Research Paper *IJMSRR*
*Impact Factor :**3.029*** *E- ISSN - 2349-6746*
ISSN -2349-6738

DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN LUNG CANCER: AN INTEGRATED APPROACH

Sivakumar Loganathan[1, 2], Murugesan Sivakumar[2], S. Venkatesan[2] and Shahid S. Siddiqui[1, 3, 4]
[1] *Department of Medicine, University of Chicago, Chicago, IL 60637, USA*
[2] *Department of Environmental Science, Periyar University, Salem- 636011, Tamilnadu, India.*
[3] *Department of Basic and Clinical Oral Sciences, Faculty of Dentistry, Umm Al Qura University, Makkah, Saudi Arabia.*
[4]*Department of Medical Genetics, Faculty of Medicine, Umm Al Qura University, Makkah, Saudi Arabia.*

Abstract
Lung cancer is the common type of cancer continues to increase worldwide today. The International Agency for Research on Cancer (IARC) GLOBOCAN reported more than 1 million people per year affected by lung cancer worldwide. All lung cancer cases classified as Non-small-cell lung cancer (NSCLC) which accounts for major part and the remainder comes under Small-Cell lung cancer (SCLC). The prognosis is poor with overall survival rate is very low compare to all cancers due to lack of effective early detection methods and treatment. This review provides a comprehensive discussion of the latest developments in diagnosis and treatment of lung cancer. However, the signs and symptoms vary depending on tumor type and extent of metastasis. Treatment options and prognosis are correlated to the type and stage of the tumor. The low dose computed tomography in lung cancer screening is comparatively high rate of tumor detection. Surgical resection is remains single most continual and successful option for treatment. In addition to this, the successful development of a handful of new targeted agents could potentially leads to earlier diagnosis and the development of novel investigational approaches to the treatment of lung cancer. The Video Assisted Thoracoscopic (VATS) lobectomy, as a suitable procedure for patients with early-stage lung cancer, and morbidity remains lower. However, the molecular identification of over-expression of oncogenes and signature miRNAs are associated with lung cancer may be an important approach for early diagnosis and provide novel therapeutic reagents of lung cancer. However currently there are no standard treatment options, hence new approaches for the treatment of lung cancer are very essential.

INTRODUCTION

Lung cancer is the utmost common universal cause of cancer-related death in men, and second only to breast cancer in women (Jemal *et al*., 2011). In 2011 estimated 1,608,800 new lung cancer cases worldwide and estimated 1,387,400 deaths from this (Jemal *et al*., 2011). In 2015, there will be an estimated 1,665,540 new cancer cases diagnosed and 585,720 cancer deaths in the US (Siegel *et al*., 2014). An assessed 158,040 Americans are expected to die from lung cancer in 2015, it's accounting for approximately 27% comparatively of all cancer deaths (Cancer Facts and Figures, 2015). Siegel and colleagues reviewed current lung cancer data and estimated a total of 239,320 new cases and 161,250 deaths from lung cancer in the United States in 2010 (Siegel *et al*., 2011). In lung cancer non-small-cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases, and the remainder classified as small cell lung cancer (SCLC) (Herbst *et al*., 2008; NCCN Guidelines, 2014). Adenocarcinoma (AC), squamous cell carcinoma (SQCC) and large cell carcinoma (LCLC) is the most common subtype of NSCLC. Recently, genomic-based classification of LCLC eliminated this subtype, demonstrating that it can be molecularly sub-classified as either adenocarcinoma or neuroendocrine tumor (Clinical Lung Cancer Genome, 2013). The International Agency for Research on Cancer (IARC) GLOBOCAN reported, one million people were affected worldwide in a year by lung cancer and it has highest mortality rates comparatively (Ferlay *et al*., 2010; Siegel *et al*., 2013). In 1912, lung cancer was defined as "one of the rarest forms of cancer" (Adler, 1912). An estimated 85% of lung cancer cases in the United States are caused by cigarette smoking. For illustration, a longer smoking duration, a younger age of initiation and a higher number of packs-per-day increase the risk of lung cancer (Knoke *et al*., 2004), lung cancers in heavy smokers have the poorest prognosis due to the huge mutation load that has accumulated in cancers. In fact, more lung cancer occurs in individuals who have stopped smoking (Tong *et al*., 1996). The presence of sputum atypia is considerably associated with the development of cancer (Prindiville *et al*., 2003).

