American College of Radiology ACR Appropriateness Criteria® Radiologic Management of Pulmonary Nodules and Masses

<u>Variant: 1</u> Adult. Stable 1 to 3 cm solitary solid pulmonary nodule. Unchanged in diameter for 2 years. Person who smokes. Next step.

Procedure	Appropriateness Category
Follow-up imaging only	May Be Appropriate
Percutaneous lung biopsy	May Be Appropriate (Disagreement)
Endobronchial ultrasound and biopsy	Usually Not Appropriate
Percutaneous ablation lung	Usually Not Appropriate
Stereotactic body radiotherapy	Usually Not Appropriate
Surgical management	Usually Not Appropriate
Fiducial marker and surgical management	Usually Not Appropriate

<u>Variant: 2</u> Adult. Serially, enlarging solitary solid pulmonary nodule, now 1 to 3 cm in diameter. Person who smokes. Next step.

Procedure	Appropriateness Category
Percutaneous lung biopsy	Usually Appropriate
Endobronchial ultrasound and biopsy	Usually Appropriate
Fiducial marker and surgical management	Usually Not Appropriate
Follow-up imaging only	Usually Not Appropriate
Stereotactic body radiotherapy	Usually Not Appropriate
Surgical management	Usually Not Appropriate
Percutaneous ablation lung	Usually Not Appropriate

<u>Variant: 3</u> Adult. 1 to 3 cm solitary solid pulmonary nodule near the hilum. Identified on initial screening CT chest. Person who smokes. Next step.

Procedure	Appropriateness Category
Endobronchial ultrasound and biopsy	Usually Appropriate
Percutaneous lung biopsy	May Be Appropriate
Follow-up imaging only	May Be Appropriate
Surgical management	Usually Not Appropriate
Fiducial marker and surgical management	Usually Not Appropriate
Percutaneous ablation lung	Usually Not Appropriate
Stereotactic body radiotherapy	Usually Not Appropriate

<u>Variant: 4</u> Adult. Serially, enlarging solitary solid pulmonary nodule in the periphery of the lung, now 1 to 3 cm in diameter. High risk of poor surgical outcome. Next step.

Procedure	Appropriateness Category
Percutaneous lung biopsy	Usually Appropriate
Stereotactic body radiotherapy	May Be Appropriate
Endobronchial ultrasound and biopsy	May Be Appropriate
Follow-up imaging only	May Be Appropriate

Percutaneous ablation lung	May Be Appropriate
Fiducial marker and surgical management	Usually Not Appropriate
Surgical management	Usually Not Appropriate

<u>Variant: 5</u> Adult. 1 to 3 cm solitary solid pulmonary nodule in the periphery of the lung. Previously treated nonpulmonary primary malignancy. Next step.

Procedure	Appropriateness Category	
Percutaneous lung biopsy	Usually Appropriate	
Endobronchial ultrasound and biopsy	May Be Appropriate	
Fiducial marker and surgical management May Be Appropriate (Disagreeme		
Follow-up imaging only	May Be Appropriate	
Surgical management	May Be Appropriate (Disagreement)	
Percutaneous ablation lung	Usually Not Appropriate	
Stereotactic body radiotherapy	Usually Not Appropriate	

<u>Variant: 6</u> Adult. 1 to 3 cm solitary ground glass pulmonary nodule which has persisted on short interval follow-up. Findings suspicious for primary lung adenocarcinoma. Next step.

Procedure	Appropriateness Category	
Percutaneous lung biopsy	Usually Appropriate	
Endobronchial ultrasound and biopsy	May Be Appropriate	
Fiducial marker and surgical management	May Be Appropriate	
Follow-up imaging only	May Be Appropriate	
Percutaneous ablation lung	Usually Not Appropriate	
Stereotactic body radiotherapy	Usually Not Appropriate	
Surgical management	Usually Not Appropriate	

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Summary of Literature Review

Introduction/Background

Despite advances in diagnosis and intervention, lung cancer remains the leading cause of cancer-related mortality in the United States [1]. The 5-year survival rate is 15% for all lung cancers. However, early disease has a 70% 5-year survival rate. As a result of improved outcomes with early detection, the Fleischner Society guidelines have outlined updated recommendations for screening based on nodule characteristics and patient smoking history [2]. Screening guidelines are discussed in the ACR Appropriateness Criteria® topic on "Lung Cancer Screening" [3]. In contrast, this document seeks to provide guidance on management of pulmonary nodules for interventional radiologists.

Decision on which intervention to pursue is heavily dependent on disease status, lesion location, and etiology. The interventional radiologist has a role in performing tissue sampling and percutaneous ablation and in determining when patients are best served with alternate interventions including surgery and endobronchial biopsy. Using the following clinical variants, the appropriateness of each treatment option will be described.

Discussion of Procedures by Variant

Variant 1: Adult. Stable 1 to 3 cm solitary solid pulmonary nodule. Unchanged in diameter for 2 years. Person who smokes. Next step.

This variant depicts a solid nodule in a patient who smokes. Smoking places this patient into a high-risk category according to the Fleischer Society [2]. The size of the lesion places the lesion in the ACR Lung-RADS category 4 (suspicious) [4]. However, the prolonged stability is a favorable prognosticator.

Variant 1: Adult. Stable 1 to 3 cm solitary solid pulmonary nodule. Unchanged in diameter for 2 years. Person who smokes. Next step.

