SEMPI Priority clinical area: Cancer of the Lung

INTRODUCTION

Importance of Lung Cancer

Lung cancer is the second most prevalent cancer in the world. According to National Cancer Institute 2019 estimates, cancer of the lung will account for 12.9% of all new cancer diagnoses and 23.5% of cancer deaths in the United States alone (National Cancer Institute, 2019). Unfortunately, the diagnosis of lung cancer is often made too late in the disease process when treatment options are limited, and the prognosis is poor. Nevertheless, there have been several advances in medical imaging in the recent past that identify individuals with lung cancer earlier in the disease process and improve staging of Lung Cancer. Improved imaging technology can offer earlier diagnosis, more appropriate treatment decisions and improved patient survival or management.

Occurrence and Risk Factors

The number of new lung cancer cases in adults in 2016 occurred at a rate of 46/100,000 and caused deaths at a rate of 38/100,000 population (National Cancer Institute, 2019).

Cigarette smoking is the number one risk factor for lung cancer. In the United States, cigarette smoking is linked to about 30% of all cancers (Samet et al., 2004). High levels of pollution, radiation, asbestos exposure, prior family history, secondary smoke exposure and genetic predisposition are other associated risk factors for lung cancer (Samet et al., 2006; O'Reilly et al., 2007; Howlader et al., 2016).

Classification of Lung Cancer

Lung cancer is most commonly classified as small cell lung carcinoma (SCLC) or non-small cell lung carcinoma (NSCLC) (Cai et al., 2015). NSCLC is more common than SCLC, accounting for 80-90% of all lung cancers. The treatment and prognosis also differ for NSCLC and SCLC. Surgical resection offers the best chance for long term survival/curative treatment in NSCLC. SCLC exhibits more rapid growth and at diagnosis often has identifiable metastasis to regional lymph nodes and distant sites. Due to this biological behavior SCLC is usually treated by chemotherapy and radiation therapy.

NSCLC is further classified into three categories based on cell type: lung adenocarcinoma (LADC), squamous cell lung cancer (SQCLC) and large cell lung cancer (Cai et al., 2015). The World Health Organization (WHO) has published new guidelines to use immunohistochemistry for classification and staging of lung cancer so that treatment strategies can be individualized to improve diagnostic accuracy and outcomes in advanced stages of lung cancer (Travis et al., 2015). Staging for NSCLC uses the tumor node metastasis (TNM) system in which anatomic involvement is used to describe the primary tumor (T), regional lymph node involvement (N) and the presence of metastasis (M). The current guidelines for TNM staging are based on the eighth edition of TNM classification (proposed by the International Association for the Study of Lung Cancer (IASLC) and accepted by both the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC)) (Lim, et al., 2018; Detterbeck et al., 2017).

History and Presenting Symptoms

A comprehensive history is imperative to determine whether lung cancer should be included in a differential diagnosis and thus initiate a targeted diagnostic workup including imaging. Earlier diagnosis of lung cancers may be improved by the application of systematic screening with low dose CT in high-risk individuals (The National Lung Screening Trial Research Team, 2011). Smoking, as indicated earlier, is an established risk factor for lung cancer (Cassidy et al., 2008; Crispo et al., 2004; Subramanian & Govidan, 2007; Lubin et al., 2007). However, not all smokers develop lung cancer, and a significant proportion of lung cancers develop in non-smokers (Crispo et al., 2004; Subramanian & Govindan, 2007). Other risk factors including age, previous history of other cancers, pneumonia and asbestos exposure increase the likelihood of developing lung cancer independent of smoking exposure.

The presence of specific symptoms such as hemoptysis, loss of appetite, dyspnea and persistent cough, combined with the above-mentioned risk factors or smoking history should suggest a diagnosis of lung cancer (Hamilton et al., 2005; Hippisley-Cox & Coupland, 2011).