In many lung tumorigenesisis results from a series of genetic and epigenetic alterations in pulmonary epithelial cells. Genome associated studies have identified with inherited susceptibility variants of lung cancer on several chromosomal loci, including 6q, 8q, 12q, and 15q (Hung *et al*., 2008; Amos *et al*., 2008). Alberg et al. (2013) discussed in more details about the genetic associations of lung Cancer. Now receding in some nations where tobacco control has reduced smoking (World Health Organization, 2011). Overall age-adjusted incidence rate per 100,000 populations (2005–2009) are higher in men than women (Howlander *et al*., 2011). The lowermost female lung cancer incidence rates are reported in Africa and India, however the highest rates are in Pacific Rim countries (Philippines, Hong Kong, Japan, and the Chinese population of Singapore) and in China (Jonathan *et al*., 2009). Advances in early detection and in the various treatment modalities for many

cancers have become curable and the survival rates for newly diagnosed lung cancer approximately as 17% (Pollack *et al*., 2009; Rajani *et al*., 2009). Average 5-year lung cancer survival is among the poorest (15%) of all cancers. The poor survival is attributable to lack of effective early detection methods and treatment for metastatic disease, and more than 75% of patients present with stage III or IV disease and it's rarely curable with current therapies (Fred *et al*., 2001; Howlander *et al*., 2012). In distant tumors the five-year survival rate is only 4.05% (SEER Cancer Statistics Review, 1975-2011). However, as yet there are no standard indicators of clinical significance in lung cancer. This paper will review a complete overview of diagnostic and treatment option of the lung cancer.

DIAGNOSIS

The physician performing diagnostic procedures, adequate tissue is acquired to achieve accurate histologic and molecular characterization of cancer cells. Early diagnosis of patients with stage I and II lung cancer benefit from surgical resection. In patients with early stage NSCLC, thoracotomy is the recommended experiment for diagnosis and staging of tissue (Lauren *et al*., 2007). Small cell or metastatic non–small cell carcinomas, the diagnosis should be made using thoracocentesis of a pleural effusion, excisional biopsy of an accessible node, bronchoscopy and transthoracic needle aspiration (Rivera *et al*., 2003). Further evaluation for metastases depends on the clinical presentation. Sputum cytology is an acceptable method of establishing the diagnosis, with a pooled sensitivity and specificity rate is (66%, 99%) considerably higher according to the location of the tumor (Rivera *et al*., 2013) and this test detects 71 percent of central tumors but less than 50 percent of peripheral tumors (Rivera *et al*., 2003). Understanding of molecular abnormalities in lung cancer could potentially lead to earlier diagnosis and the development of novel investigational approaches to the treatment of lung cancer (Salgia and Skarin, 1998). Daniel et al. (2013) concluded that complement fragment C4d may serve as a biomarker for early diagnosis of lung cancer. (Daniel *et al*., 2013)

SYMPTOMS

Mostly the lung cancers symptoms occur in advanced stage but in some people occur on early stage. Patients may present with primary tumor caused by symptoms of fatigue, anorexia, and weight loss. Pneumonia occurs in up to 75 percent, Dyspnea in 60 percent and Hemoptysis in 35 percent of patients with symptoms from a primary tumor (Beckles *et al*., 2003). Symptoms may include persistent cough, sputum streaked with blood, chest pain, voice change, and recurrent pneumonia or bronchitis (Cancer Facts & Figures 2014).

SCREENING OF LUNG CANCER

Screening studies for lung cancer have only been done in high risk populations, such as smokers and workers with occupational exposure to certain substances. Earlier lung cancer screening trials using chest radiography (Brett, 1969; Oken *et al*., 2011) and sputum cytology (Marcus *et al*., 2000), however chest X-rays beginning in the 1930s (US Department of Health, Education, and Welfare, 1964), flexible bronchoscopy since the late 1960s (Ikeda *et al*., 1968), thin needle aspiration and computerized scans during 1980s (Wittenberg, 1983) and helical computed tomography (CT) scans since late 1990s (Henschke *et al*., 2004). The American Cancer Society (ACS) had recommended lung cancer screening with chest X-ray (CXR) in the 1970s for current and former smokers (Eddy *et al*., 1980), However sensitivity of CXR is reliant on the size and location of the lesion, the image quality, and the skill of the interpreting physician. Lung cancer screening with LDCT is the comparatively high rate of identification of noncalcified nodules, and, the average nodule detection rate per round of screening was better. In 1999, Early Lung Cancer Action Project (ELCAP) investigators comparing the lung cancer screening with low-dose CT (LDCT) and CXR in volunteers aged 60 years and over with a smoking history (Henschke *et al*., 1999). Only lesser evidence mentions the screening approach to reduce mortality.

