APP/AH Challenge

AABIP/AIPPD Evidence-Based Medicine Series

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Pulmonary Nodule Management

Case Presentation # 1

A 65-year-old male who has been undergoing lung cancer screening for the past 2 years presents for follow-up after a yearly-low-dose chest CT was completed. He has a 50 pack-year tobacco history and quit smoking two years ago. The patient has no concerning symptoms as required for the screening CT. His chest CT demonstrates a new 5mm solid nodule in the right upper lobe.

Case Presentation # 2

A 50-year-old male with a 12 pack-year tobacco history was seen urgently in the emergency room after a motor vehicle accident. As part of a trauma work up, a CT of the chest is obtained which demonstrates an incidental 5mm solitary, solid, spiculated lung nodule in the left upper lobe. The patient does not have any prior history of malignancy.

How do you optimally manage these two respective patients?

Introduction:

With the widespread use of chest computed tomography (CT), solitary pulmonary nodules (SPNs) are being increasingly detected. The fundamental goal of SPN evaluation and management algorithms, whether incidentally diagnosed or identified as part of a low-dose CT (LDCT) lung cancer screening program in high risk patients, requires clear risk stratification. LDCT in asymptomatic individuals who meet criteria for screening significantly reduces lung cancer mortality.[1]

The primary goal of screening is to diagnose malignant nodules promptly in order to permit timely curative management while avoiding unnecessary invasive testing or surgery in patients with benign nodules.[1,2] The risk of malignancy for a SPN is estimated based on morphological features suggestive of a probable malignant nodule and clinical probability of cancer. Additional factors utilized in risk calculators to better predict the likelihood of a lung nodule being malignant or benign may be beneficial, however these may vary widely based on the patient population.[3] Ongoing studies look to validate less invasive molecular analyses in blood and nasal swabs to further predict lung nodule malignancy and may be integrated in clinical pathways in the future. Shared decision making between the provider and patient to discuss both the risks and benefits of different management strategies (non-surgical biopsy vs. surgical risks vs. surveillance), patient values and preferences and desire for curative treatment are important.[3,4,5]

A solid SPN is characterized as a well-circumscribed opacity less than or equal to 30mm and not associated with hilar enlargement, pleural effusion or atelectasis.[2] Incidental pulmonary nodules that are less than 8mm in size overall have a lower likelihood of malignancy. The evaluation of an incidental solid SPN that ranges from 8mm-30mm in size may be further guided by clinical pathways based on the pre-test probability of malignancy.[3] Most studies have shown the probability of malignancy is linear and increases with the diameter of the pulmonary nodule: 5mm (0-1%), 11-20mm (33-64%), >20mm (64-82%).[1] Based on the Fleischner Society Guidelines, when evaluating the radiographic features of incidental solid SPN, recommendations for follow up are based on risk (Table 1).[5]

Based on the probability of malignancy, pulmonary nodules are generally managed with CT scan follow-up, diagnostic testing or surgical resection. There are also formal Fleischner Society guidelines for multiple nodules and those that are ground glass or partially solid.

Table 1

Lung nodule size	**Low risk**	**High risk**
<6mm	No follow up	Optional CT chest 12mo
6-8mm	CT chest 6-12mo, then consider CT at 18-24 months	CT chest 6-12mo, then consider CT at 18-24 months
>8mm	CT chest 3mo, PET/CT or tissue sampling	CT chest 3mo, PET/CT or tissue sampling
Subsolid lung nodule size	**Ground glass**	**Part solid**
<6mm	No routine follow-up	No routine follow-up
>=6mm	CT at 6-12 months to confirm persistence, then CT every 2 years until 5 years	CT at 3-6 months to confirm persistence. If unchanged and solid component remains <6mm, annual CT should be performed for 5 years

**Fleischner Society Guidelines 2017* [5]

Distinct from incidentally discovered pulmonary nodules, those patients who meet the specific criteria for lung cancer screening and undergo a LDCT should undergo radiology interpretation utilizing one of the validated radiology protocols for lung cancer screening to more specifically guide the action plan, such as Lung-RADS Version 1. Most recent update to Lung-RADS 1.1 is Lung-RADS 2022 with new classification criteria for cysts, growth rate (increase >1.5mm mean diameter in 12 month interval) and concept for stepped management approach.[6] Diagnostic plans for follow-up of pulmonary nodules or other incidental findings in patients who are part of a lung cancer screening program and considered uniformly high risk are listed in Table 2.[6,7]

