrathoracic or distant metastases in two of 855 patients (0.2%). For lymph node staging, FDG PET/CT showed a sensitivity of 44.0%, specificity of 81.5%, positive predictive value of 9.6%, negative predictive value of 97.0%, and accuracy of 79.9%, which were lower than those of chest CT for accuracy ($p < 0.0001$). FDG PET/CT could not accurately detect any intrathoracic or distant metastasis. After propensity score matching, the diagnostic accuracy for lymph node staging of FDG PET/CT in the group who underwent both CT and FDG PET/CT was lower than that of chest CT in the group who did not undergo FDG PET/CT ($p = 0.002$). The authors conclude that FDG PET/CT had limited utility in preoperatively detecting lymph node or distant metastasis in those with subsolid NSCLCs with a solid portion size of $\leq$ 3cm.

Subramanian et al (2019), in a retrospective cohort study, hypothesized that surveillance intensity was not associated with 5-year overall survival in patients with resected stage I NSCLC. Patients undergoing CT surveillance were placed into three groups: high intensity (3 month), moderate intensity (6 month), and low intensity (annual). A total of 2,442 patients identified through cancer registrars and the National Cancer Database were included, with 805 (33%), 1,216 (50%), and 421 (17%) patients in high, moderate, and low surveillance intensity groups. Five-year overall survival was similar between intensity groups (p value 0.547). Additionally, surveillance on asymptomatic patients detected 210 (63%) cases of locoregional recurrences and 128 (72%) cases of new primary lung cancer. The authors concluded that, in a national dataset of long-term outcomes for stage I NSCLC, surveillance intensity was not associated with 5-year overall survival.

PICO 5: Staging, management, and surveillance of small cell lung cancer (SCLC):

Note: Multidisciplinary evaluation is recommended to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy (Ettinger et al [*NCCN*] 2021).

Staging and management/restaging

- **Green** – CT chest (including adrenals) with IV contrast
- **Green** – CT abdomen and pelvis with IV contrast
- **Green** – FDG-PET/CT
- **Green** – MRI brain without and with IV contrast or MRI brain without IV contrast
- **Yellow** – CT chest without IV contrast
- **Yellow** – CT abdomen and pelvis without IV contrast
- **Yellow** – MRI chest without and with IV contrast or MRI chest without IV contrast
- **Yellow** – MRI abdomen without and with IV contrast or MRI abdomen without IV contrast
- **Yellow** – CT head without and with IV contrast or CT head with IV contrast
- **Yellow –** Whole body bone scan

Surveillance (in patient without symptoms)

- **Green** – CT chest (including adrenals) with IV contrast
- **Green** – CT abdomen and pelvis with IV contrast
- **Green** – MRI brain without and with IV contrast or MRI brain without IV contrast
- **Green** – Follow-up low-dose CT chest without IV contrast (annually*, after two years of surveillance with no evidence of recurrent disease*)
- **Yellow** – CT chest (including adrenals) without IV contrast
- **Yellow** – CT abdomen and pelvis without IV contrast
- **Yellow** – CT head without and with IV contrast or CT head with IV contrast
- **Red** – FDG-PET/CT
- **Red** – Bone Scan

Level of Evidence: CT chest, PET/CT, MRI brain: moderate-to-high; bone scan: insufficient

Notes concerning applicability and/or patient preferences:
Chosen investigations should give the most information about diagnosis and staging with the least risk to the person (*NICE* 2019).

Guideline and PLE expert panel consensus opinion summary:
Pathologic evaluation is performed to determine the histologic classification of lung tumors and relevant staging parameters (Ganti et al [*NCCN*] 2021).

Staging and management/restaging
Clinical noninvasive staging by radiologic imaging is the first step in determining the appropriate management for patients with lung cancer (de Groot et al [*ACR*] 2019). Site specific symptoms warrant directed evaluation of that site with the most appropriate study (Silvestri et al [*ACCP*] 2013).

CT chest/abdomen/pelvis
CT with IV contrast is indicated for the initial evaluation of SCLC; if a concurrent CT of the abdomen and pelvis is not obtained, the exam should be extended through the adrenal glands (Ganti et al [*NCCN*] 2021; Dingemans et al [*ESMO*] 2021: level IV evidence, grade A recommendation; de Groot et al [*ACR*] 2019). CT with IV contrast can aid in identifying mediastinal or chest wall invasion by tumor, evaluation of hilar and mediastinal lymphadenopathy, assessment for liver metastases, and distinguishing central obstructing tumor from surrounding atelectasis (de Groot et al [*ACR*] 2019).

CT abdomen and pelvis with IV contrast is usually appropriate; however, FDG-PET/CT is more sensitive for lymph node and adrenal metastases, and is more sensitive than CT for the detection of bone metastases (de Groot et al [*ACR*] 2019). Up to 60% of SCLC patients have metastases to the abdominal organs at presentation, with the liver and adrenal gland being the most frequent sites (de Groot et al [*ACR*] 2019). [Because SCLC is typically hypervascular] dual phase imaging is recommended (de Groot et al [*ACR*] 2019).