TREATMENT

Surgery

Patients with resectable disease may be cured by surgery or surgery followed by chemotherapy. Most stage I and stage II non-small cell lung cancers are treated with surgery by surgeon to removes the lobe, or section of the lung containing tumor. Surgery can be divided into three major groups: lobectomy (removal of a lobe), bilobectomy (removal of two lobes on the right side) and pneumonectomy (removal of an entire lung). In 1947 the first sleeve resection was achieved for a carcinoid tumour in the right upper-lobe (Naef, 2003). The final aim of non-small-cell lung cancer (NSCLC) surgical treatment is complete (R0) resection, however this specific criteria have been established by a working group of the International Association for the Study of Lung Cancer (IASLC) (Rami *et al*., 2005). Significantly improved survival rates are reported in surgical series. Several surgeons practice video-assisted thoracoscopic surgery (VATS), this process, the surgeon makes a small incision, or cut, in the chest and inserts a tube called a thoracoscope, that has a light and a minute camera connected

with video monitor, lung tumor can be removed through the scope. VATS lobectomy, is a suitable procedure for a number of patients with early-stage NSCLC. Morbidity remains lower with the VATS approach, although in a nationwide database of 13,619 patients who underwent lobectomy by thoracotomy or VATS (*Gopaldas et al*., 2010). Pierre Denoit (1912-1990), a surgical oncologist, first started using the tumour, node, metastasis (TNM) classification system and defines the anatomic extent of disease (Goldstraw, 2009), a complete intraoperative systematic lymph node dissection is important to provide an accurate pathological TNM staging. A complete mediastina lymph-node dissection identified more levels of N2 disease in patients with stages II and IIIA NSCLC, and was associated with improved survival (Sakurai *et al*., 2004; Schulte *et al*., 2009).

Radiation therapy

The main aim of radiation therapy is to deprive multiplication potential of cancer cells. There are two main types of radiation therapy, external beam radiation therapy and brachytherapy (internal radiation therapy); External beam radiation therapy (EBRT) focuses radiation from outside the body on the cancer that is most often used to treat a primary lung cancer. External beam radiation therapy most often used to treat small cell lung cancer (SCLC). Radiation therapy contributes to around 40% towards curative treatment (Delaney *et al*., 2005). High-energy radiation damages genetic material (deoxyribonucleic acid, DNA) of cells and thus blocking their ability to divide and proliferate (Jackson and Bartek, 2009). Rapid progress in this field continues to be boosted by advances in imaging techniques, computerized treatment planning systems, radiation treatment machines (with improved X-ray production and treatment delivery) as well as improved understanding of the radiobiology of radiation therapy (Bernier *et al*., 2004). The effects of fractionated radiation therapy in the 1920s eventually led to the development of regimes comparing different treatment schedules based on total dose, number of fractions and overall treatment time (Bernier *et al*., 2004). Programmed cell death or apoptosis is a major cell death mechanisms involved in cancer therapy and in radiation therapy in particular (Rupnow and Knox, 1999; Cragg *et al*., 2009). Radiation therapy to the chest may damage your lungs and cause a cough and breathing problems. Radiation is also being delivered in combination with molecular targeted therapy with the aim of further improving the therapeutic ratio of the radiation treatment (Tofilon *et al*., 2003; Begg *et al*., 2009). Local control can be achieved with radiation therapy in a large number of patients with unresectable disease. Conventional Radiation therapy (RT) alone resulted in a median survival of 10 months and a 5-year survival rate of 5%. Many phase 3 trials have confirmed that cisplatin based chemotherapy plus RT produces better survival rates than RT alone (Schaake-Koning *et al*., 1992; Le Chevalier *et* al., 1992).

Chemotherapy

Chemoprevention is demarcated as the use of nutritional or pharmaceutical interventions to slow or converse the development of premalignancy to invasive cancer, the main consideration for chemoprevention trials is the safety profile and reduces the incidences and mortality of lung cancer. Clinical trials have revealed that chemopreventive agents may have dramatically different results in current and former smokers (Omenn *et al*., 1996). A diet rich in fruits and vegetables is associated with a lower cancer incidence. A large clinical study evaluated N-acetyl cysteine agent in 1,023 patients with NSCLC (pT1-T3, N0-1, or T3, N0) treated by therapeutic intent, but there is no significant differences were noted among the groups (van Zandwijk *et al*., 2000). A large randomized trial of 1,166 patients with stage I NSCLC treated with placebo or isotretinoin and this no improvement in reduce tumor size, recurrence rate and mortality (Lippman *et al*., 2001). Fritz *et al* investigated selenium as a lung cancer chemo preventive agent (Fritz *et al*., 2011).