Screening for Pre-Clinical/Occult Lung Cancer

Imaging, CT and CXR have been evaluated to determine if systematic use of chest imaging would improve survival from lung cancer. In 2011 a study indicated that annual CXRs did not improve survival from lung cancer (Oken et al., 2011). Subsequently, low dose chest CT repeated annually for three years was found to reduce mortality from lung cancer compared to annual CXR (The National Lung Screening Trial Research Team, 2001). Additional methods for screening for early lung cancer are under consideration (Sharma et al., 2015).

RADIOLOGICAL EVALUATION OF LUNG CANCER

The presence of symptoms, clinical history, and physical findings suggesting significant lung pathology warrant properly timed and selected diagnostic imaging (Birt et al., 2014). The evaluation of high-risk individuals (i.e. smokers) with concerning symptoms calls for a screening evaluation to detect lung cancer in its earliest stage (Kocher et al., 2015). Imaging studies can facilitate making an early diagnosis, determine extent of disease, provide insight into prognosis and thus guide the treatment decisions.

Radiography

The use of chest radiography (CXR) as initial evaluation for suspected lung cancer is common. This is primarily related to the widespread availability of CXR, including in primary care settings. As the first imaging modality used, CXR is often helpful in detecting abnormalities consistent with lung carcinoma. CXR is sensitive in finding spiculated lung lesions, identifying hilar enlargement or increased hilar opacity, or demonstrating perihilar and/or mediastinal masses. A combination of these findings often occurs (Reed, 2010). CXR also detects solitary pulmonary nodules, an uncommon initial presentation for this malignancy (Quoix et al., 1990). However, CXR lacks sensitivity in detecting occult mediastinal lymph node metastasis and tumor invasion of the chest wall.

Computed Tomography (CT)

CT, contrast enhanced, is the modality of choice for initial evaluation of the entire thorax and upper abdomen when lung cancer is present on CXR (Cascade et al., 1998; Tsim et al., 2010). CT enables evaluation of peripheral masses, hilar enlargement, mediastinal adenopathy and liver and adrenal gland anatomy. Recent studies have demonstrated a role for PET/CT for staging lung cancer to assist in determining appropriate patient management (De Wever et al., 2007; Shim et al., 2005).

Evaluation of indeterminant peripheral lung nodules is dependent initially on CT scanning. CT can define specific anatomic features present in lung nodules (e.g. AV fistulae, rounded atelectasis, fungus balls, mucous plugs and calcification) (Webb, 1990). Spiral or helical CT is more efficient in identifying small nodules (size less than 10mm). Serial CT imaging may be appropriate to monitor nodule stability or growth. Spiral CT with iodinated contrast provides dynamic imaging that can assist in separating malignant from benign lesions. Use of PET/CT can assist in some situations to further define the nature of a peripheral nodule (Truong et al., 2014). Lymphangitic spread of lung cancer, an uncommon occurrence, can be identified on CT even in situations with a normal CXR.

Magnetic Resonance Imaging (MR)

MR has an advantage over CT when imaging soft tissue. It can detect tumor invasion into the mediastinum, superior sulcus and parietal pleural/chest wall and is more accurate than CT in differentiating stage 3a (resectable) from 3b (unresectable) tumors in selected patients thus determining definitive treatment (Hochhegger et al., 2011; Tsim et al., 2010; Padovani et al., 1993). MR is sensitive in detecting invasion of myocardium, brain, liver and adrenal glands because of better soft tissue contrast and multiplanar imaging capability. MR diagnostic accuracy is further enhanced by using intravenous gadolinium contrast medium.

MR is increasingly recognized as an effective alternative to PET/CT for staging of lung cancer. A three-way comparative study using MR, PET/MR and PET/CT concluded "Accuracies of whole-body MR imaging and PET/MR imaging with SI assessment are superior to PET/MR without SI assessment and PET/CT for identification of TNM factor, clinical stage, and operability evaluation of NSCLC patients" (Ohno et al., 2015). A recent, 2019 study demonstrated the equivalent performance of Whole-Body MRI (WB-MRI) compared to PET/CT in staging NSCLC regarding distant metastases (Taylor et al., 2019).