A. Endobronchial ultrasound and biopsy

In this scenario, a nodule that has been stable for 2 years is usually benign and does not need tissue sampling. If the lesion was seen on the initial scan, 3-month short-term follow-up imaging is supported by the Fleischner Society guidelines. However, biopsy should be considered in any nodule with suspicious features. Suspicious features include nodules with spiculated margins, mixed solid/ground glass with solid component >6 mm, and nodules with new microcystic components. Furthermore, a recent study found that Lung-RADS category 4A nodules (such as this case) had a malignancy rate of 15% [4].

Location of the lesion relative to the bronchial tree will determine accessibility for the endobronchial approach. If the nodule is near the bronchus, endobronchial ultrasound (EBUS) can safely provide a tissue diagnosis. Linear EBUS uses a convex probe with a curvilinear transducer and can access mediastinal lesions. Radial EBUS can be used for more peripheral lesions. The overall positive predictive value of EBUS in diagnosing central lesions ranges from 93% to 95% [5]. However, in peripheral lesions, diagnostic yield ranges from 67% to 73% [6,7]. Considering the potential of poor sampling, EBUS may not be the first choice for lesions in the periphery.

Lesions > 2 cm are more technically amenable to biopsy, with a higher overall reported yield [7]. Reported complications include pneumothorax and infection. Rates of pneumothorax range from 1.5% to 2.1% [7]. A study evaluating incidence of infection from EBUS reported both pneumonia and mediastinal infectious complications. However, the overall rate of infection was 0.48% [8]. Necrotic lesions and esophageal perforation increased the likelihood of infection. However, complication rates are reportedly lower than with the percutaneous approach [9]. Percutaneous biopsy pneumothorax rates are between 18% and 28% for comparison [10-13].

Variant 1: Adult. Stable 1 to 3 cm solitary solid pulmonary nodule. Unchanged in diameter for 2 years. Person who smokes. Next step.

B. Fiducial marker and surgical management

There are no data on primary fiducial marker placement before tissue diagnosis. Fiducial marker may be useful in a nodule, which exhibits suspicious features and resection is planned. Once surgical resection is planned, marking with either coil or hook-wire may be performed. Coil

placement has a lower rate of displacement and fewer complications compared with the hook method [14,15].

Variant 1: Adult. Stable 1 to 3 cm solitary solid pulmonary nodule. Unchanged in diameter for 2 years. Person who smokes. Next step.

C. Follow-up imaging only

For solid solitary nodules >8 mm, the Fleischner Society guidelines recommend a 3-month follow-up CT after initial CT, given an estimated rate of malignancy of <5% [2]. In a patient with a stable solitary solid pulmonary nodule with smoking history, the goal of follow-up imaging should be to differentiate factors that could potentially be malignant. To this end, PET/CT can provide valuable information for a lesion of this size. However, maximum standardized uptake values (SUVmax) alone cannot differentiate benign from malignant nodules. SUVmax and total lesion glycolysis has been shown to reliably identify malignant nodules, with a sensitivity of up to 85% [16]. Despite the 2-year stability in this case, if imaging alone is elected, PET/CT would be the most evidence-based imaging modality [17].

Furthermore, if the patient continues to smoke, although they may not need further follow-up imaging for this nodule, they may qualify for annual lung cancer screening.

Variant 1: Adult. Stable 1 to 3 cm solitary solid pulmonary nodule. Unchanged in diameter for 2 years. Person who smokes. Next step.

D. Percutaneous ablation lung

Percutaneous ablation would be useful after tissue diagnosis confirms presence of malignancy. There are no robust data on percutaneous lung ablation are tissue diagnosis. Following established tissue diagnosis, a solitary nodule between 1 and 3 cm in diameter would be amenable to ablation. In such cases, a phase II trial demonstrated an 84% 2-year survival rate after microwave ablation (MWA), which has equal outcomes as video-assisted surgery (VATS) [18].

Variant 1: Adult. Stable 1 to 3 cm solitary solid pulmonary nodule. Unchanged in diameter for 2 years. Person who smokes. Next step.

E. Percutaneous lung biopsy

In this scenario, a nodule that has been stable for 2 years is usually benign and may not need tissue sampling. If the lesion was seen on an initial scan, a 3-month short-term follow-up imaging is supported by the Fleischner Society guidelines. However, biopsy should be considered in any nodule with suspicious features. Suspicious features include nodules with spiculated margins, mixed solid/ground glass with solid component >6 mm, and nodules with new microcystic components. Furthermore, a recent study found that Lung-RADS category 4A nodules (such as this case) had a malignancy rate of 15% [4]. Evidence supports tissue sampling given the high rate of malignancy.

In this case, percutaneous CT-guided biopsy could be useful. CT-guided biopsy is both accurate and well tolerated, with a reported yield of 63% to 98% with a core needle biopsy [10,11,13]. Percutaneous biopsy can be performed using either conventional CT or cone-beam CT [19].