Targeted therapy

Scientific advances in understanding lung cancer at the molecular level have accelerated to make improvements in diagnostics and therapeutics. Particular mutations in growth factor receptors are the hallmarks of definite lung cancer phenotypes and form the basis of molecularly targeted therapies (Pao *et al*., 2011). One randomized experimental in Japan showed a considerably prolonged progression-free survival (PFS) in patients proceeding gefitinib versus standard chemotherapy (Maemondo *et al*., 2010). However these targets are KRAS, BRAF, ERBB2, PI3KC and translocations involving RET and ROS, as well as RTK MET, which is activated mainly in tumors that develop resistance to targeted therapies. The discovery of activating mutations in the *EGFR* gene heralded a new era of personalized medicine in thoracic oncology, however presently existing tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib and afatinib target EGFR provide dramatic tumor responses compared with conventional chemotherapy in patients with Non-small-cell lung cancer NSCLC (Salgia, 2015). Over expression of EGFR occurs 60% in NSCLC. Inhibitors of targeting EGFR or anaplastic lymphoma kinase (ALK) have demonstrated major efficacy in the treatment and diagnostic assays of lung cancer, patients are benefit from these treatments (Salgia, 2015). EGFR inhibitors that bind to EGFR or other receptors in the EGFR family, however Afatinib is an irreversible Erbβ family blocker that covalently binds to the cysteine residue of EGFR, and providing

longer inhibition of EGFR (Nelson *et al*., 2013). Recent studies have been shows several mechanisms are resistance to EGFR inhibitors (Chong *et al*., 2013). MET over expression has been observed in 25% to 61% of NSCLC patients. A comparative study of MET inhibitor tivantinib (ARQ 197), in combination with erlotinib treated patients, has shown better activity versus erlotinib alone (Sequist *et al*., 2011). KRAS mutations are observed in close to 30% of adenocarcinomas of the lung, but are uncommon in SQCC about 5% only. A preclinical study based on shRNA screening recognized BCL-XL and MEK inhibition as a potentially active approach for treatment of KRAS-mutant adenocarcinoma (Corcoran *et al*., 2013). The MEK inhibitor selumetinib combined with docetaxel in a phase 2 clinical trials showed promising results in KRAS-mutated NSCLC (Janne *et al.,* 2013). The PAX5 gene might be a key regulator of c-MET transcription and an approaching target for therapy in Small cell lung cancer (SCLC) (Rajani *et al*., 2009). The combining of KIF14 kinesin and miRNAs in associated with lung cancer may be an important approach for early diagnosis of lung cancer, and may provide novel therapeutic reagents (Shahid *et al*., 2014; Xi Liu *et al*., 2010).

Immunotherapy

The principles of tumor biology and immunology have been critical in the development of immunotherapy in laboratory and implementation of immunotherapy in the clinic, this better understanding of immunotherapy and the mechanisms underlying immunity in cancer has powered an increasing of new therapeutic agents for a different cancers. In the 1970s and 1980s, immunologists searched for antibodies that would bind to tumors in the serum of cancer patients, and lymphocytes activated with lectins or interleukin-2 (IL-2) were found in target tumor cells *in vitro* (Grimm *et al*., 1982; Mazumder *et al*., 1982). Bevacizumab is a recombinant, humanized mAb that binds and neutralizes, vascular endothelial growth factor (VEGF), preventing its association with endothelial receptors like Flt-1, and KDR, Bevacizumab is approved for the suggestions of nonsquamous NSCLC (Miller *et al*., 2007).