Table 2

Lung-RADS	**Size/growth**	**Management**
Lung-RADS 1	no lung nodules or nodules with benign radiographic features	annual screening with low dose CT (LDCT)
Lung-RADS 2	< 6mm or new < 4mm Category 3 that is stable or decreased OR Category 3 or 4A that resolve on follow up OR Category 4B proven to be benign based on appropriate work up	continue annual screening with LDCT
Lung-RADS 3	>= 6mm to < 8mm or new 4mm to < 6mm Atypical pulmonary cyst: -w/ growing cystic component or thick wall cyst (>2mm) Category 4A nodule that is stable or decreased in size on follow up 3 mo CT	6 months LDCT

Lung-RADS 4A	>= 8mm to < 15mm or growing < 8mm or new 6mm to < 8mm Atypical pulmonary cyst : -Thick wall (>2mm) OR -Multiloculated OR -Thin/Thick walled cyst that becomes multiloculated	3 months LDCT, PET/CT (when the solid component is >=8mm)
Lung-RADS 4B	>=15mm or new or growing and >=8mm Atypical pulmonary cyst: -Thick wall cyst (>2mm) w/ growing nodularity/wall thickness - Growing multiloculated cyst - Multiloculated cyst w/ increased loculation or new/increased opacity	CT chest w/ or w/out contrast, PET/CT and/or tissue sampling

This is an excerpt from, Lung-RADS 2022* ***focusing* *on new solid or growing pulmonary nodule, atypical cyst, stepped management*[6,7]

In this module we will review landmark studies which are the basis for guideline recommendations for the management of solid SPNs: 1) computed tomography scan lung nodule morphology and associated estimated probability for malignancy of pulmonary nodules, 2) independent predictors of malignancy and cancer validated models, 3) lung cancer screening NLST 4) management/multimodality bronchoscopic biopsy approaches.[3,4,5]

CT scan morphology in estimation of probability of malignancy

Harders SW, Madsen HH, Rasmussen TR, Hager H, Rasmussen F. High resolution spiral CT for determining the malignant potential of solitary pulmonary nodules: refining and testing the test. Acta Radiol. 2011 May 1; 52(4):401-9.

Description:

Prospective randomized controlled trial from Denmark that identified many of the distinguishing morphological characteristics that are suggestive of malignant SPNs based on high resolution spiral CT image (HRCT). Additionally, diagnostic accuracy and reproducibility were assessed.

Population:

All patients with no prior malignancy and SPNs 5-30mm were eligible. N=213, Mean age 65, 46% male.

Intervention:

All patients underwent HRCT. A definitive histopathological diagnosis was obtained by transthoracic needle aspiration or surgical biopsy in 191 of 213 patients. The following HRCT characteristics were assessed: margin risk categories (spiculated, ragged, lobulated, smooth, polygonal), calcification patterns (dystrophic, amorphous, eccentric, central lamellar, chondroid) and presence of pleural retraction.

Comparison:

Morphologic characteristics of nodules on HRCT and tissue diagnosis of the SPN.

Outcomes:

- Nodules were more likely to be malignant with: spiculated or ragged margins (likelihood ratio [LR] =5.5), pleural retraction (LR=1.9), vessel sign.
- Nodules were less likely to be malignant when a bronchus sign was present or if there were lobulated, smooth or polygonal margins.
- Sensitivity of 98% but specificity of only 23% after qualitative assessment of the above-mentioned features.

Clinical probability of cancer: validated model vs clinical judgement

Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES .The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. Arch Intern Med. 1997 Apr 28; 157(8):849-55.

Description:

A retrospective cohort study from January 1, 1984 – May 1, 1986 that used multiple logistic regression to identify six independent predictors of malignancy for SPNs. A clinical prediction model to estimate the pretest probability of malignancy for SPNs was then developed by investigators at Mayo Clinic.

Population:

419/629 patients (320 men, 309 women) with SPN 4mm – 30mm identified on *chest radiograph*.

Exclusion criteria: Cancer within the last 5 years.

Intervention:

Patients getting a conventional chest radiograph.