The most encountered complication of a percutaneous lung biopsy is a pneumothorax, with rates between 18% and 28% [10-13]. In a study of patients with postbiopsy pneumothorax, 37% required pigtail catheter placement, whereas the remainder of the patients improved with either simple needle aspiration or spontaneous absorption [13]. Risk factors for pneumothorax include

anterior and lateral pleural surface puncture and crossing more than one pleural surface with the biopsy device [12]. Additional risk factors include emphysema, especially in the path of the target. As a result, care must be taken to plan an optimal path without crossing multiple pleural surfaces. Tract embolization conversely has been shown to decrease the risk of pneumothorax [20-22]. Tract embolization can be performed with gelatin sponge impregnated with iodine, blood patch, or a hydrogel plug [20,22]. Furthermore, positioning the patient biopsy-side down has been shown to reduce the incidence of pneumothorax [23]. Pulmonary hemorrhage is the second-most common complication, occurring in 5% to 10% of patients [24]. Interestingly, it is postulated that hemorrhage can be protective against pneumothorax.

Variant 1: Adult. Stable 1 to 3 cm solitary solid pulmonary nodule. Unchanged in diameter for 2 years. Person who smokes. Next step.

F. Stereotactic body radiotherapy

There are no data for radiotherapy alone before tissue diagnosis. However, following tissue sampling, stereotactic body radiation therapy (SBRT) is comparable to thermal ablation in terms of overall survival for stage I disease [25].

Variant 1: Adult. Stable 1 to 3 cm solitary solid pulmonary nodule. Unchanged in diameter for 2 years. Person who smokes. Next step.

G. Surgical management

Surgical management is typically reserved for after tissue diagnosis. There are no data for routine surgical resection in the absence of a tissue diagnosis.

However, following tissue diagnosis of malignancy in a solid solitary pulmonary nodule, surgery would be indicated. VATS has a reported local recurrence rate of 7% for malignant lesions with no recurrence of adenocarcinoma in situ [14]. Predominantly solid nodules are shown to have higher risk of recurrence and worse survival compared with subsolid nodules [26].

Variant 2: Adult. Serially, enlarging solitary solid pulmonary nodule, now 1 to 3 cm in diameter. Person who smokes. Next step.

A serially enlarging nodule is highly suspicious for malignancy and would be considered at least a very suspicious (4B) lesion by Lung-RADS criteria. According to the ACR Lung-RADS 2022 document, growth is defined as an increase in > 1.5 mm in diameter in a 12-month interval [17].

The goal of therapy should be diagnosis, followed by definitive treatment.

Variant 2: Adult. Serially, enlarging solitary solid pulmonary nodule, now 1 to 3 cm in diameter. Person who smokes. Next step.

A. Endobronchial ultrasound and biopsy

An acceptable sampling technique includes EBUS and biopsy if a lesion is medial or near the mediastinum [27]. EBUS has a reported sampling accuracy ranging from 92% to 95% [5]. Typically, EBUS is used in obtaining a histopathologic diagnosis when there is suspicion of non–small-cell lung cancer and mediastinal disease.

In a peripheral nodule, diagnostic yield is smaller using the endobronchial technique, with yields between 73% and 80% [28].

Variant 2: Adult. Serially, enlarging solitary solid pulmonary nodule, now 1 to 3 cm in diameter. Person who smokes. Next step.

B. Fiducial marker and surgical management

In a lesion highly suspicious for lung malignancy, if surgical management is planned, fiducial placement can be accomplished simultaneously with biopsy. This technique would not generally be needed for a peripheral solid nodule; however, it can be employed for deeper lesions for surgical localization. Fiducial can be placed by either a percutaneous or transbronchial approach. Transbronchial fiducial marker placement can be successful in up to 95% of cases [29]. However, in a single-center comparison of percutaneous and endobronchial techniques, transbronchial technique had a higher failure rate compared with the percutaneous technique, which saw a technical success rate of 100% [30]. The percutaneous technique has similar complications to percutaneous biopsy, including pulmonary hemorrhage and pneumothorax. A retrospective study of hook-wire localization reported a 2% rate of clinical significant pneumothorax but a 98% diagnostic yield for surgically resected specimens [31].

Variant 2: Adult. Serially, enlarging solitary solid pulmonary nodule, now 1 to 3 cm in diameter. Person who smokes. Next step.

C. Follow-up imaging only

In a serially enlarging lesion, the risk of malignancy is substantial, with a range of 36% to 76%, depending on additional features [4]. Optimal management is focused on diagnosis and treatment; thus, follow-up imaging may not be useful unless there is reason for low concern for malignancy or high concern for biopsy or treatment. If the noninvasive approach is taken, PET/CT could provide insight into the lesion.

Variant 2: Adult. Serially, enlarging solitary solid pulmonary nodule, now 1 to 3 cm in diameter. Person who smokes. Next step.

D. Percutaneous ablation lung

Ablation may be helpful following biopsy. In a serially enlarging nodule of a smoker, tissue sampling would be the first step. In a patient with a high risk of poor surgical outcome, ablation could be beneficial. In a study comparing outcomes from MWA versus surgical lobectomy, MWA was found to be a viable alternative local treatment for early disease [32]. In a phase II trial, the 2-year survival rate after radiofrequency ablation for unresectable primary, recurrent, or metastatic thoracic malignancy was 84% [18]. MWA has been shown to be equally effective as VATS [33]. When comparing MWA and RFA, there is no significant difference in local recurrence [34]. Additionally there is no difference between MWA and cryoablation with reference to clinical outcomes. Subsequent studies have affirmed RFA following biopsy confirmation of diagnosis in disease. In a prospective study comparing RFA with SBRT, there was no difference in overall survival. Additionally, there was no significant change in pulmonary function post-RFA [35]. Similarly, there is no difference in local recurrence between MWA and cryoablation [36].

