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Semantics of Lungs Cancer - Then, Now, Tomorrow

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Abstract:

Cancer is a major problem in today's world. Lung cancer is the most common type of cancer in the world (12.3% of all cancer types), with an estimated 1.2 million new cases in the year of 2000, recorded alone (D.M , 2001). Tobacco smokers are at a 20 to 30 fold higher risk of developing Lung cancers. In 2000, it was found that lung cancer resulted in 1.1 million deaths worldwide, or 17.8% of all cancer deaths. However, only 11% of heavy cigarette smokers ultimately developed lung cancer, suggesting the prevalence, involvement of genetic factors (SM & MR, 2001). A brief review of molecular aberrations, chromosomal changes, mutations, signalling patterns shall be briefly encountered in this review article. In this present article, major histologic types of lung cancer- squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and large cell carcinoma, alongwith more specific subtypes such as lepidic predominant subtype of adenocarcinoma or the basaloid variant of large cell carcinoma shall be briefly encountered upon.The present Global statistics shall also be briefly portrayed herein.

Keywords: p53, Histology, Adenosarcoma, K-ras, 3q26

Introduction:

Worldwide, Lung cancer is the most common malignancy and the most commoncause of cancer deaths in the past few decades. In 2012, a total of 1.8 million new cases were estimated, accounting for 12.9% of all new cancer diagnoses. Lung cancer is the most common Cancer type and reason of cancer related mortality in males and the third most frequent among females. The major types of lung cancer include adenocarcinoma, squamous cell carcinoma, small cell and large cell carcinoma. The most important risk factor for lung cancer is tobacco smoking. Tobacco smokers above the age of 5 are at the highest risk. This, however presents a gender bias, with incidences among women, being much lower. Other carcinogens include environmental exposure to radon; asbestos; certain heavy

metals such as chromium, cadmium and arsenic; some organic chemicals, radiation; coal smoke; as well as indoor emission of fuel burning (Travis & Rekhtman, 2011). Cigarette smoke alone consists of 20 known carcinogens such as polycyclic aromatic hydrocarbons and the tobacco-specific nitrosamine 4 - (methylnitrosamino) – 1 - (3 - pyridyl) - 1-butanone (NNK). Family history attributes to a 25 fold increase in the chances, with reports suggesting the presence of a rare autosomal dominant genetic predisposition (Amos, Xu, & Spitz, 1999). Genetic polymorphisms are frequent in population. Polymorphisms that inhibits the activity of glutathione–s transferase family, which can exhibit inactivation of carcinogens, and of ones that increase the activity of P450 family that has a activating effect on carcinogens, increases the susceptibility of cancer occurrence. The Carcinogens form an adduct with the DNA, leading to mutation. especially G to T transversions. The literary objective of this work is to study about the successive progress, improvements in the screening, underlying factor aberrations, the upgradation of terminologies, specifications, over the years.

Pathological Distinctions/Classifications:

Lung Cancer can be addressed for diagnosis either by a pathologic or a cytologic approach. Broadly, lung cancer is classified into small cell lung carcinoma (SCLC) and non–small cell lung carcinoma (NSCLC) (WD, E, & Mu¨ ller- Hermelink HK, 2004). However, with successive additions to Medical terminologies by WHO, over years, and with the new International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/ European Respiratory Society (ERS) Lung Adenocarcinoma Classification making major changes in how lung adenocarcinoma must be diagnosed, over the erstwhile 2004 World Health Organization (WHO) classification of lung tumors (Travis, Brambilla, Schi, & Scagliotti, 2011).

Histologic Classification of Lung Cancers:

1. Preinvasive lesions

- ✓ Squamous dysplasia/carcinoma in situ (CIS)
- ✓ Atypical adenomatoushyperplasia (AAH)
- ✓ Adenocarcinoma in situ (AIS) (nonmucinous, mucinous, or mixed nonmucinous/ mucinous)
- ✓ Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)