Comparison:

Patient factors and nodule characteristics on chest imaging compared to pathologic diagnosis from a transthoracic needle aspiration (TTNA), bronchoscopy, thoracoscopy or thoracotomy.

Outcomes:

- Independent predictors of malignancy included: older age, current or past smoker, history of extrathoracic cancer ≥5 years prior, nodule diameter, spiculation and upper lobe location.
- 65% of nodules were benign, 23% were malignant

McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med. 2013 Sep 5;369(10):910.

Description:

This is a population-based prospective study of two high risk cohorts that evaluated factors that would predict probability that lung nodules identified on the *first screening* low-dose CT are malignant. Data from two cohorts was analyzed: the development data set from Pan-Canadian Early Detection of Lung Cancer Study (PanCan) and the validation data set from British Columbia Cancer Agency (BCCA).

Population:

PanCan 1871 persons had 7008 nodules, 102 were malignant (median overall follow-up 3 years)

BCCA 1090 persons had 5021 nodules, 42 were malignant

Both populations had the following similar baseline characteristics: age, sex, BMI, % of patients with emphysema, FEV1.

Intervention:

Patients undergoing low dose chest CT scan for lung cancer screening

Comparison:

Patient factors and nodule characteristics on chest imaging compared to histopathologic examination of needle aspiration biopsy samples or resection specimens

Outcomes:

- Rate of cancer in patients with nodules in two data sets: PanCan 5.5%, BCCA 3.7%
- Majority of nodules were solid in appearance
- Relationship between nodule size and cancer were non-linear, the largest lung nodule was not the one that was determined to be malignant in 20% of participants
- Probability of lung cancer from two studies in peri-fissural nodules was zero
- Large number of nodules and cancers were observed in upper lobes
- Predictors of malignancy were: older age, female sex, family history of lung cancer, emphysema, larger nodule size, upper lobe location, part-solid nodule, lower nodule count, and spiculation

Lung cancer screening reduces mortality from lung cancer

Berg CD, et al. Reduced lung cancer mortality with low-dose computed tomographic screening. The New England Journal of Medicine. 2011. 365(5):395-409.

Description:

Multicenter, prospective, randomized controlled trial at 33 centers in the US from 2002 to 2004. High risk patients who were asymptomatic were assigned to annual LDCT chest screening vs chest radiography (CXR) for three years with nodules or suspicious findings characterized as positive on the imaging. This study demonstrated that in patients high risk for lung cancer, screening with LDCT rather than CXR reduced mortality from lung cancer.

Population:

N=53,464, age 55-74, >=30 pack years, active smokers or quit within 15 years

LDCT group: 26,715, 24.2% had positive results over all three rounds

CXR group: 26,724, 6.9% had positive results over all three rounds

Intervention:

Patients undergoing annual lung cancer screening with either LDCT or CXR for three years

Comparison:

Lung cancer mortality between the two groups with an intention-to-screen principle

Outcomes:

- LDCT group: 24.2% positive results over all rounds with 23.3% being false positive
- CXR group 6.9% positive results over all rounds with 6.5% being false positive
- There was higher incidence of early stage IA/IB cancer in LDCT group than in the CXR group, most were treated with surgery alone
- Fewer stage IV cancers were seen in the LDCT group than in the radiography group during the second and third screening rounds
- LDCT was associated with a **20%** relative risk reduction in the rate of death from lung cancer when compared to CXR
- The study was terminated early after a 2010 interim analysis demonstrated there was survival benefit with number needed to screen with LDCT to prevent one lung cancer death of 320

Diagnostic Studies/Management

Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. Eberhardt R, Anantham D, Ernst A, Feller-Kopman D, Herth F Am J Respir Crit Care Med. 2007 Jul 1; 176(1):36-41.

Description:

Randomized controlled trial comparing the diagnostic yield of Endobronchial ultrasound (EBUS)-transbronchial needle aspiration (TBNA), Electronavigational bronchoscopy (ENB) and EBUS-TBNA plus ENB without fluoroscopic guidance.