Variant 2: Adult. Serially, enlarging solitary solid pulmonary nodule, now 1 to 3 cm in diameter. Person who smokes. Next step.

E. Percutaneous lung biopsy

An enlarging pulmonary nodule unequivocally meets criteria for tissue sampling. PET/CT has variable accuracy in diagnosis of lesions, and a lesion that is increasing in size is suspicious for malignancy. Therefore, if tissue sampling can be performed, percutaneous CT-guided biopsy could be useful. CT-guided biopsy is both accurate and well tolerated, with reported yield of 63% to 98% with a core needle biopsy [10,11,13]. Percutaneous biopsy can be performed using either conventional CT or cone-beam CT [19].

The most encountered complication of a percutaneous needle biopsy is a pneumothorax, with rates between 18% and 28% [10-13]. Pulmonary hemorrhage is the second-most common complication, in which the majority of hemorrhages are low grade without clinical significance and are diagnosed based on the presence of perilesional hemorrhage on postbiopsy CT. Hemorrhage with new ground glass surrounding the lesion between 2 and 4 cm is reported as occurring in between 27% and 33% of cases [24]. Despite the presence of positive findings, these rarely result in clinical significance [24]. A recent observational study evaluating incidence of pulmonary hemorrhage reports a 2.9% rate of postbiopsy hemoptysis [37]. Interestingly, it is postulated that hemorrhage can be protective against pneumothorax. Risk factors for pneumothorax include anterior and lateral pleural surface puncture and crossing more than one pleural surface with the biopsy device [12]. Additional risk factors include emphysema, especially in the path of the target. As a result, care must be taken to plan an optimal path without crossing multiple pleural surfaces. Tract embolization conversely has been shown to decrease the risk of pneumothorax [20-22]. Tract embolization can be performed with gelatin sponge impregnated with iodine, blood patch, or a hydrogel plug [20,22]. Furthermore, positioning the patient biopsy-side down has been shown to reduce the incidence of pneumothorax [23].

Variant 2: Adult. Serially, enlarging solitary solid pulmonary nodule, now 1 to 3 cm in diameter. Person who smokes. Next step.

F. Stereotactic body radiotherapy

In cases of a positive biopsy, SBRT can be used in patients with a risk of poor surgical outcome [38]. A 2018 national cancer database study found no significant difference in mortality between SBRT and percutaneous lung ablation, which may be high risk in a patient unable to undergo anesthesia. Additionally, SBRT has been employed in tumors considered operable, with up to 96% primary tumor control [39]. Without a positive biopsy, however, SBRT would not usually be appropriate.

Variant 2: Adult. Serially, enlarging solitary solid pulmonary nodule, now 1 to 3 cm in diameter. Person who smokes. Next step.

G. Surgical management

Following histological confirmation, surgical management may be a helpful consideration in this patient if the patient has adequate pulmonary function tests. Surgery (either sublobar or lobar resection) is considered the best definitive therapy for prolonged disease-free survival [40]. In a randomized controlled trial comparing outcomes of lobar resection, sublobar resection, and wedge resection, there was no significant difference in 5-year disease-free survival. Lung cancer free survival ranged between 86.8% (lobar resection group) and 89% (sublobar resection group) [41]. It would be important to note the concurrent presence of emphysema in this patient, because emphysema was shown to have a worse occurrence-free survival rate than patients without emphysema [42]. Additionally, providers should bear in mind the impact of social determinants of health and disparities on surgical decision making. A study found that Black/African American patients in the National Lung Screening Trial had significantly lower surgery rates when compared with age-matched White patients [43].

Complications are also of concern for an operative approach, with complications including prolonged atelectasis, empyema, catastrophic blood loss, acute respiratory distress syndrome, chylothorax, and long hospital stays. The VATS approach has an overall better survival and fewer complications compared with open thoracotomy for resection [44]. The parenchymal sparing sleeve lobectomy has reported better overall 90-day survival and fewer empyema [45]. Overall,

however, in this scenario, surgery as the next step would not usually be appropriate.

Variant 3: Adult. 1 to 3 cm solitary solid pulmonary nodule near the hilum. Identified on initial screening CT chest. Person who smokes. Next step.

The goal of therapy in this case is to safely diagnose a suspicious lesion. Incidental finding of a lesion >8 mm is very suspicious for malignancy, and this lesion would be considered category 4B/very suspicious by Lung-RADS criteria [4]. Furthermore, proximity to the hilum may present technical challenges for a percutaneous approach.

Variant 3: Adult. 1 to 3 cm solitary solid pulmonary nodule near the hilum. Identified on initial screening CT chest. Person who smokes. Next step.

A. Endobronchial ultrasound and biopsy

Lesions near the hilum are often particularly accessible for EBUS and endobronchial biopsy [27]. EBUS has a sampling accuracy of up to 95% [5]. Typically, EBUS is used in obtaining a histopathologic diagnosis when there is suspicion of non–small-cell lung cancer and mediastinal disease.

US-based biopsy can be used for diagnosis of hilar lesions as a safe alternative to mediastinoscopy [46]. EBUS biopsy has been seen as sensitive for the more advanced histochemical evaluations [47].

Furthermore, EBUS-transbronchial needle aspiration is reportedly superior to mediastinoscopy in terms of diagnostic performance, with a sensitivity and sampling accuracy of 88% and 93% compared with 81% and 89% [46].