Response assessment following primary treatment should include chest/abdomen/pelvis CT with contrast, along with brain MRI (preferred) or CT head with contrast (Ganti et al [*NCCN*] 2021).

FDG-PET/CT
Initial evaluation of SCLC or combined SCLC/NSCLC should consider use of PET/CT scan if limited stage is suspected or if needed to clarify stage (Ganti et al [*NCCN*] 2021; de Groot et al [*ACR*] 2019; Jett et al [*ACCP*] 2013: grade 2C recommendation). Patients who could potentially have treatment with curative intent should be offered PET/CT (*NICE* 2019; de Groot et al [*ACR*] 2019), as FDG-PET has superior sensitivity and specificity compared to CT in identifying metastatic disease (other than brain metastases) in SCLC patients (de Groot et al [*ACR*] 2019). This includes > 90% sensitivity, specificity, accuracy, and negative predictive value for bone metastases, which is superior to bone scintigraphy (de Groot et al [*ACR*] 2019). PET/CT, superior to PET alone, can increase staging accuracy in patients with SCLC, as it is a highly metabolic disease (Ganti et al [*NCCN*] 2021). Findings that modify treatment decisions should be pathologically confirmed (Dingemans et al [*ESMO*] 2021: level II evidence, grade C recommendation). The use of PET/CT is optional if extensive stage-(ES) SCLC is established (de Groot et al [*ACR*] 2019).

The selective use of FDG-PET/CT may also be recommended to work up indeterminate CT findings after stereotactic ablative radiotherapy and other treatment modalities when recurrence is suspected (Postmus et al [*ESMO*] 2017: level III evidence, grade B recommendation; PLE expert panel consensus opinion).

Brain MRI (or CT head)
Initial evaluation of SCLC or combined SCLC/NSCLC should include brain MRI (preferred) or head CT with contrast (de Groot et al [*ACR*] 2019; Ganti et al [*NCCN*] 2021; *NICE* 2019; Dingemans et al [*ESMO*] 2021: level III evidence, grade A recommendation). Brain MRI with IV contrast is more sensitive than CT for identifying intracranial metastases (Ganti et al [*NCCN*] 2021; Jett et al [*ACCP*] 2013: grade 1B recommendation; de Groot et al [*ACR*] 2019). MRI brain without IV contrast may be performed if there is contraindication to contrast (de Groot et al [*ACR*] 2019). CT head with IV contrast can used as an alternate imaging modality if brain MRI is not performed (de Groot et al [*ACR*] 2019; Ganti et al [*NCCN*] 2021).

MRI chest
MRI chest without and with IV contrast may be indicated in specific clinical circumstances in SCLC

patients with equivocal findings on CT chest, and may also be useful for assessing chest wall or spinal invasion and tumor involvement of mediastinal structures (de Groot et al [*ACR*] 2019).

MRI abdomen
MRI abdomen can be used to characterize adrenal nodules when findings on CT are equivocal and FDG-PET/CT is not performed. It also has a higher sensitivity than CT or PET imaging for detecting and characterizing small liver lesions (de Groot et al [*ACR*] 2019). It can also be considered in patients with intolerance or other contraindication to CT contrast (PLE expert panel consensus opinion).

Bone imaging
Conventional radiographs can be performed as the first test for those with localized signs or symptoms of bone metastasis (*NICE* 2019). Bone scintigraphy should be avoided when PET-CT does not show bone metastases (*NICE* 2019; Jett et al [*ACCP*] 2013). However, if PET/CT is not available, bone scintigraphy can be offered to evaluate for extrathoracic bone metastases in SCLC patients (*NICE* 2019; Ganti et al [*NCCN*] 2021; de Groot et al [*ACR*] 2019; Dingemans et al [*ESMO*] 2021: level V evidence, grade B recommendation). Additional workup for limited stage SCLC should include bone imaging (radiographs or MRI) as appropriate if PET/CT is equivocal (Ganti et al [*NCCN*] 2021).

Follow-up / surveillance imaging
In general, for curatively treated stage I-III SCLC, patients should undergo surveillance imaging for recurrence at least every 6 months for the duration of 2 years (Schneider et al [*ASCO*] 2020: informal consensus, low evidence quality, moderate strength of recommendation). After this, patients should undergo surveillance imaging for detection of new primary lung cancers annually (Schneider et al [*ASCO*] 2020: evidence based, intermediate evidence quality, moderate strength of recommendation). Surveillance imaging may be omitted in SCLC patients who are clinically unsuitable for or unwilling to accept further treatment, and consideration of overall health status, chronic medical conditions, and patient preference is recommended (Schneider et al [*ASCO*] 2020: informal consensus, low evidence quality, weak strength of recommendation).

