CHAPTER 56

NEW DIAGNOSTIC TECHNIQUES FOR LUNG CANCER

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INTRODUCTION

Lung cancer which is the most common cancer worldwide is also the most common cause of mortality. The majority of diagnosed patients are treated with palliative treatment only. Therefore screening tests for lung cancer have critical importance. Early detection of cancer, low risk, easy to apply and low-cost methods are ideal for screening test features. With the new methods targeting screening and early diagnosis, it may be possible to obtain cancer diagnosis at an early stage, and surgical resection, which is the only therapeutic method can be applied. Although there is no ideal lung cancer screening test, low-dose computed tomography is the most used method. Biomarkers, which can be detected in serum, plasma or sputum, are promising as an effective and easily applicable screening method in lung cancer in the future. The aim is identifying lung cancer at an early stage in the absence of a clinical symptom. The generally recommended group of patients in the guidelines for screening tests are advanced elderly patients who smoke. Multidisciplinary teamwork in lung cancer is an appropriate approach for community screening.

IDEAL FEATURES OF (QUALIFICATIONS OF DIAGNOSTIC TECHNIQUES)

Each laboratory test and imaging method have its own features and findings that are expected to differ the patients with and without the disease. *The sensitivity* indicates the proportion of positive (abnormal) results in patients with the disease, and *specificity* measures the percent of negative (normal) results in patients without the disease. When an examination is required for screening or ruling out the disease, generally the test with the highest sensitivity is more valuable and preferred. In our day, only a small number of comprehensive tests exist. Usually, more than one test result is examined among patients with and without a specific disease. Multiple normal results tend to rule out disease convincingly, and following tests with results that are all abnormal tend to confirm disease convincingly. Tests or procedures are performed when the information available from the historical review, physical examination, and any previous testing is considered insufficient to address the questions at hand.

On the other hand when screening is the issue the population under risk should be carefully identified. The intelligent use of the new information obtained from testing requires that the clinician be aware of the probability of disease that