Small cell lung cancer (SCLC) have been shown to reduced expression of class I and class II antigens due to reduced gene transcription, with diminished immunogenicity (Ball *et al*., 1986; Marley *et al*., 1989). Interferon IFN-α have been exposed to bring the expression of MHC antigens on SCLC cells in both in vitro and in vivo (Kelly *et al*., 1995). Some immunotherapeutic agents have been assessed without significant toxicity in patients with SCLC; Such as fucosyl monosialoganglioside (GM1), polysialic acid, disialoganglioside (GM2), and the gangliosides (GD2 and GD3) (Zhang *et al*., 1997). However, these trials failed to demonstrate significant improvement in Overall survival (OS) or PFS compared with observation (Giaccone *et al*., 2005; Bottomley *et al*., 2008). Tumor vaccination strategies have also been tested in NSCLC randomized trial of the BLP25 liposome vaccine immunizing against the MUC1 antigen, a cell surface glycoprotein was associated with a trend toward improved survival (Butts *et al.,* 2005). The international trials in the cancer germline melanoma-associated antigen (MAGE)-A3 as a vaccination in NSCLC on the phase 2 studies that suggest a potential benefit of vaccination with this antigen (Ding *et al*., 1994).

CONCLUSION

The increasing lung cancer incidents are a fact. The increasing lung cancer incidents and poor prognosis are mainly due to lack of effective early detection methods and treatments of metastatic lung cancer. The patients present with advanced stage (III or IV) disease are rarely curable with current therapies. Creating the essential novel treatments are the presently more demanding. Diagnosis of lung cancer, LDCT screening is comparatively high rate of tumor detection and understanding of molecular abnormalities in lung cancer that could potentially lead to earlier diagnosis. Several surgeons practice video-assisted thoracoscopic surgery; however the morbidity remains lower. Advances in biologically targeted therapeutic agents advanced the better treatment of lung cancer should continue to make incremental improvements. However past several decades, we have made only a few small strides in our fight against lung cancer, in medical research community. New approaches for the standard treatment of lung cancer are very essential to save lives.

RECOMMENDATIONS

Diagnosis

- Thoracotomy is the recommended for diagnosis and staging of tissue patients with early stage NSCLC.
- Sputum cytology is an acceptable method of establishing the diagnosis and its sensitivity and specificity rate is higher according to the location of the tumor
- LDCT is highly recommended for the early examination of lung cancer screening and its nodule detection rate per round of screening was better.

Surgery

- VATS lobectomy is a suitable procedure for patients with early-stage NSCLC and Morbidity remains lower.

Immunotherapy

- Bevacizumab is recommended immunotherapy for the suggestions of nonsquamous NSCLC.

Chemotherapy

- Placebo or isotretinoin is a chemotherapy for stage I NSCLC patients

Targeted therapy

- The inhibitors of targeting EGFR or ALK have major efficacy in the treatment and diagnostic assays of lung cancer.