Chest CT
Surveillance of SCLC should consist of surveillance CT (chest with or without abdomen/pelvis) every 2-6 months, more frequently in years 1-2 and less frequently thereafter (Ganti et al [*NCCN*] 2021; Dingemans et al [*ESMO*] 2021: level V evidence, grade C recommendation). This can be done with contrast (preferred) or without contrast (Schneider et al [*ASCO*] 2020: informal consensus, low evidence quality, moderate strength of recommendation). For curatively treated stage I-III SCLC, clinicians should use a low-dose screening chest CT when conducting surveillance for new lung primaries after the first 2 years post treatment (Schneider et al [*ASCO*] 2020: evidence based, low evidence quality, moderate strength of recommendation). As patients with a history of lung cancer are at high risk of developing a second primary, yearly follow-up with a low-dose CT starting from the end of regular follow-up may also be considered (Dingemans et al [*ESMO*] 2021: level V evidence, grade C recommendation). There is no evidence of added benefit for a CT of the abdomen and pelvis over a chest CT (through the adrenals) as a surveillance imaging modality for recurrence (Schneider et al [*ASCO*] 2020).

MRI brain (or CT head)
Surveillance of SCLC should also consist of MRI brain (preferred) or CT head with contrast every 3-4 months during year 1, then every 6 months during year 2 regardless of PCI status (Ganti et al [*NCCN*] 2021; Schneider et al [*ASCO*] 2020: informal consensus, low evidence quality, weak strength of recommendation; Dingemans et al [*ESMO*] 2021: level II evidence, grade C recommendation). Brain MRI

should not be routinely offered to asymptomatic patients after 2 years of disease-free survival (Schneider et al [*ASCO*] 2020).

FDG-PET/CT
For curatively treated stage I-III SCLC, clinicians should not use FDG-PET as a surveillance tool (Ganti et al [*NCCN*] 2021; Schneider et al [*ASCO*] 2020: informal consensus, low evidence quality, moderate strength of recommendation).

Clinical notes:

- Small-cell lung cancer (SCLC) accounts for approximately 13-15% of lung cancer cases and is typically associated with bulky hilar or mediastinal adenopathy and distant metastasis (de Groot et al [*ACR*] 2019; Ost et al [*ACCP*] 2013).
- When assessing mediastinal and chest wall invasion, CT alone may not be reliable, and other techniques such as ultrasound [or MRI] can be considered if there is doubt (*NICE* 2019).
- The TNM system is the most widely used cancer staging system. In the *TNM system* (*National Cancer Institute* 2015):
    - T refers to the size and extent of the main (primary) tumor);
    - N refers to the number of nearby lymph nodes that have cancer; and
    - M refers to whether the cancer has metastasized from the primary tumor to other parts of the body.
- The CT component of the FDG-PET/CT examination improves anatomical localization and can provide additional growth/morphological information that may strengthen a diagnosis of lung malignancy or raise the possibility of alternative benign diagnoses (Callister et al [*BTS*] 2015).

Evidence update (2016-present):
Low Level of Evidence:
Martucci et al (2020), in a systematic review and meta-analysis, aimed to provide quantitative data about the impact of ^{18}F-FDG PET/CT in staging small cell lung cancer (SCLC). Two authors performed a comprehensive literature search and independently reviewed the articles. A total of nine studies (n = 721 patients) with SCLC were included. Compared to conventional staging, a superior accuracy of ^{18}F-FDG PET/CT was found. A change in binary SCLC staging using ^{18}F-FDG PET/CT was demonstrated in 15% of patients (95% CI 9-21%) with SCLC. The authors conclude that ^{18}F-FDG PET/CT is a useful molecular imaging method for staging patients with SCLC as it can change management in a significant number of patients. They encourage additional large prospective studies on the impact of ^{18}F-FDG PET/CT in staging SCLC patients.

Quartuccio et al (2019), in a multicenter retrospective study, evaluated the prognostic value yielded by ^{18}F-FDG PET/CT in restaging patients with SCLC, and assessed the diagnostic agreement between ^{18}F-FDG PET/CT and contrast-enhanced CT (ceCT). A total of 164 patients with SCLC who underwent ^{18}F-FDG PET/CT for restaging purposes were included. The agreement between PET/CT and ceCT in detecting metastases was evaluated in 119 patients on a patient-based analysis (Cohen's κ; $P < 0.05$). Results found that the presence of metastatic lesions on ^{18}F-FDG PET/CT was associated with a significantly shorter overall survival (p value = 0.039) and progression-free survival (p value < 0.001). Higher maximum standardized uptake value showed a trend toward a shorter overall survival (p value = 0.065). The K-agreement between ceCT and PET/CT in recurrent SCLC was 0.37 (p value < 0.001). PET/CT and ceCT showed the same number of lesions in 52 (43.7%) patients, while PET/CT detected additional lesions in 35 (29.4%) patients. The authors conclude that detection of metastatic lesions at restaging by ^{18}F-FDG PET/CT can predict a higher rate of progression in patients with SCLC. Additionally, ^{18}F-FDG

PET/CT and ceCT seem to be complementary imaging modalities in patients with metastatic SCLC.

Guideline exclusions:

- Cases meeting the definition of a suspected or confirmed emergency medical condition
- Scenarios where patient is treated in an inpatient setting
- Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)
- Typical and atypical carcinoid tumors of the lung
- Pregnant patients
- Pediatric patients
- AI applications for the detection, characterization, and tracking of lung nodules

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