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REFERENCES

1. Baker RR, Carter D, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. Am Rev Respir Dis 1984; 130(4):549-54.
2. J, Adamec M. Lack of benefit from semi- annual screening for cancer of the lung : follow-up report of a randomized controlled trial on a population of high-risk males in Czechoslovakia. Int J Cancer 1990;45(1):26-33.
3. Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR, et al. Screening for lung cancer. A critique of the Mayo Lung Project. Cancer 1991;67(4 Suppl): 1155-64.
4. Memorial Sloan-Kettering Cancer Center. Screening Guidelines: Lung Cancer. [July 20, 2012]; Available from: http://www.mskcc.org/cancer-care/screening-guidelines/screening-guidelines-lung.
5. National Cancer Institute at the National Institutes of Health. Computed Tomography (CT): Questions and Answers. [July 20, 2012]; Available from: http::://www.cancer.gov/cancertopics/factsheet/detection/CT.
6. Cedars-Sinai. CT Lung Screening. [July 20, 2012]; Available from: http://www.cedars-sinai.edu/Patients/Programs-and-Services/Imaging-Center/For-Patients/Exams-by-Procedure/CT-Scans/CT-Lung-Screening.aspx.
7. International Early Lung Cancer Action Pro- gram Investigators, Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Mi- ettinen OS. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355(17):1763-71.
8. Clapp JD, Fagerstrom RM, et al. National Lung Screening Trial Research Team. Re- duced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
9. Shreiber, G.; McCrory, D.C. Performance characteristics of different modalities for diagnosis of suspected lung cancer: Summary of published evidence. *Chest* **2003**, *123* (Suppl. 1), S115–S128. [CrossRef]
10. Baalini, W.A.; Reinoso, M.A.; Gorin, A.B.; Sharafkaneh, A.; Manian, P. Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. *Chest* **2000**, *117*, 1049–1054. [CrossRef]
11. Rivera, P.; Mehta, A.C.; Wahidi, M.M. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* **2013**, *143*, e143S–e165S. [CrossRef] [PubMed]
12. Li, H.; Boiselle, P.M.; Shepard, J.O.; Trotman-Dickenson, B.; McLoud, T.C. Diagnostic accuracy and safety of CT-guided percutaneous needle aspiration biopsy of the lung: Comparison of small and large pulmonary nodules. *Am. J. Roentgenol.* **1996**, *167*, 105–109. [CrossRef] [PubMed]
13. Klein, J.S.; Salomon, G.; Stewart, E.A. Transthoracic needle biopsy with a coaxially placed 20-gauge automated cutting needle: Results in 122 patients. *Radiology* **1996**, *198*, 715–720. [CrossRef] [PubMed]
14. Zarbo, R.J.; Fenoglio-Preiser, C.M. Interinstitutional database for comparison of performance in lung fine-needle aspiration cytology. A College of American Pathologists Q-Probe Study of 5264 cases with histologic correlation. *Arch. Pathol. Lab. Med.* **1992**, *116*, 463–470. [PubMed]
15. Manhire, A.; Charig, M.; Clelland, C.; Gleeson, F.; Miller, R.; Moss, H.; Pointon, K.; Richardson, C.; Sawicka, E. Guidelines for radiological guided lung biopsy. *Thorax* **2003**, *58*, 920–936. [CrossRef] [PubMed]
16. Ost, D.E.; Ernst, A.; Lei, X.; Kovitz, K.L.; Benzaquen, S.; Diaz-Mendoza, J.; Greenhill, S.; Toth, J.; Feller-Kopman, D.; Puchalski, J.; et al. Diagnostic yield and complications of bronchoscopy for peripheral lung lesions: Results of the AQuIRE registry. *Am. J. Respir. Crit. Care Med.* **2016**, *193*, 68–77. [CrossRef] [PubMed]
17. Kazerooni, E.A.; Lim, F.T.; Mikhail, A.; Martinez, F.J. Risk of pneumothorax in CT-guided transthoracic needle aspiration biopsy of the lung. *Radiology* **1996**, *198*, 371–375. [CrossRef] [PubMed]
18. Yeow, K.M.; See, L.C.; Lui, K.W.; Lin, M.C.; Tsao, T.C.; Ng, K.F.; Liu, H.P. Risk factors for pneumothorax and bleeding after CT-guided percutaneous coaxial cutting needle biopsy of lung lesions. *J. Vasc. Interv. Radiol.* **2001**, *12*, 1305–1312. [CrossRef]
19. Wiener, R.S.; Schwartz, L.M.; Woloshin, S.; Welch, H.G. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: An analysis of discharge records. *Ann. Inter. Med.* **2011**, *155*, 137–144. [CrossRef] [PubMed]
20. Chen, A.; Chenna, P.; Loiselle, A.; Massoni, J.; Mayse, M.; Misselhorn, D. Radial probe endobronchial ultrasound for peripheral pulmonary lesions: A 5-year Institutional experience. *Ann. Am. Thorac. Soc.* **2014**, *11*, 578–582. [CrossRef] [PubMed]
21. Steinfort, D.P.; Khor, Y.H.; Manser, R.L.; Irving, L.B. Radial probe endobronchial ultrasound for the diagnosis of peripheral lung cancer: Systematic review and meta-analysis. *Eur. Respir. J.* **2011**, *37*, 902–910. [CrossRef] [PubMed]
22. Steinfort, D.P.; Vincent, J.; Heinze, S.; Antippa, P.; Irving, L.B. Comparative effectiveness of radial probe endobronchial ultrasound versus CT-guided needle biopsy for evaluation of peripheral pulmonary lesions: A randomized pragmatic trial. *Respir. Med.* **2011**, *105*, 1704–1711. [CrossRef] [PubMed]
23. Becker, H.D.; Herth, F.; Ernst, A.; Schwarz, Y. Bronchoscopic biopsy of peripheral lung lesions under electromagnetic guidance: A pilot study. *J. Bronchol. Interv. Pulmonol.* **2005**, *12*, 9–13. [CrossRef]
24. 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**, *176*, 36–41. [CrossRef] [PubMed]
25. ERBE Flexible Cryoprobes for Bronchoscopic Diagnosis and Treatment. NICE Guidelines 2015. Available online: www.nice.org.UK (accessed on 10 May 2018).
26. Hetzel, J.; Hetzel, M.; Hasel, C.; Moeller, P.; Babiak, A. Old meets modern: The use of traditional cryoprobes in the age of molecular biology. *Respiration* **2008**, *76*, 193–197. [CrossRef] [PubMed]