Positron Emission Tomography (PET)

PET is used to assess metabolic activity rather than the anatomical or morphologic features of lesions. PET performed with FDG (F-2-deoxy-D-glucose) highlights the difference in glucose metabolism in normal and cancerous cells. This allows differentiation between benign and malignant pulmonary lesions identifying abnormal uptake in regional lymph nodes and distant lesions in both soft tissue and skeletal structures (Gupta et al., 1996). FDG uptake is directly proportional to tumor activity and growth rate (Duhaylongsod et al., 1995). In lesions ≥ 10 mm, PET scan can detect malignancy in pulmonary opacities with a sensitivity of 96% and specificity of 88% (Gupta et al., 1996; Hübner et al., 1996; Patz et al., 1993).

PET/CT has generally replaced PET alone for evaluation of thoracic nodal and distant metastatic disease (De Wever et al., 2007; Shim et al., 2005). Recent studies associated with the availability of PET/MR technology have identified a role for this technology in tumor staging (Ohno et al., 2015).

Imaging-Guided Biopsy

Imaging-guided biopsy has become an accepted technique for pathologic diagnosis especially when distinguishing benign lesions from malignant ones. Ultrasonography, computed tomography, and magnetic resonance imaging can all be used to guide biopsy procedures in potential or

known lung cancer settings. Several endoscopic based techniques, including Radial Endobronchial Ultrasound, Electromagnetic Navigation Bronchoscopy, Virtual Bronchoscopy and Ultrathin Bronchoscopy, have demonstrated sensitivity, specificity and safety in the evaluation of pulmonary nodules (Wang Memoli et al., 2012; Zuñiga et al., 2019; Zhang et al., 2015). The exact role of these techniques in this clinical situation is evolving. The literature also supports the use of endoscopic US-guided biopsy (EBUS) of lesions and nodules in the mediastinal area and has demonstrated superior results compared to PET or CT for staging (Herth et al., 2006; Yasufuku et al., 2006).

Image-guided biopsy of nodules, pulmonary lesions and mediastinal lymph nodes is safe, reliable and accurate. As such, it may alter clinical management by avoiding more invasive surgical procedures (Kim et al., 2008; Charig & Phillips, 2000; Wang Memoli et al., 2012).

Identifying Distant Metastatic Disease

CT of the adrenal, abdomen, head, and pelvis can be used to evaluate for distant metastasis which is more common in SCLC (Cascade et al., 1998). PET scans also may be useful in detecting distant metastases when whole-body imaging is performed. Due to a false-positive rate in patients with tuberculosis, histoplasmosis and rheumatoid lung disease, invasive staging procedures or tissue biopsy samples may still be required for diagnostic confirmation (Steinert et al., 1997; Yasufuku et al., 2006). A recent 2019 study demonstrated the equivalent performance of Whole-Body MRI (WB-MRI) compared to PET/CT in staging NSCLC regarding distant metastases (Taylor et al., 2019). A meta-analysis concluded, “PET and MRI were found to be comparable and both significantly more accurate than CT and BS (Bone scan) for the diagnosis of bone metastases,” (Yang et al., 2011).

Post Treatment Surveillance

For lung cancer patients who have undergone initial curative treatment with radiotherapy, chemotherapy, or resection, there is a high recurrence rate, especially within the first 2 years (Crabtree et al., 2015; Sugimura & Yang, 2006). Two recent clinical practice guidelines and a single study suggested a role for CT for surveillance of both NSCLC and SCLC within the first 2 years (Früh et al., 2013; Colt et al., 2013; Nakamura et al., 2010). A single study has indicated PET/CT was superior to CT alone for surveillance after curative surgery for NSCLC (Dane et al., 2013).