Variant 3: Adult. 1 to 3 cm solitary solid pulmonary nodule near the hilum. Identified on initial screening CT chest. Person who smokes. Next step.

B. Fiducial marker and surgical management

In a smoker, a nodule of this size on initial screening should be considered suspicious, and if biopsy results are positive, endobronchial fiducial placement and surgical management may be helpful. There are no robust data on endobronchial versus percutaneous placement of fiducial marker for hilar lesions. However, in a retrospective review, endobronchial technique was successful in 90% of cases in which nodule was a mean of 2.2 cm [48]. However, as a next step, fiducial marker and surgical management is usually not appropriate.

Variant 3: Adult. 1 to 3 cm solitary solid pulmonary nodule near the hilum. Identified on initial screening CT chest. Person who smokes. Next step.

C. Follow-up imaging only

The ACR Lung-RADS would categorize this lesion as very suspicious, and if follow-up imaging is elected, PET could be performed for confirmation [49]. Fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET uptake has been shown to correlate with poor recurrence-free survival rates [50].

Variant 3: Adult. 1 to 3 cm solitary solid pulmonary nodule near the hilum. Identified on initial screening CT chest. Person who smokes. Next step.

D. Percutaneous ablation lung

There are no randomized clinical trials for ablation of central or hilar lesions. However, there are reports of cryoablation being used in this location with technical success [51]. There are also small retrospective studies describing technically successful MWA while employing an artificial CO2 pneumothorax technique for hilar metastases [52]. However, as a next step, lung ablation is usually not appropriate.

Variant 3: Adult. 1 to 3 cm solitary solid pulmonary nodule near the hilum. Identified on initial screening CT chest. Person who smokes. Next step.

E. Percutaneous lung biopsy

Hilar masses can be challenging to access via a percutaneous approach due to the proximity to major vascular structures and distance for parenchymal traversal. In cases of indeterminate results from endobronchial biopsy, CT-guided biopsy can be helpful [53]. There is an absence of robust data on diagnostic yield and complication rates for CT-guided biopsy based on lesion location. However, case reports describe hilar biopsy as safe and effective with rare complications of pulmonary hemorrhage and pneumothorax [54].

Variant 3: Adult. 1 to 3 cm solitary solid pulmonary nodule near the hilum. Identified on initial screening CT chest. Person who smokes. Next step.

F. Stereotactic body radiotherapy

In patients able to tolerate surgery, resection is the standard of care for definitive therapy of histologically confirmed malignancies, with previously published 5-year survival rates of 59% versus 28% compared with radiotherapy [55]. However, following tissue sampling, radiotherapy may be helpful, given the surgical challenges of resection of perihilar lesions [56]. In a prospective nationwide study in Japan, 5-year overall survival for patients with operable early-stage lung cancer was 82% [57]. However, as a next step, SBRT is usually not appropriate.

Variant 3: Adult. 1 to 3 cm solitary solid pulmonary nodule near the hilum. Identified on initial screening CT chest. Person who smokes. Next step. G. Surgical management

For patient's biopsy-proven stage I disease, surgery can provide excellent outcomes for primary lung malignancy. Segmentectomy and wedge resection have a lower complication rate than lobectomy [58]. The overall survival rate is up to 98% following resection [58]. Furthermore, data support a VATS approach. In a 2019 propensity-matched study comparing VATS versus thoracotomy for hilar lesion resection, the VATS group had shorter length of stay, less blood loss, and a longer recurrence-free survival [59]. However, as a next step, surgical management is usually not appropriate.

Variant 4: Adult. Serially, enlarging solitary solid pulmonary nodule in the periphery of the lung, now 1 to 3 cm in diameter. High risk of poor surgical outcome. Next step.

An enlarging lesion has a high probability of malignancy. Therefore, intervention should focus on both diagnosis and treatment. Patients with significant comorbidities such as severe cardiovascular disease or pulmonary disease may be considered high surgical risk.

Variant 4: Adult. Serially, enlarging solitary solid pulmonary nodule in the periphery of the lung, now 1 to 3 cm in diameter. High risk of poor surgical outcome. Next step. A. Endobronchial ultrasound and biopsy

EBUS and biopsy is an acceptable method of tissue sampling. However, given the lesion's location at the periphery, the sampling yield may be lower than with the percutaneous approach. In a peripheral nodule, the diagnostic yield is lower using the endobronchial technique, with yields up to 73% [28]. Transbronchial navigational biopsy can be considered if a bronchus is close to the nodule or in the presence of emphysema [60].

Variant 4: Adult. Serially, enlarging solitary solid pulmonary nodule in the periphery of the lung, now 1 to 3 cm in diameter. High risk of poor surgical outcome. Next step. B. Fiducial marker and surgical management

In a patient with high risk of poor surgical outcome, surgery would be a last resort. However, fiducial placement could be considered for radiotherapy planning. Percutaneous fiducial marker placement can be accomplished via CT and has been validated as safe and effective in SBRT [61].

Variant 4: Adult. Serially, enlarging solitary solid pulmonary nodule in the periphery of the lung, now 1 to 3 cm in diameter. High risk of poor surgical outcome. Next step. C. Follow-up imaging only

A serially enlarging nodule, >1 cm would be very suspicious for malignancy. Therefore, either further characterization by PET could assist in identifying areas to target for biopsy or support clinical decision making and identify metastatic disease. FDG-PET uptake has been shown to correlate with poor recurrence-free survival rates [50].