Population:

N=118

Intervention:

Bronchoscopy under moderate sedation or general anesthesia for diagnosis of peripheral lung lesions or SPNs

Comparison:

Diagnostic yield of EBUS-TBNA, ENB alone and EBUS-TBNA plus ENB

Outcomes:

- Independent of nodule size – diagnostic yield for malignancy was higher for combined procedures **(88%)** than EBUS-TBNA (69%) or ENB alone (59%)
- Similar results when restricting analysis to nodule 20mm-30mm or < 20mm
- EBUS and EBUS+ENB also had diagnostic yields independent of lobar distribution
- ENB alone had a significantly lower diagnostic yield from the lower lobes
- Overall pneumothorax rate was 6% and similar between the groups

Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. Wang Memoli JS, Nietert PJ, Silvestri GA Chest. 2012 Aug; 142(2):385-393.

Description:

Meta-analysis to determine the diagnostic yield of guided bronchoscopy using multiple modalities. A MEDLINE search between 2002-2010 for "bronchoscopy" and "pulmonary nodule" was performed with inclusion of studies evaluating ENB, virtual bronchoscopy (VB), R-EBUS and ultrathin bronchoscope. This study demonstrated the diagnostic yield of guided bronchoscopic techniques is better than traditional transbronchial biopsy, although lower than transthoracic needle aspiration (TTNA).

Population:

Total 3004 patients with 3052 lesions from 39 studies were included

Intervention:

Bronchoscopy with lung nodule biopsy via multiple modalities

Comparison:

Diagnostic yield using multiple bronchoscopic modalities for lung nodule biopsy

Outcome:

- Pooled diagnostic yield of 70%, lower than TTNA which approaches 90%
- Yield was affected by the size of the lesion: <20mm yield 61.3%, >20mm yield 82.2%
- Diagnostic yield appeared to be highest (73%) when a guide sheath was used
- The diagnostic yield for VB (72%) and R-EBUS (71%) were higher than the overall weighted diagnostic yield

- Low risk of pneumothorax (1.5%) requiring chest tube (0.6%) when compared to TTNA (25% and 5%, respectively).
- Across the studies diagnostic yield ranged 46-82%. Variability between studies may be due to: various locations of target lesions, definition of peripheral nodule, options for obtaining biopsy specimen

Biomarkers for Lung Cancer Screening and Detection. Ostrin, E. J., Sidransky, D., Spira, A., & Hanash, S. M. *Cancer Epidemiology Biomarkers & Prevention*, *29*(12), 2411–2415. (2020). https://doi.org/10.1158/1055-9965.epi-20-0865

Description:

The U.S population undergoes chest CTs for various reasons with incidental pulmonary nodules found in 24-31% of those scanned. For both low dose CT screening as part of lung cancer screening for high risk patients and incidentally discovered nodules there is a need for biomarkers to discriminate benign lesions from early cancers to guide the diagnostic workflow.

Blood Based biomarkers:

EarlyCDT-Lung (OncImmune)

- Seven-autoantibody panel extensively validated in seven different cohorts including post validation cohorts of newly diagnosed lung cancer vs control
- Good performance in classifying indeterminate pulmonary nodules (IPN)
- Specificity of ~90% and sensitivity of ~40%
- EarlyCDT-Lung did not increase frequency of detection of lung cancer but lung cancers were detected were at earlier stage

Nodify XL2 (Biodesix)

- Mass spectrometry based assay of blood protein (13-protein proteomic classifier)
- Based on logistic regression of IPN between 4-20mm and lung cancer incidence of 20%, which resulted in 90% NPV for benign nodules
- Panel validated in two independent tests
- PANOPTIC study revealed that Biodesix panel's best performance was when clinician assessed pretest probability of cancer was <50%. In 178 patients who had a lung cancer prevalence of 16%, the classifier showed a sensitivity of 97% and a specificity of 44%, with an NPV of 98% (and a LR− of 0.07)

Airway Gene Expression Classifiers (Percepta):

AEGIS-1 and AEGIS-2

- Enrolled patients undergoing bronchoscopy with high prevalence of lung cancer

- Airway brushing performed of normal main stem bronchi
- Samples underwent RNA expression profiling by microarray
- Classifier showed sensitivity of 88 and 89% in both trials but lower specificity in both of 47%
- Combining classifier with bronchoscopy sensitivity increased from 74-76% with bronchoscopy alone to 96-98% with classifier and bronchoscopy.
- In patients with indeterminate pretest probability and negative bronchoscopy the classifier had NPV of 91%
- A negative classifier in patients with non-diagnostic bronchoscopy and intermediate probability of cancer may allow patients to avoid an unnecessary invasive procedure

Conclusion
Biomarkers play a very important future role in risk stratification and classification and in the early detection of lung cancer. Biomarker panels must be used in an appropriate clinical context.