REFERENCE

1. Adler I. Primary malignant growth of the lung and bronchi. New York: Longman, Green, Company; 1912
2. Alberg A, Brock M , Ford J , Samet JM , Spivack SD . Epidemiology of 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): e1S - e29S .
3. American Cancer Society. Cancer Facts and Figures, 2015.
4. Amos CI , Wu X , Broderick P , et al . Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1 . *Nat Genet* .2008 ; 40 (5): 616 - 622 .
5. Ball ED, Sorenson GD, Pettengill OS. Expression of myeloid and major histocompatibility antigens on small cell carcinoma of the lung cell lines analyzed by cytofluorography: modulation by gamma-interferon. Cancer Res. 1986; 46:2335–2339.
6. Beckles MA, Spiro SG, Colice GL, Rudd RM. Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes. Chest 2003;123(1 suppl):97S-104S.
7. Begg M, Mo F-M, Offertáler L, Bátkai S, Pacher P, Razdan RK, Lovinger DM, Kunos G. G protein-coupled endothelial receptor for atypical cannabinoid ligands modulates a Ca2+-dependent K+ current. The Journal of Biological Chemistry.2003a;278(46):46188–46194.
8. Bernier J, Hall EJ, Giaccia A: Radiation oncology: a century of achievements. Nature 2004; 4: 737-747.
9. Bottomley A, Debruyne C, Felip E, et al. Symptom and quality of life results of an international randomised phase III study of adjuvant vaccination with Bec2/BCG in responding patients with limited disease small-cell lung cancer. Eur J Cancer. 2008; 44:2178–2184.
10. Brett, G.Z. Earlier diagnosis and survival in lung cancer. *Br. Med. J.* 1969, *4*, 260–262.
11. Butts C, Murray N, Maksymiuk A, et al. Randomized phase IIB trial of BLP25 liposome vaccine in stage IIIB and IV non-small-cell lung cancer. J Clin Oncol.2005; 23:6674–6681.
12. Chong CR and Janne PA. The quest to overcome resistance to EGFR-targeted therapies in cancer. Nature medicine. 2013; 19(11):1389-1400.
13. Clinical Lung Cancer Genome P and Network Genomic M. A genomics-based classification of human lung tumors. Science translational medicine. 2013; 5(209):209ra153.
14. Corcoran RB, Cheng KA, Hata AN, Faber AC, Ebi H, Coffee EM, Greninger P, Brown RD, Godfrey JT, Cohoon TJ, Song Y, Lifshits E, Hung KE, Shioda T, Dias-Santagata D, Singh A, et al. Synthetic lethal interaction of combined BCL-XL and MEK inhibition promotes tumor regressions in KRAS mutant cancer models. Cancer cell. 2013; 23(1):121-128.
15. Cragg MS, Harris C, Strasser A, Scott CL: Unleashing the power of inhibitors of oncogenic kinases through BH3 mimetics. Nat Rev Cancer 2009; 9: 321-326.
16. Daniel Ajona, María J. Pajares, Leticia Corrales, *et* al. Investigation of Complement Activation Product C4d as a Diagnostic and Prognostic Biomarker for Lung Cancer J Natl Cancer Inst;2013;105:1385–1393
17. Delaney G, Jacob S, Featherstone C, Barton M: The role of radi-otherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer 2005; 104: 1129-1137.
18. Ding M, Beck RJ, Keller CJ, Fenton RG. Cloning and analysis of MAGE-1-related genes. Biochem Biophys Res Commun.1994; 202:549–555.
19. Eddy D. ACS report on the cancer-related health checkup. CA Cancer J Clin.1980; 30:193–240.
20. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010 15;127:2893-917.
21. Fred R. Hirsch2, Wilbur A. Franklin, Adi F. Gazdar, and Paul A. Bunn Jr. Early Detection of Lung Cancer: Clinical Perspectives of Recent Advances in Biology and Radiology[1] Clin Cancer Res January 2001 *7;* 5

22. Fritz H, Kennedy D, Fergusson D et al. Selenium and lung cancer: a systematic review and meta-analysis. PLoS One. 2011; 6(11):e26259.
23. Giaccone G, Debruyne C, Felip E, et al. Phase III study of adjuvant vaccination with Bec2/bacilli Calmette-Guerin in responding patients with limited-disease small-cell lung cancer (European Organisation for Research and Treatment of Cancer 08971–08971B; Silva Study).J Clin Oncol. 2005; 23:6854–6864.
24. Goldstraw P. eds. IASLC staging manual in thoracic oncology. FL: Editorial Rx Press, 2009.
25. Gopaldas RR, Bakaeen FG, Dao TK, Walsh GL, Swisher SG, Chu D. Video-assisted thoracoscopic versus open thoracotomy lobectomy in a cohort of 13,619 patients. Ann Thorac Surg 2010; 89:1563–70.
26. Grimm EA, Mazumder A, Zhang HZ, Rosenberg SA. Lymphokine-activated killer cell phenomenon. Lysis of natural killer-resistant fresh solid tumor cells by interleukin 2-activated autologous human peripheral blood lymphocytes. J Exp Med. 1982; 155:1823–1841.
27. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet.1999; 354:99–105.
28. Henschke CI, Yankelevitz DF, Naidich DP, et al. CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. Radiology.2004; 231:164–8.
29. Herbst RS, Heymach JV, Lippman SM. Lung cancer. *N. Engl. J. Med.* 359(13), 1367–1380 (2008).
30. Howlander, N.; Noone, AM.; Krapcho, M., et al., editors. SEER Cancer Statistics Review, 1975–2008. Bethesda, MD: National Cancer Institute; 2011.
31. Howlander, N.; Noone, AM.; Krapcho, M., et al., editors. SEER Cancer Statistics Review, 1975–2009. Bethesda, MD: National Cancer Institute; 2012.
32. Hung RJ , McKay JD , Gaborieau V , et al . A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. *Nature* .2008; 452 (7187): 633 - 637.
33. Ikeda S, Yanai N, Ishikawa S. Flexible bronchofiberscope. Keio J Med. 1968; 17:1–16.
34. Jackson SP, Bartek J: The DNA-damage response in human biology and disease. Nature 2009; 461: 1071-1078.
35. Janne PA, Shaw AT, Pereira JR, Jeannin G, Vansteenkiste J, Barrios C, Franke FA, Grinsted L, Zazulina V, Smith P, Smith I and Crino L. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. The lancet oncology. 2013; 14(1):38-47.
36. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J. Clin.* 61(2), 69–90 (2011).
37. Jonathan M. Samet, Erika Avila-Tang, Paolo Boffetta, Lindsay M. Hannan, Susan Olivo- Marston, Michael J. Thun, and Charles M. Rudin. Lung cancer in never smokers: clinical epidemiology and environmental risk factors. Clin Cancer Res. 2009 September 15; 15(18): 5626–5645. doi:10.1158/1078-0432.CCR-09-0376.
38. Kelly K, Crowley JJ, Bunn PA Jr, et al. Role of recombinant interferon alfa-2a maintenance in patients with limited-stage small-cell lung cancer responding to concurrent chemoradiation: a Southwest Oncology Group study.J Clin Oncol.1995; 13:2924–2930.
39. Knoke JD, Shanks TG, Vaughn JW, Thun MJ, Burns DM. Lung cancer mortality is related to age in addition to duration and intensity of cigarette smoking: an analysis of CPS-I data. *Cancer Epidemiology, Biomarkers & Prevention*. 2004;13(6):949-57.
40. Lauren G. Collins, M.D., Christopher Haines, M.D., Robert Perkel, M.D., and Rober T E. Enck, M.D. Lung Cancer: Diagnosis and Management American Family Physician January 1, 2007; 75:1
41. Le Chevalier T, Arriagada R, Tarayre M, et al. Significant effect of adjuvant chemotherapy on survival in locally advanced non-small-cell lung carcinoma [letter]. J Natl Cancer Inst 1992;84(1):58.
42. Lippman SM, Lee JJ, Karp DD, et al.: Randomized phase III intergroup trial of isotretinoin to prevent second primary tumors in stage I non-small-cell lung cancer. J Natl Cancer Inst 93 (8): 605-18, 2001.
43. M. Patricia Rivera, MD, FCCP; Atul C. Mehta, MBBS, FCCP; Momen M. Wahidi, MD, MBA, FCCP. Establishing the Diagnosis of Lung Cancer:Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. May 2013, Vol 143, No. 5_suppl
44. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. The New England journal of medicine. 2010; 362(25):2380-2388.
45. Marcus PM, Bergstralh EJ, Fagerstrom RM, et al. Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. J Natl Cancer Inst. 2000; 92:1308–1316.