Variant 4: Adult. Serially, enlarging solitary solid pulmonary nodule in the periphery of the lung, now 1 to 3 cm in diameter. High risk of poor surgical outcome. Next step. D. Percutaneous ablation lung

In patients with a high risk of poor surgical outcome, percutaneous management may be helpful. In a study comparing outcomes from MWA versus surgical lobectomy, MWA was found to be a viable alternative local treatment for early disease [32]. In a phase II trial, the 2-year survival rate after RFA for unresectable primary, recurrent, or metastatic thoracic malignancy was 84% [18]. MWA has been shown to be equally effective as VATS with reference to overall 3-year survival, disease-free survival, and local progression-free survival [33]. When comparing MWA and RFA, there is no significant difference in local recurrence [34]. Subsequent studies have affirmed the efficacy of RFA for achieving long-term disease-free survival following biopsy confirmation of diagnosis in disease. FDG-PET/CT can be useful to follow treatment response [62]. Thermal ablation carries the usual risks of pneumothorax and pulmonary hemorrhage but also phrenic nerve injury, especially in lesions <2 cm from the phrenic nerve [63].

Cryoablation is also widely used for treatment without demonstrable differences in lung ablation zone volume [64]. Furthermore, cryoablation has reported similar rates of technical success, local control, and recurrence rates as MWA [36]. Despite few differences in outcome, cryoablation has reported a significant lower risk of postablative air leak (9% versus 25%) [65].

Additionally, cryoablation provides comparatively better preservation of collagen architecture on the periphery of the treatment zone [66]. This can aid with safely treating lesions near airways or pleura, minimizing undesired tissue injury.

Variant 4: Adult. Serially, enlarging solitary solid pulmonary nodule in the periphery of the lung, now 1 to 3 cm in diameter. High risk of poor surgical outcome. Next step. E. Percutaneous lung biopsy

For peripheral lesions, CT-guided biopsy may be more helpful than endoscopic approaches. CT-guided biopsy is both accurate and well tolerated, with a reported yield of 63% to 98% [10,11,13]. The complication rate of pneumothorax ranges between 18% and 28% [10-13]. Pulmonary hemorrhage with new ground glass surrounding the lesion between 2 and 4 cm is reported as occurring in between 27% and 33% of cases [24]. Percutaneous biopsy can be performed using either conventional CT or cone-beam CT [19].

Variant 4: Adult. Serially, enlarging solitary solid pulmonary nodule in the periphery of the lung, now 1 to 3 cm in diameter. High risk of poor surgical outcome. Next step. F. Stereotactic body radiotherapy

Given the risk of poor surgical outcome, radiotherapy may be helpful. If possible, a tissue diagnosis would ideally be attained before therapy. However, if the patient is too high risk, empiric therapy can be considered. In a prospective nationwide study in Japan, 5-year overall survival for patients with operable early-stage lung cancer was 82% [57]. Complications of radiotherapy include fatigue, skin changes, and chest pain. In a prospective study evaluating outcomes of SBRT in stage I cancer, 10% of patients experienced skin changes, whereas 10% of patients experienced grade I pneumonitis (cough but not requiring intervention) [67].

Variant 4: Adult. Serially, enlarging solitary solid pulmonary nodule in the periphery of the lung, now 1 to 3 cm in diameter. High risk of poor surgical outcome. Next step. G. Surgical management

In a patient with high risk of poor surgical outcome, surgery would be a last resort. For example, the presence of emphysema portends a very poor surgical outcome compared with patients without emphysema, with reported survival at 5 years being 89% in the nonemphysema group and 61% in the emphysema group [42]. Similarly, other chronic lung diseases such as pulmonary fibrosis are associated with poor high postoperative mortality (7.2%) and poor 5-year survival [68].

Variant 5: Adult. 1 to 3 cm solitary solid pulmonary nodule in the periphery of the lung. Previously treated nonpulmonary primary malignancy. Next step.

In a patient with high risk of poor surgical outcome, surgery would be a last resort. For example, the presence of emphysema portends a very poor surgical outcome compared with patients without emphysema, with reported survival at 5 years being 89% in the nonemphysema group and 61% in the emphysema group [42]. Similarly, other chronic lung diseases such as pulmonary fibrosis are associated with poor high postoperative mortality (7.2%) and poor 5-year survival [68].

Variant 5: Adult. 1 to 3 cm solitary solid pulmonary nodule in the periphery of the lung. Previously treated nonpulmonary primary malignancy. Next step. A. Endobronchial ultrasound and biopsy

EBUS and biopsy is an acceptable method of tissue sampling. However, given this lesion's location at the periphery, the sampling yield may be lower than the percutaneous approach. In a peripheral nodule, diagnostic yield is lower using the endobronchial technique, with yields up to 73% [28]. If there is a bronchus within the vicinity of the nodule, a transbronchial approach could be feasible.

Variant 5: Adult. 1 to 3 cm solitary solid pulmonary nodule in the periphery of the lung. Previously treated nonpulmonary primary malignancy. Next step. B. Fiducial marker and surgical management

In a patient with suspicion for metastatic disease, a new nodule on screening should be considered suspicious, and if biopsy results are positive, fiducial placement and surgical management may be helpful. In a retrospective study of placements of fiducial markers for SBRT including 121 thoracic metastases, there was 100% success in placement, with complications occurring in 28% of cases. Reported complications included self-limiting pneumothorax, pulmonary hemorrhage and 11% rate of pneumothorax requiring chest tube insertion [69]. If there is low suspicion of metastatic disease, or the nodule is peripheral, a wedge resection could be performed with a frozen section.