2. Squamous cell carcinoma

#Variants

- ❖ Papillary
  - ✓ Clear cell

3. Small cell carcinoma

- ✓ Combined small cell carcinoma

4. Adenocarcinoma

- ❖ Minimally invasive adenocarcinoma (MIA) (3 cm lepidic predominant tumor with 5 mm invasion)
- ✓ nonmucinous, mucinous, mixed mucinous / nonmucinous
- ❖ Invasive adenocarcinoma
- ✓ Lepidic predominant (formerly nonmucinous bronchioloalveolar carcinoma (BAC) pattern, with > 5mm invasion)
- ✓ Acinar predominant
- ✓ Papillary predominant
- ✓ Micropapillary predominant
- ✓ Solid predominant with mucin# Variants of invasive adenocarcinoma
  - ➢ Invasive mucinous adenocarcinoma(formerly mucinous BAC)
  - ➢ Colloid
  - ➢ Fetal
  - ➢ Enteric

5. Large cell carcinoma

#Variants

- ➢ Large cell neuroendocrine carcinoma(LCNEC)
- ➢ Combined LCNEC
- ❖ Basaloid carcinoma
- ❖ Lymphoepithelioma-like carcinoma
- ❖ Clear cell carcinoma
- ❖ Large cell carcinoma with rhabdoidphenotype

6. Adenosquamous carcinoma

7. Sarcomatoid carcinomas

- ✓ Pleomorphic carcinoma
- ✓ Spindle cell carcinoma
- ✓ Giant cell carcinoma

8. Carcinoid tumor

- ✓ Typical carcinoid (TC)
- ✓ Atypical carcinoid (AC)

9. Carcinomas of salivary gland type

- ✓ Mucoepidermoid carcinoma
- ✓ Adenoid cystic carcinoma
- ✓ Epimyoepithelial carcinoma

Adapted from (William D. Travis, 2011), 2004 WHO Classification (WD, E, & Mu¨ ller-Hermelink HK, 2004), 2011 IASLC/ATS/ERS Classification of Lung Adenocarcinoma. (E & A, 2009)

Aberrations/Mutagenesis :

Lung cancer pathogenicity is manifested by accumulation of molecular abnormalites, collected over a significant period of time. This might incorporate methylation based

Gene silencing, acetylation, or sequence changes viz; G-T transversions, DNA segment amplification, deletion or entire chromosome gains and losses. (Massion & Carbone, 2003). Loss of 3p, 9p regions have been recognised as early events in the progression of cancer, as compared to p53, K-ras mutations , which are recorded in the later stages of lesions (L, et al., 1995), (V, et al., 1995). Completion of Human Genome Sequencing and development of High throughput technologies, such as Microarray, FACS have been a blessing in this venture. Spontaneous accumulation errors in DNA replication, leading to misincorporation of erroneous nucleotides , occurs at a rate of 1/10,000 to 1/100,000base pairs. p53 is a prototype Tumor suppressor gene, is the most common genetic leisions in all types of cancers. p53 mutation, prominently G-T transversion is observed in almost two-thirds of lung cancer, and is observed frequently in small cell carcinoma and squamous carcinoma of lungs. occur at a rate of 1/10,000 to 1/100,000 (CC, 1995) (MF, A, & GP, 1996). p16 is another tumor suppressor gene and critical member of the Rb pathway, is inactivated in over 40% of NSCLCs (SA, 1998). K-ras mutations are also observed in 30% of lung adenocarcinomas. (Westra WH, 1993). K-Ras mutations (mostly 12 G-T transversions) modulates the activation of ERK-MAP kinase in the airway epithelial cells, is found early in alveolar atypical hyperplasia. Cigarette smoking is the major risk factor in Lung cancers. It is responsible for DNA Adduct responsible for DNA adduct formation such as polycyclic aromatic hydrocarbons (PAH), aromatic amines, and tobacco-specific nitrosamines (NKK), which may escape the normal repair mechanisms, resulting in frameshift point mutations ,viz; conversion of G-C base pairs to T-A, which further leads to activation of K-ras and inactivation of p53 tumor suppressor gene (Hecht, 1999). Cancer cells are however characterised not just by mutations, but also by a significant no. of Chromosomal Aberrations. Loss of regions of chromosomes 3p21 and 9p21, deletions of chromosomal arm on 5q21 and mutations of p53 associated with LOH on 17p and K-ras point mutations are reported (Luc Thiberville, 1995). LOH on chr. 9 and 17 targets for p16 and p53 are also reported respectively. Copy Number abnormalities are well characterised by CGH Analysis and reports claim amplification of regions on chromosomal arms 1q, 3q, 5p, 8q, 11q, 12p, 17q and 20q, with ones on chromosomal region 3q26, being most frequent, followed by 3p deletion, closely followed by. 3q26 genes, ones being amplified are mostly candidate oncogenes (phosphatidylinositol-3 kinase catalytic subunit, PIK3CA) or are described to be involved in tumor progression including the somatostatin gene (SST), p63 (p53 homolog gene), telomerase RNA component gene (hTER), and neutral endopeptidase (NEP) (Massion PP, 2002).