Digital Tomosynthesis of the Chest

Digital tomosynthesis (DTS) of the chest is a technique whose basic components are like digital radiography, but DTS also provides benefits of computed tomography (CT). The major advantages of DTS over CXR are improved visibility of the pulmonary parenchyma and depiction of abnormalities such as pulmonary nodules. Calcifications, vessels, airways, and chest wall abnormalities are readily visualized by DTS. DTS

generates coronal “slices” through the chest whose resolution is superior to that of coronal reconstructed CT images. DTS is limited by suboptimal depth resolution and susceptibility to motion. However, the radiation dose and projected cost of chest DTS are lower than those of the standard chest CT. Besides pulmonary nodule detection, applications of DTS being studied include evaluation of pulmonary mycobacterial disease, cystic fibrosis, interstitial lung disease, and asbestos-related thoracic diseases (Chou et al., 2014).

Radiomics

Radiomics is defined as the conversion of images to higher-dimensional data and the subsequent mining of these data for improved decision support. Two recent articles summarized the role of Radiomics in lung cancer (Lee et al., 2017; Thawani et al., 2018). Another study demonstrated Radiomics ability to predict distant metastasis in lung cancer (Coroller et al., 2015). The tools available to apply radiomics are specialized and limited in scope, thereby restricting widespread use and clinical integration.

SUMMARY

Lung cancer is an insidious disease with an overall poor prognosis. Survival is dependent on early detection and diagnosis when the tumor is resectable. Cross-sectional (CT and MR) imaging is the focus of diagnostics. CXR is still used as an initial imaging modality that may or may not result in a preliminary diagnosis. However, due to the poor sensitivity of CXR, low dose CT is now preferred for screening purposes. There is little or no difference between MR and CT as the imaging modality for staging in lung cancer. CT is more widely available and less costly compared to MR. PET imaging analyzes the lesion at a metabolic level and has high sensitivity for detection of both primary lesions and metastatic spread of lung cancer.

Increased availability of PET/MRI, PET/CT and WB-MRI increases the efficacy of evaluating patients for both regional and distant metastases. Changes in imaging technology, most recently Radiomics and Tomosynthesis, continue to the expand the role of imaging in managing patients with Lung Cancer.

References

Birt, L., Hall, N., Emery, J., Banks, J., Mills, K., Johnson, M., . . . Walter, F.M. (2014). Responding to symptoms suggestive of lung cancer: a qualitative interview study. *British Medical Journal (BMJ) Open Respiratory Research*, *1*(1), 1-15.

Cai, Z., Xu, D., Zhang, Q., Zhang, J., Ngai, S.M., & Shao, J. (2015). Classification of lung cancer using ensemble-based feature selection and machine learning methods. *Molecular BioSystems, 11*(3), 791-800.

Cascade, P.N., Gross, B.H., Kazerooni, E.A., Quint, L.E., Francis, I.R., Strawderman, M., & Korobkin, M. (1998). Variability in the detection of enlarged mediastinal lymph nodes in staging lung cancer: a comparison of contrast-enhanced and unenhanced CT. *American Journal of Roentgenology*, *170*(4), 927-931.

Cassidy, A., Myles, J.P., van Tongeren, M., Page, R.D., Liloglou, T., Duffy, S.W., & Field, J.K. (2008). The LLP risk model: an individual risk prediction model for lung cancer. *British Journal of Cancer*, *98*(2), 270-276.

Charig, M.J., & Phillips, A.J. (2000). CT-guided cutting needle biopsy of lung lesions—safety and efficacy of an out-patient service. *Clinical Radiology*, *55*(12), 964-969.

Chou, S.H., Kicska, G.A., Pipavath, S.N., Reddy, G.P. (2014). Digital tomosynthesis of the chest: current and emerging applications. *RadioGraphics, 34*(2), 359-372.

Colt, H.G., Murgu, S.D., Korst, R.J., Slatore, C.G., Unger, M., & Quadrelli, S. (2013). Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest, 143*(5), e437S-e454S.

Coroller, T.P., Grossmann, P., Hou, Y., Rios Velazquez, E., Leijenaar, R.T., Hermann, G., . . . Aerts, H.J. (2015). CT-based radiomic signature predicts distant metastasis in lung adenocarcinoma. *Radiotherapy and Oncology, 114*(3), 345-350.