Variant 5: Adult. 1 to 3 cm solitary solid pulmonary nodule in the periphery of the lung. Previously treated nonpulmonary primary malignancy. Next step. C. Follow-up imaging only

Given a history of malignancy and presence of a new nodule, follow-up imaging with PET to assess for FDG uptake may be useful. Furthermore PET/CT could assess for other areas of metastasis,

which may impact clinical decision making and survival. However, SUVmax alone cannot differentiate benign from malignant nodules. SUVmax and total lesion glycolysis has been shown to reliably identify malignant nodules, with a sensitivity of up to 85% [16].

Variant 5: Adult. 1 to 3 cm solitary solid pulmonary nodule in the periphery of the lung. Previously treated nonpulmonary primary malignancy. Next step.

D. Percutaneous ablation lung

Ablation is safely employed in both metastatic disease and primary lung cancer. A solitary nodule in the periphery of the lung would be amenable to any of the treatment modalities mentioned for a solitary biopsy. Thermal ablation for curative intent in pulmonary metastases has similar oncologic outcomes to surgery [70]. An important consideration is maintaining an ablative margin >2 mm [71]. However, as a next step, lung ablation is usually not appropriate.

Variant 5: Adult. 1 to 3 cm solitary solid pulmonary nodule in the periphery of the lung. Previously treated nonpulmonary primary malignancy. Next step.

E. Percutaneous lung biopsy

Given the fact that this lesion is at the periphery of the lung, it is likely that CT-guided biopsy would be helpful. Especially for lesions such as described in the clinical scenario, CT-guided biopsy is both accurate and well tolerated, with a reported yield of 63% to 98% with a core needle biopsy [10,11,13]. Percutaneous biopsy can be performed using either conventional CT or cone-beam CT [19].

Variant 5: Adult. 1 to 3 cm solitary solid pulmonary nodule in the periphery of the lung. Previously treated nonpulmonary primary malignancy. Next step.

F. Stereotactic body radiotherapy

Following biopsy, SBRT may be considered. SBRT has been shown to be effective in achieving local control from multiple different primary metastases [72]. There is no significant difference in tumor-free survival between patients undergoing SBRT compared with ablation [73]. However, ablation has been shown to be effective for patients with inoperable disease [74]. However, as a next step, SBRT is usually not appropriate.

Variant 5: Adult. 1 to 3 cm solitary solid pulmonary nodule in the periphery of the lung. Previously treated nonpulmonary primary malignancy. Next step. G. Surgical management

Following biopsy confirmation of metastatic disease, surgery for oligometastatic disease in the lung can be considered in the absence of metastases to other organs [75]. Unfortunately, there are no published randomized control trials on surgery for oligometastatic disease to the lung. However, several retrospective studies suggest surgical resection of pulmonary metastasis from colorectal cancer confers a survival benefit. In patients who undergo resection, the 5-year survival rate ranges from 40% to 68% [76]. There is also evidence that surgery has a 36% to 47% survival for renal cell carcinoma metastasis [76].

Surgical intervention should also be considered in the context of when the primary tumor was resected. Patients with 47 to 57 months of disease-free interval had a longer disease-free interval than patients with synchronous metastasis [76]. There is no reported difference between VATS and thoracotomy in terms of complete resection rate. However, VATS has a lower complication rate and length of stay.

Variant 6: Adult. 1 to 3 cm solitary ground glass pulmonary nodule which has persisted on

short interval follow-up. Findings suspicious for primary lung adenocarcinoma. Next step.

A lesion with ground glass and suspicious features, such as an enlarging or persistent solid component, is considered suspicious according to the ACR Lung-RADS criteria [17]. Primary lung adenocarcinoma needs to be excluded and management should be focused on diagnosis.

Variant 6: Adult. 1 to 3 cm solitary ground glass pulmonary nodule which has persisted on short interval follow-up. Findings suspicious for primary lung adenocarcinoma. Next step. A. Endobronchial ultrasound and biopsy

Depending on lesion size and location, an endobronchial approach can be attempted for tissue sampling. An acceptable sampling technique includes EBUS and biopsy especially if a lesion is medial or near the mediastinum [27]. EBUS has a sampling accuracy of up to 95% [5].

In a peripheral nodule, diagnostic yield is lower using the endobronchial technique, with yields up to 73% [28].

Variant 6: Adult. 1 to 3 cm solitary ground glass pulmonary nodule which has persisted on short interval follow-up. Findings suspicious for primary lung adenocarcinoma. Next step. B. Fiducial marker and surgical management

If the patient is a surgical candidate, fiducial placement can be accomplished by either a percutaneous or endobronchial approach. In a lesion highly suspicious for lung malignancy, if surgical management is planned, fiducial placement can be accomplished simultaneously with biopsy. Transbronchial fiducial marker placement can be successful in up to 95% of cases [29]. However, in a single-center comparison of percutaneous and endobronchial techniques, the transbronchial technique had a higher failure rate compared with the percutaneous technique, which has a technical success rate of 100% [30]. Wedge resection could be considered if the ground glass opacity is increasingly prominent or the patient is an appropriate surgical candidate.