Statistical analysis:

In both sexes combined, Lung cancer is the most commonly diagnosed cancer (11.6%) and also tops the list for the cancer deaths (18.4 %), followed by female breast cancer (11.6

%), prostate cancer (7.1%), colorectal cancer (6.1%) for incidence and colorectal cancer (9.2%), stomach cancer (8.2%), and liver cancer (8.2%) for mortality. Lung cancer is most frequent among males followed by prostate and colorectal for incidence and liver, stomach cancer for mortality. Reports : (Bray, Ferlay, Soerjomataram, Siegel, & Jemal, 2018).

Fig A.

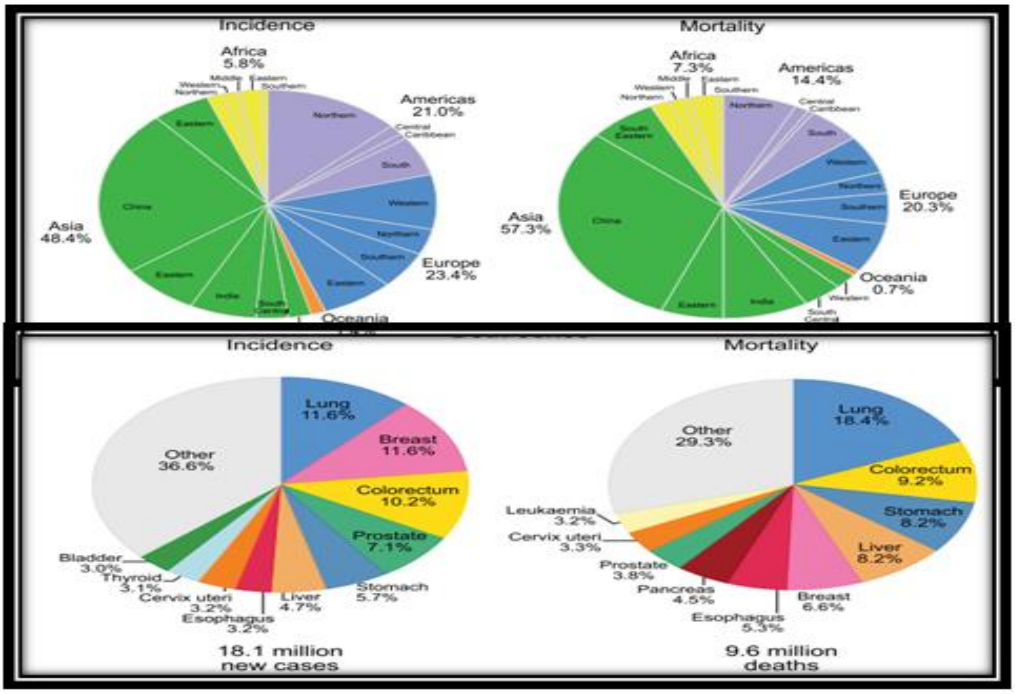

Fig. B.

Figure A : Piechart reflecting the area wise cancer distribution in 2018 (Both sexes)

Figure B : Piechart reflecting the Distribution of Cases and Deaths for the 10 Most Common Cancers in 2018 (Both sexes), GLOBOCAN 2018 Reports : (Bray, Ferlay, Soerjomataram, Siegel, & Jemal, 2018).

Conclusion:

Occurrence of Lung cancer taken it's worst possible shape and it takes no mention to say that's it's the most harrowing variant of Carcinomas in Humans. Smoking, particularly Tobacco is the biggest risk to Lung cancer. There are however several factors involved like age of initiation, years of smoking, total consumption that complements to the formation of a potential form of lung cancer, along with genetic predisposition factors etc, as per the 1964 Report of the U.S. Surgeon General. Cessation of smoking has shown considerable fall in the death and risks to lung cancer, suggesting that Lung cancer is also the most preventable of all cancer types (Darby, et al., 2000).