27. Hetzel, J.; Eberhardt, R.; Herth, F.J.F.; Petermann, C.; Reichle, G.; Freitag, L.; Dobbertin, I.; Franke, K.J.; Stanzel, F.; Beyer, T.; et al. Cryobiopsy increases the diagnostic yield of endobronchial biopsy: A multicentre trial. *Eur. Respir. J.* **2012**, *39*, 685–690. [CrossRef] [PubMed]
28. Schuhmann, M.; Bostanci, K.; Bugalho, A.; Warth, A.; Schnabel, P.A.; Herth, F.J.; Eberhardt, R. Endobronchial Ultrasound-guided cryobiopsies in peripheral pulmonary lesions: A feasibility study. *Eur. Respir. J.* **2014**, *43*, 233–239. [CrossRef] [PubMed]
29. Herbst RS, Heymach JV, Lippman SM. Mo- lecular origins of cancer lung cancer. N Eng J Med 2008;359:1367-80.
30. Horner MJ, Ries LAG, Krapcho M, et al., eds. SEER Cancer Statistics Review, 1975-2006. Bethesda, MD: National Cancer Institute 2009: http:// seer.cancer.gov/ csr/1975_2006/, based on November 2008 SEER data.
31. Kanodra NM, Silvestri GA, Tanner NT. Screening and early detection efforts in lung cancer. Cancer. 2015;121(9):1347–1356. doi: 10.1002/ cncr.29222. [PubMed] [CrossRef] [Google Scholar]
32. Sozzi G, Boeri M. Potential biomarkers for lung cancer screening. Translational lung cancer research. 2014;3(3):139–148. [PMC free article] [PubMed] [Google Scholar]
33. Hasan N, Kumar R, Kavuru MS: Lung cancer screening beyond low-dose computed tomography: the role of novel biomarkers. Lung 2014, 192(5):639–648. [PubMed]
34. Li CM, Chu WY, Wong DL, Tsang HF, Tsui NB, Chan CM, Xue VW, Siu PM, Yung BY, Chan LW, et al. Current and future molecular diagnostics in non-small-cell lung cancer. Expert Rev Mol Diagn. 2015;15(8):1061–1074. doi: 10.1586/14737159.2015.1063420. [PubMed] [CrossRef] [Google Scholar]
35. Balgkouranidou I, Liloglou T, Lianidou ES. Lung cancer epigenetics: emerging biomarkers. Biomark Med. 2013;7(1):49–58. doi: 10.2217/bmm.12.111. [PubMed] [CrossRef] [Google Scholar]
36. Pinsky PF. Principles of cancer screening. Surg Clin North Am. 2015;95(5):953–966. doi: 10.1016/j. suc.2015.05.009. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
37. Etzel CJ, Bach PB. Estimating individual risk for lung cancer. Seminars in respiratory and critical care medicine. 2011;32(1):3–9. doi: 10.1055/s-0031-1272864. [PubMed] [CrossRef] [Google Scholar]
38. Brothers JF, Hijazi K, Mascaux C, El-Zein RA, Spitz MR, Spira A. Bridging the clinical gaps: genetic, epigenetic and transcriptomic biomarkers for the early detection of lung cancer in the post-National Lung Screening Trial era. BMC Medicine. 2013;11:168. [PMC free article] [PubMed]
39. Hassanein M, Callison JC, Callaway-Lane C, Aldrich MC, Grogan EL, Massion PP. The state of molecular biomarkers for the early detection of lung cancer. Cancer prevention research (Philadelphia, Pa) 2012;5(8):992–1006. doi: 10.1158/1940-6207.CAPR-11-0441. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
40. Herbst RS, Lippman SM. Moleküler signature of lung cancer – two personalized therapy. N Eng J Med 2007;356:76-8.
41. Boyle P, Chapman CJ, Holdenrieder S, Mur- ray A, Robertson C, Wood WC, et al. Clinical validation of an autoantibody test for lung can- cer. Ann Oncol 2011;22:383-9.
42. Ajona D, Pajares MJ, Corrales L, et al. Investigation of complement activation product C4d as a diagnostic and prognostic biomarker for lung cancer. J Natl Cancer Inst. 2013;105:1385–1395.
43. Ajona D, Okrój M, Pajares MJ, et al. Complement C4d-specific antibodies for the diagnosis of lung cancer. Oncotarget. 2018;9:6346–6355.
44. Verri C, Borzi C, Holscher T, et al. Mutational profile from targeted NGS predicts survival in LDCT screening– detected lung cancers. J Thorac Oncol. 2017;12: 922–931.
45. Sozzi G, Boeri M, Rossi M, et al. Clinical utility of a plasma-based miRNA signature classifier within computed tomography lung cancer screening: a correlative MILD trial study. J Clin Oncol. 2014;32: 768–773.
46. Montani F, Marzi MJ, Dezi F, et al. MiR-test: a blood test for lung cancer early detection. J Natl Cancer Inst. 2015;107:djv063.
47. Sestini S, Boeri M, Marchiano A, et al. Circulating microRNA signature as liquid-biopsy to monitor lung cancer in low-dose computed tomography screening. Oncotarget. 2015;6:32868–32877.
48. Jenkins S, Yang JCH, Ramalingam SS, et al. Plasma ctDNA analysis for detection of the EGFR T790M mu- tation in patients with advanced non–small cell lung cancer. J Thorac Oncol. 2017;12:1061–1070.
49. Giroux Leprieur E, Herbretau G, Dumenil C, et al. Circulating tumor DNA evaluated by next-generation sequencing is predictive of tumor response and prolonged clinical benefit with nivolumab in advanced non-small cell lung cancer. Oncoimmunology. 2018;7:e1424675.
50. Merker JD, Oxnard GR, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists joint review. J Clin Oncol. 2018;36: 1631–1641.
51. Cohen JD, Li L, Wang Y, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science. 2018;359:926–930.
52. Ehrlich M. DNA hypomethylation in cancer cells. Epigenomics. 2009;1:239–259.
53. Esteller M, Sanchez-Cespedes M, Resell R, Sidransky D, Baylin SB, Herman JG. Detection of aberrant promoter hypermethylation of tumor suppressor genes in serum DNA from non-small cell lung cancer patients. Cancer Res. 1999;59:67–70.
54. Doseeva V, Colpitts T, Gao G, Woodcock J, Knezevic V. Performance of a multiplexed dual analyte immuno- assay for the early detection of non-small cell lung cancer. J Transl Med. 2015;13:55.
55. Mazzone PJ, Wang X, Han X, et al. Evaluation of a serum lung cancer biomarker panel. Biomark Insights. 2018;13:1177271917751608.