US Preventive Services Task Force Recommendation (2021)

Annual screening for lung cancer with LDCT:
- Age 50-80 years
- 20 pack-year smoking history
- Currently smoke or quit within the past 15 years

Stop screening when:
- A person has not smoked for > 15 years
- Develops a health problem that limits life expectancy or the ability or willingness to have curative lung surgery

This updates the 2013 USPSTF recommendations with age range of 55-80 years and 30 pack-year smoking history[15]

The Bottom Line

Whether incidentally identified and stratified based on risk factors for malignancy, or identified as part of a lung cancer screening program in the established high-risk patient, the main goal of SPN management algorithms is to reduce lung cancer mortality through prompt diagnosis and management. There are several clinical calculators for predicting the probability of malignancy in SPNs. There are also guidelines for follow-up of incidentally identified pulmonary nodules as well as nodules identified on lung cancer screening CTs. Patient-specific factors and nodule characteristics on imaging are important for predicting the probability of malignancy in pulmonary nodules.

Additional Articles of Interest

1. Kalanjeri S, Holladay RC, Gildea TR. State-of-the-Art Modalities for Peripheral Lung Nodule Biopsy. Clin Chest Med. 2018 Mar;39(1):125-138. doi: 10.1016/j.ccm.2017.11.007. Epub 2017 Dec 14. PMID: 29433709.

2. Vachani A, Maldonado F, Laxmanan B, Kalsekar I, Murgu S. The Impact of Alternative Approaches to Diagnostic Yield Calculation in Studies of Bronchoscopy. Chest. 2022 May;161(5):1426-1428. doi: 10.1016/j.chest.2021.08.074. Epub 2021 Sep 7. PMID: 34506792.

References

1. Loverdos K, Fotiadis A, Kontogianni C, Iliopoulou M, Gaga M. Lung nodules: A comprehensive review on current approach and management. *Ann Thorac Med*. 2019;14(4):226-238. doi:10.4103/atm.ATM_110_19

2. Zhan P, Xie H, Xu C, Hao K, Hou Z, Song Y. Management strategy of solitary pulmonary nodules. J Thorac Dis. 2013;5(6):824-829. doi:10.3978/j.issn.2072-1439.2013.12.13

3. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e93S-e120S.

4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Lung Cancer Screening. Version 1.2020, 05/14/19 © 2019 National Comprehensive Cancer Network® (NCCN®)

5. Macmahon H, Naidich DP, Goo JM, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology. 2017;284(1):228-243.

6. Lung- RADS Category Descriptor Findings Management 0. (n.d.). Retrieved December 28, 2022, from https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/Lung-RADS-2022.pdf

7. ACoR. Lung-Screening Reporting and Data System (LungRADS) Version 1.1. 2019. Accessed August 17 2020. Available online: https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADSAssessmentCategoriesv1-1.pdf

8. Harders SW, Madsen HH, Rasmussen TR, Hager H, Rasmussen F. High resolution spiral CT for determining the malignant potential of solitary pulmonary nodules: refining and testing the test. Acta Radiol. 2011 May 1; 52(4):401-9.

9. Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. Arch Intern Med. 1997 Apr 28; 157(8):849-55.

10. McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med. 2013 Sep 5;369(10):910.

11. Berg CD, et al. "Reduced lung cancer mortality with low-dose computed tomographic screening". The New England Journal of Medicine. 2011. 365(5):395-409.

12. Eberhardt R, Anantham D, Ernst A, Feller-Kopman D, Herth F. Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. Am J Respir Crit Care Med. 2007 Jul 1; 176(1):36-41.

13. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. Chest. 2012 Aug; 142(2):385-393.

14. Ostrin, Edwin J., et al. “Biomarkers for Lung Cancer Screening and Detection.” *Cancer Epidemiology Biomarkers & Prevention*, vol. 29, no. 12, 22 Oct. 2020, pp. 2411–2415, 10.1158/1055-9965.epi-20-0865.

15. US Preventive Services Task Force, Krist AH, Davidson KW, Mangione CM, et al. Screening for lung cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2021 Mar 9;325(10):962-970.