Reference :

1. Amos, C. I., Xu, W., & Spitz, M. R. (1999). Is There a Genetic Basis for Lung

Cancer Susceptibility? Recent Results in Cancer Research, (pp. 3-12).
2. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., & Jemal, R. L. (2018). Global Cancer Statistics 2018: GLOBOCAN Estimates. (68), 394–424. doi:doi: 10.3322/caac.21492
3. CC, H. (1995). 1995 Deichmann Lecture--p53 tumor suppressor gene: at the crossroads of molecular carcinogenesis, molecular epidemiology and cancer risk assessment. Toxicol Letter.
4. D.M , P. e. (2001, September 1). Cancer burden in the year 2000. The global picture. European Journal of Cancer, 4-66. doi:https://doi.org/10.1016/S0959-8049(01)00267-2
5. Darby, S., Peto, R., Silcocks, P., Deo, H., Whitley, E., & Doll, R. (2000). Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. 321-323.
6. E, B., & A, G. (2009). Pathogenesis of lung cancer signalling pathways: roadmap for therapies. European Respiratory Journal, 1485-1497. doi:10.1183/09031936.00014009
7. Hecht, S. S. (1999, July 21). Tobacco Smoke Carcinogens and Lung Cancer. JNCI: Journal of the National Cancer Institute, 91(14), 1194–1210. doi:https://doi.org/10.1093/jnci/91.14.1194
8. L, T., P, P., J, V., J, L., D, H., G, N., & S, P. B. (1995). Evidence of cumulative gene losses with progression of premalignant epithelial lesions to carcinoma of the bronchus. Cancer Res, 5133-5139.
9. Luc Thiberville, P. P. (1995). Evidence of Cumulative Gene Losses with Progression of Premalignant Epithelial Lesions to Carcinoma of the Bronchus. Cancer Research, 5133-5139.
10. Massion PP, K. W.-s. (2002, July 1). Genomic Copy Number Analysis of Non-small Cell Lung Cancer Using Array Comparative Genomic Hybridization. Cancer Research, 62(13), 3636-3640.
11. Massion, P. P., & Carbone, D. P. (2003). The molecular basis of lung cancer: molecular abnormalities and therapeutic implications. Respiratory Research.
12. MF, D., A, P., & GP, T. M. (1996). Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in P53. Science, 430-432.
13. Minna, J. D., Roth, J. A., & Gazdar, A. F. (n.d.). Focus on lung cancer.
14. SA, B. (1998). Role of the cytosine DNA-methyltransferase and p16INK4a genes in the development of mouse lung tumors. Exp Lung Res, 463-479.
15. SM, L., & MR, S. (2001). Lung cancer chemoprevention: an integrated approach. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology,.
16. Travis, W. D., & Rekhtman, N. (2011, April 15). Pathological Diagnosis and Classification of Lung Cancer in Small Biopsies and Cytology: Strategic Management of Tissue for Molecular Testing.
17. Travis, W., Brambilla, E., Schi, P. V., & Scagliotti, G. (2011). Paradigm shifts in lung cancer as defined in the new IASLC/ATS/ERS lung adenocarcinoma classification. European Respiratory Journal, 239-243. doi:10.1183/09031936.00026711
18. V, S., A, H.-P., N, C., Miozzo, S. G., R, B., . . . P, F. W. (1995). Somatic genetic changes in lung cancer and precancerous lesions. Ann Oncol., 27-31.
19. WD, T., E, B., & Mu¨ ller-Hermelink HK, e. a. (2004). Pathology and genetics:

tumours of the lung, pleura, thymus and heart. Lyon (France). IARC.

20. Westra WH, S. R. (1993). K-ras oncogene activation in lung adenocarcinomas from former smokers. Evidence that K-ras mutations are an early and irreversible event in the development of adenocarcinoma of the lung. Cancer, 432-438.

21. William D. Travis, M. (2011, December 1). Pathology of Lung Cancer. Clinics in Chest Medicine, 669-692. doi:https://doi.org/10.1016/j.ccm.2011.08.005