Variant 6: Adult. 1 to 3 cm solitary ground glass pulmonary nodule which has persisted on short interval follow-up. Findings suspicious for primary lung adenocarcinoma. Next step. C. Follow-up imaging only

A lesion with ground glass and suspicious features, such as an enlarging or persistent solid component, is considered suspicious according to the ACR Lung-RADS criteria. If the lesion is pure ground glass, it is likely adenocarcinoma in situ. PET/CT could be considered if the solid component is >8 mm [49]. PET/CT alone would not be considered most useful given the high index of suspicion for this lesion, but it could guide further management and evaluate for metastatic disease.

Variant 6: Adult. 1 to 3 cm solitary ground glass pulmonary nodule which has persisted on short interval follow-up. Findings suspicious for primary lung adenocarcinoma. Next step. D. Percutaneous ablation lung

For biopsy-confirmed malignancies, percutaneous ablation of ground glass nodules is safe and effective, with similar rates of overall survival compared with surgery [33]. However, ablation has a decreased length of stay compared with surgery. However, as a next step, lung ablation is usually not appropriate.

Variant 6: Adult. 1 to 3 cm solitary ground glass pulmonary nodule which has persisted on short interval follow-up. Findings suspicious for primary lung adenocarcinoma. Next step. E. Percutaneous lung biopsy

CT of the chest with a solitary ground glass nodule >8 mm and concerning for adenocarcinoma

has several options for management, which are appropriate. For purely ground glass nodules/opacities, there is a high potential for these lesions to reflect adenocarcinoma [77]. Even beyond the recommended 5-year surveillance guidelines, pure ground glass opacities can reflect indolent malignancy [78]. Therefore, tissue sampling to confirm diagnosis is considered. After diagnosis has been confirmed, ablation or surgical management could be considered depending on the patient's surgical risk. If the lesion is a stable solitary ground glass nodule, the likelihood of adenocarcinoma in situ has been shown to be up to 59% [77]. Therefore, biopsy, surgical management, or ablation may be useful in this scenario.

Variant 6: Adult. 1 to 3 cm solitary ground glass pulmonary nodule which has persisted on short interval follow-up. Findings suspicious for primary lung adenocarcinoma. Next step. F. Stereotactic body radiotherapy

Considering the high-risk features from imaging in this patient, surgery, ablation, and SBRT can be helpful considerations with biopsy-confirmed malignancy. There is no significant difference in tumor-free survival between patients undergoing SBRT compared with ablation [73]. However, ablation has been shown to be effective for patients with inoperable disease [74]. However, as a next step, SBRT is usually not appropriate.

Variant 6: Adult. 1 to 3 cm solitary ground glass pulmonary nodule which has persisted on short interval follow-up. Findings suspicious for primary lung adenocarcinoma. Next step. G. Surgical management

Surgical management of heterogeneous ground glass or part-solid nodules has proven long-term disease-free survival rates for malignant ground glass nodules, although there is a shorter disease-free-survival rate in the part-solid group [79]. In a cohort comparing MWA and surgery, the surgical group had a 100% cancer-specific survival rate [33]. An additional cohort of more than 1,000 patients demonstrated 100% recurrence-free survival rates in adenocarcinoma in situ who underwent resection [80]. However, as a next step, surgical management is usually not appropriate.

Summary of Highlights

This is a summary of the key recommendations from the variant tables. Refer to the complete narrative document for more information.

- **Variant 1**: Follow-up imaging is usually appropriate. Tissue sampling is generally unnecessary unless suspicious imaging features are present. Endobronchial or percutaneous biopsy is only considered if concerning features arise and is usually not appropriate.
- **Variant 2**: Percutaneous lung biopsy and EBUS with biopsy are usually appropriate and are considered complementary approaches depending on nodule size and location. PET/CT may guide planning but is not a substitute for sampling.
- **Variant 3**: EBUS with biopsy is usually appropriate, particularly for central or hilar lesions. Percutaneous biopsy may be appropriate as an alternative in select cases in which endobronchial access is limited.
- **Variant 4**: Percutaneous lung biopsy is usually appropriate. SBRT, endobronchial biopsy, follow-up imaging, or percutaneous ablation may be appropriate alternatives depending on patient comorbidities and procedural risks.
- **Variant 5**: Percutaneous lung biopsy is usually appropriate. Endobronchial biopsy, surgical resection, or fiducial marker placement may be appropriate depending on the clinical scenario and oncologic history.

• **Variant 6**: Percutaneous lung biopsy is usually appropriate. Endobronchial biopsy, surgical resection, or fiducial placement may be appropriate alternatives depending on nodule location and patient candidacy for surgery.

Supporting Documents

The evidence table, literature search, and appendix for this topic are available at https://acsearch.acr.org/list. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents, please go to the ACR website at https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria.

Gender Equality and Inclusivity Clause

The ACR acknowledges the limitations in applying inclusive language when citing research studies that predates the use of the current understanding of language inclusive of diversity in sex, intersex, gender, and gender-diverse people. The data variables regarding sex and gender used in the cited literature will not be changed. However, this guideline will use the terminology and definitions as proposed by the National Institutes of Health.

Appropriateness Category Names and Definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable riskbenefit ratio for patients.
May Be Appropriate		The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

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Disclaimer

The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

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