46. Marley GM, Doyle LA, Ordonez JV, Sisk A, Hussain A, Yen RW. Potentiation of interferon induction of class I major histocompatibility complex antigen expression by human tumor necrosis factor in small cell lung cancer cell lines. Cancer Res. 1989; 49:6232–6236.
47. Mazumder A, Grimm EA, Zhang HZ, Rosenberg SA. Lysis of fresh human solid tumors by autologous lymphocytes activated in vitro with lectins. Cancer Res. 1982; 42:913–918.
48. Miller K, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007; 357:2666–2676.
49. Naef AP. The mid-century revolution in thoracic and cardiovascular surgery. Part 2: prelude to 20th century cardio-thoracic surgery. Interact Cardiovasc Thorac Surg 2003; 2:431–49.
50. NCCN Guidelines: NSCLC. v3. (2014). www.nccn.org.
51. NCIN. Cancer Incidence and Mortality by Cancer Network, UK, 2005. London: NCIN; 2008.
52. Nelson V, Ziehr J, Agulnik M and Johnson M. Afatinib: emerging next-generation tyrosine kinase inhibitor for NSCLC. OncoTargets and therapy 2013; 6:135-143.
53. Oken MM, Hocking WG, Kvale PA, et al. PLCO Project Team. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA.2011; 306:1865–1873.
54. Omenn GS , Goodman GE , Thornquist MD , et al . Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* .1996; 334 (18): 1150 - 1155 .
55. PaoW ,Iafrate AJ , Su Z . Genetically informed lung cancer medicine .*J Pathol*.2011 ; 223 (2): 230 - 240 .
56. Pollack LA, Rowland JH, Crammer C, Stefanek M: Introduc-tion: charting the landscape of cancer survivors' health-related outcomes and care. Cancer 2009; 115: 4265-4269.
57. Prindiville SA, Byers T, Hirsch FR, et al. Sputum cytological atypia as a predictor of incident lung cancer in a cohort of a cohort of heavy smokers with airflow obstruction. Cancer Epidemiol Biomarkers Prev. 2003; 12:987.
58. Rajani Kanteti, Sivakumar Loganathan, Soundararajan Krishnaswamy, Leonardo Faoro, Deborah Lang, Everett Vokes, and Ravi Salgia. Abstract #LB-119: Expression and Function of PAX5 Transcription Factor and Regulation of c-MET in SCLC -Potential for Novel Biomarkers and Therapeutics Cancer Res May 1, 2009 *69;* LB-119
59. Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definition. Lung Cancer 2005;49:25–33.
60. Ravi Salgia. Diagnostic challenges in non-small-cell lung cancer: an integrated medicine approach. *Future Oncol.* (2015) 11(3), 489–500
61. Rivera MP, Detterbeck F, Mehta AC, for the American College of Chest Physicians. Diagnosis of lung cancer: the guidelines. Chest 2003;123(1 suppl):129S-36S.
62. Rupnow BA, Knox SJ: The role of radiation-induced apoptosis as a determinant of tumor responses to radiation therapy. Apoptosis 1999; 4: 115-143.
63. Sakurai H, Maeshima A,Watanabe S, et al. Grade of stromal invasion in small adenocarcinoma of the lung: histopathological minimal invasion and prognosis. Am J Surg Pathol 2004;28:198–206.
64. Salgia R, Skarin AT. Molecular abnormalities in lung cancer. J Clin Oncol. 1998 Mar;16(3):1207-17.
65. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. N Engl J Med 1992;326(8):524–530.
66. Schulte T, Schniewind B, Dohrmann P, Kuchler T, Kurdow R.The extent of lung parenchyma resection significantly impacts long-term quality of life in patients with non-small cell lung cancer. Chest 2009;135:322–9.
67. Sequist LV, von Pawel J, Garmey EG, Akerley WL, Brugger W, Ferrari D, Chen Y, Costa DB, Gerber DE, Orlov S, Ramlau R, Arthur S, Gorbachevsky I, Schwartz B and Schiller JH. Randomized phase II study of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated non-small-cell lung cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2011; 29(24):3307-3315.
68. Shahid S. Siddiqui, Sivakumar Loganathan, Fathy M. El-Faskhany, Faisal A. Allaf, Zeba K. Siddiqui, Hanadi Lamfon, Mohammad Beyari. Overexpression of Cytokinesis Mediating Kinesin Motor KIF14 in Recurring Head and Neck Cancer: Implications for Regulation by MicroRNAs. Clinical Medicine and Diagnostics 2014, 4(1A): 1-7
69. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J. Clin.* 64(1), 9–29 (2014).
70. Siegel R, Naishadham, D, Jemal, A. Cancer statistics, 2013. *CA Cancer J. Clin.*2013, *63*, 11–30.
71. Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011; 61(4): 212–236.
72. Tofilon PJ, Saxman S, Coleman CN: Molecular targets for radi-ation therapy: bringing preclinical data into clinical trials. Clin Cancer Res. 2003; 9: 3518-3520.
73. Tong L , Spitz MR , Fueger JJ , Amos CA . Lung carcinoma in former smokers. *Cancer* .1996 ; 78 (5): 1004 - 1010