Crabtree, T.D., Puri, V., Chen, S.B., Gierada, D.S., Bell, J.M., Broderick, S., . . . Meyers, B.F. (2015). Does the method of radiologic surveillance affect survival after resection of stage I non-small cell lung cancer? *The Journal of Thoracic and Cardiovascular Surgery*, *149*(1), 45-53.

Crispo, A., Brennan, P., Jöckel, K.H., Schaffrath-Rosario, A., Wichmann, H.E., Nyberg, F. & Darby, S. (2004). The cumulative risk of lung cancer among current, ex-and never-smokers in European men. *British Journal of cancer, 91*(7), 1280-1286.

Dane, B., Grechushkin, V., Plank, A., Moore, W., & Bilfinger, T. (2013). PET/CT vs. non-contrast CT alone for surveillance 1-year post lobectomy for stage I non-small-cell lung cancer. *American Journal of Nuclear Medicine and Molecular Imaging, 3*(5), 408-416.

Detterbeck, F.C., Boffa, D.J., Kim, A.W., & Tanouse, L.T. (2017). The Eighth Edition Lung Cancer Stage Classification. *Chest, 151* (1), 193-203.

De Wever, W., Vankan, Y., Stroobants, S., Verschakelen, J. (2007). Detection of extrapulmonary lesions with integrated PET/CT in the staging of lung cancer. *European Respiratory Journal, 29*(5), 995-1002.

Duhaylongsod, F.G., Lowe, V.J., Patz, E.F., Vaughn, A.L., Coleman, R.E., & Wolfe, W.G. (1995). Lung tumor growth correlates with glucose metabolism measured by fluoride-18 fluorodeoxyglucose positron emission tomography. *The Annals of Thoracic Surgery, 60*(5), 1348-1352.

Früh, M., De Rysscher, D., Popat, S., Crino, L., Peters. S., Felip, E., & ESMO Guidelines Working Group. (2013). Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Annals of Oncolcogy, 24*(6), vi99-105.

Gupta, N.C., Maloof, J., & Gunel, E. (1996). Probability of malignancy in solitary pulmonary nodules using fluorine-18-FDG and PET. *The Journal of Nuclear Medicine, 37*(6), 943-8.

Hamilton, W., Peters, T.J., Round, A., & Sharp, D. (2005). What are the clinical features of lung cancer before the diagnosis is made? A population-based case-control study. *Thorax, 60*(12), 1059-1065.

Herth, F.J., Eberhardt, R., Vilmann, P., Krasnik, M., & Ernst, A. (2006). Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. *Thorax, 61*(9), 795-798.

Hippisley-Cox, J., & Coupland, C. (2011). Identifying patients with suspected lung cancer in primary care: derivation and validation of an algorithm. *British Journal of General Practice*, *61*(592), e715-e723.

Hochhegger, B., Marchiori, E., Sedlaczek, O., Irion, K., Heussel, C.P., Ley, S., . . . Kauczor, H.U. (2011). MRI in lung cancer: a pictorial essay. *The British Institute of Radiology, 84*(1003), 661-8.

Howlader, N., Noone, A.M., Krapcho, M., Miller, D., Bishop, K., Altekruse, S.F., . . . Mariotto, A. (2016). SEER Cancer Statistics Review, 1975-2013. *Bethesda, MD: National Cancer Institute, 19*.

Hübner, K.F., Buonocore, E., Gould, H.R., Thie, J., Smith, G.T., Stephens, S., & Dickey, J. (1996). Differentiating benign from malignant lung lesions using "quantitative" parameters of FDG PET images. *Clinical Nuclear Medicine, 21*(12), 941-949.

Kim, T.J., Lee, J.H., Lee, C.T., Jheon, S.H., Sung, S.W., Chung, J.H., & Lee, K.W. (2008). Diagnostic accuracy of CT-guided core biopsy of ground-glass opacity pulmonary lesions. *American Journal of Roentgenology, 190*(1), 234-239.