56. Billatos E, Vick JL, Lenburg ME, Spira AE. The airway transcriptome as a biomarker for early lung cancer detection. Clin Cancer Res. 2018;24:2984–2992 .
57. Spira A, Beane JE, Shah V, et al. Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer. Nat Med. 2007;13:361–366.
58. Blomquist T, Crawford EL, Mullins D, et al. Pattern of antioxidant and DNA repair gene expression in normal airway epithelium associated with lung cancer diag- nosis. Cancer Res. 2009;69:8629–8635.
59. Whitney DH, Elashoff MR, Porta-Smith K, et al. Derivation of a bronchial genomic classifier for lung cancer in a prospective study of patients undergoing diagnostic bronchoscopy. BMC Med Genomics. 2015;8:18.
60. Silvestri GA, Vachani A, Whitney D, et al. A bronchial genomic classifier for the diagnostic evaluation of lung cancer. N Engl J Med. 2015;373:243–251.
61. Hu Z, Whitney D, Anderson JR, et al. Analytical performance of a bronchial genomic classifier. BMC Cancer. 2016;16:161.
62. Vachani A, Whitney DH, Parsons EC, et al. Clinical utility of a bronchial genomic classifier in patients with suspected lung cancer. Chest. 2016;150:210–218.
63. Hogarth DK, Dotson TL, Lee HL, Whitten PE, Smith K, Lenburg ME. The Percepta® Registry: a prospective registry to evaluate percepta bronchial genomic classifier patient data. Paper presented at: CHEST Annual Meeting. October 22–26, 2016; Los Angeles, CA.
64. Mazzone PJ, Sears CR, Arenberg DA, et al. Evaluating molecular biomarkers for the early detection of lung cancer: when is a biomarker ready for clinical use? An official American Thoracic Society policy statement. Am J Respir Crit Care Med. 2017;196:e15–e29.