74. U.S. National Institutes of Health. National Cancer Institute. SEER Cancer Statistics Review, 1975-2011.
75. US Department of Health, Education, and Welfare. Report of the Advisory Committee to the Surgeon General. Washington, D.C: US Department of Health Education and Welfare (DHEW); 1964. Smoking and Health. Report No.: 1103
76. Van Zandwijk N, Dalesio O, Pastorino U, de Vries N, van Tinteren H. EUROSCAN, a randomized trial of vitamin A and N-acetylcysteine in patients with head and neck cancer or lung cancer. J Natl Cancer Inst. 2000 Jun 21;92(12):977-86.
77. World Health Organization. WHO Report on the Global Tobacco Epidemic, 2011: Warning About the Dangers of Tobacco. Geneva: Switzerland: World Health Organization; 2011.
78. Xi Liu, Lorenzo F. Sempere, Haoxu Ouyang, *et al*. MicroRNA-31 functions as an oncogenic microRNA in mouse and human lung cancer cells by repressing specific tumor suppressors. *J Clin Invest.* 2010; 120 (4):1298–1309.
79. Zhang S, Cordon-Cardo C, Zhang HS, et al. Selection of tumor antigens as targets for immune attack using immunohistochemistry: I. Focus on gangliosides. Int J Cancer. 1997; 73:42–49.