Kocher, F., Hilbe, W., Seeber, A., Pircher, A., Schmid, T., Greil, R., . . . Fiegl, M. (2015). Longitudinal analysis of 2293 NSCLC patients: a comprehensive study from the TYROL registry. *Lung Cancer*, *87*(2), 193-200.

Lee, G., Lee, H.Y., Park, H., Schiebler, M.L., van Beek, E.J.R., Ohno, Y., . . . Leung, A. (2017). Raiomics and its emerging role in lung cancer research, imaging biomarkers and clinical management: State of the art. *European Journal of Radiology, 86*, 297-307.

Lim, W., Ridge, C.A., Nicholson, A.G., & Mirsadraee, S. (2018). The 8th lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. *Quantative Imaging in medicine and surgery, 8*(7), 709–718.

Lubin, J.H., Alavanja, M.C., Caporaso, N., Brown, L.M., Brownson, R.C., Field, R.W., . . . Zielinski, J.M. (2007). Cigarette smoking and cancer risk: modeling total exposure and intensity. *American Journal of Epidemiology, 166*(4), 479-489.

Nakamura, R., Kurishima, K., Kobayashi, N., Ishikawa, S., Goto, Y., Sakai, M., . . . Sato, Y. (2010). Postoperative follow-up for patients with non-small cell lung cancer. *Oncology Research and Treatment, 33*(1-2), 14-18.

National Cancer Institute. Surveillance, Epidemiology, and End Results Program (SEER). (2018). *Cancer Stat Facts: Lung and Bronchus Cancer*.

The National Lung Screening Trial Research Team. (2011). Reduced lung-cancer mortality with low-dose computed tomographic screening. *The New England Journal of Medicine, 365*(5), 395-409.

Ohno, Y., Koyama, H., Yoshikawa, T., Takenaka, D., Seki, S., Yui, M., . . . Sugimura, K. (2015). Three-way Comparison of Whole-Body MR, Coregistered Whole-Body FDG PET/MR, and Integrated Whole-Body FDG PET/CT Imaging: TNM and Stage Assessment Capability for Non–Small Cell Lung Cancer Patients. *Radiology, 275*(3), 849-61.

Oken, M.M., Hocking, W.G., Kvale, P.A., Andriole, G.L., Buys, S.S., Church, T.R., . . . Berg, C.D. (2011). Screening by Chest Radiograph and Lung Cancer Mortality the Prostate, Lung, Colorectal, and Ovarian (PLCO) Randomized Trial. *Journal of the American Medical Association, 306*(17):1865-1873.

O'Reilly, K.M., Mclaughlin, A.M., Beckett, W.S., & Sime, P.J. (2007). Asbestos-related lung disease. *American Family Physician, 75*(5): 683–688.

Padovani, B., Mouroux, J., Seksik, L., Chanalet, S., Sedat, J., Rotomondo, C., . . . Serres, J.J. (1993). Chest wall invasion by bronchogenic carcinoma: evaluation with MR imaging. *Radiology, 187*(1), 33-38.

Patz Jr, E.F., Lowe, V.J., Hoffman, J.M., Paine, S.S., Burrowes, P., Coleman, R.E., & Goodman, P.C. (1993). Focal pulmonary abnormalities: evaluation with F-18 fluorodeoxyglucose PET scanning. *Radiology, 188*(2), 487-490.

Quoix, E., Fraser, R., Wolkove, N., Finkelstein, H., & Kreisman, H. (1990). Small cell lung cancer presenting as a solitary pulmonary nodule. *Cancer*, 66(3), 577-582.

Reed, J.C. (2010). Chest radiology: plain film patterns and differential diagnoses. Philadelphia, PA: Elsevier Mosby.

Samet, J.M., Norman, L.A., Wilbanks, C., & Pinto, A. (2006). The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. U.S. Department of Health and Human Services: Centers for Disease Control and Prevention, Atlanta, GA.

Samet, J.M., Norman, L.A., & Wilbanks, C. (2004). The Health Consequences of Smoking: A Report of the Surgeon General. U.S. Department of Health and Human Services: Centers for Disease Control and Prevention, Atlanta, GA.

Sharma, D., Newman, T.G., & Aronow, W.S. (2015). Lung cancer screening: history, current perspectives, and future directions. *Archives of Medical Science, 11(*5), 1033–1043.

Shim, S.S., Lee, K.S., Kim, B.T., Chung, M.J., Lee, E.J., Han, J., . . . Kim, S. (2005). Non–Small Cell Lung Cancer: Prospective Comparison of Integrated FDG PET/CT and CT Alone for Preoperative Staging. *Radiology, 236*(3), 1011-9.

Steinert, H.C., Hauser, M., Allemann, F., Engel, H., Berthold, T., Von Schulthess, G.K., & Weder, W. (1997). Non-small cell lung cancer: nodal staging with FDG PET versus CT with correlative lymph node mapping and sampling. *Radiology, 202*(2), 441-446.

Subramanian, J., & Govindan, R. (2007). Lung cancer in never smokers: a review. *Journal of Clinical Oncology, 25*(5), 561-570.

Sugimura, H., & Yang, P. (2006). Long-term survivorship in lung cancer: a review. *Chest, 129*(4), 1088-1097.

Taylor, S.A., Mallett, S., Ball, S., Beare, S., Bhatnagar, G., Bhowmik, A., . . . Halligan, S. (2019). Diagnostic accuracy of whole-body MRI versus standard imaging pathways for metastatic disease in newly diagnosed non-small-cell lung cancer: the prospective Streamline L trial. *The Lancet Respiratory Medicine, 7*(6), 523–32.

Thawani, R., McLane, M., Beig, N., Ghose, S., Prasanna, P., Velcheti, V., & Madabhushi, A. (2018). Radiomics and radiogenomics in lung cancer: A review for the clinician. *Lung Cancer, 115*, 34-41.

Travis, W.D., Brambilla, E., Nicholson, A.G., Yatabe, Y., Austin, J.H., Beasley, M.B., . . . Wistuba, I. (2015). The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *Journal of Thoracic Oncology, 10*(9), 1243-1260.

Truong, M.T., Ko, J.P., Rossi, S.E., Rossi, I., Viswanathan, C., Bruzzi, J.F., . . . Erasmus, J.J. (2014). Update in the Evaluation of the Solitary Pulmonary Nodule. *RadioGraphics, 34*(6), 1658-79.

Tsim, S., O'Dowd, C.A., Milroy, R., & Davidson, S. (2010). Staging of non-small cell lung cancer (NSCLC): A review. *Respiratory Medicine*, *104*(12), 1767–1774.

Wang Memoli, J.S., Nietert, P.J., & Silvestri, G.A., (2012). Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. *Chest*, *142*(2), 385-393.

Webb, W.R. (1990). Radiologic evaluation of the solitary pulmonary nodule. *American Journal of Roentgenology, 154*(4), 701-708.

Yang, H.L., Liu, T., Wang, X.M., & Deng, S.M. (2011). Diagnosis of bone metastases: a meta-analysis comparing ^{18}FDG PET, CT, MRI and bone scintigraphy. *European Radiology, 21*(12), 2604-2617.

Yasufuku, K., Nakajima, T., Motoori, K., Sekine, Y., Shibuya, K., Hiroshima, K., & Fujisawa, T. (2006). Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. *Chest, 130*(3), 710-718.

Zhang, W., Chen, S., Dong, X., & Lei, P. (2015). Meta-analysis of the diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules. *Journal of Thoracic Disease, 7*(5), 799–809.

Zuñiga, P.S., Vakil, E., Molina, S., & Ost, D.E. (2019). Sensitivity of Radial Endobronchial Ultrasound Guided Bronchoscopy for Lung Cancer in Patients with Lung Nodules: An Updated Meta-Analysis. *American Journal of Respiratory and Critical Care Medicine, 199*(A1408).