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Lung Cancer: Risk Factors, Management, And Prognosis

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Abstract: *Lung cancer or lung tumor the most common cause of cancer death in men and second most common in women after breast cancer. Highest rates in North America, Europe, and East Asia, with one third of new cases in China, lower rates in Africa and South Asia. Worldwide in 2012 lung cancer resulted in 1.6 million deaths. Risk factors include smoking, exposure to radon gas, asbestos, second-hand smoke, air pollution, and geneticfactors. Pathogenesis is similar to other cancers, by activation of oncogenes or inactivation of tumor suppressor genes. Two main types of lung cancer are small-cell lung carcinoma(SCLC),and non-small-cell lung carcinoma(NSCLC) Clinical manifestation include coughing, coughingblood, weight loss, weakness, fever or clubbing of the fingernails, hypercalcemia, myasthenia syndrome (muscle weakness), and metastases. Metastatic disease includes weight loss, bone pain and neurological symptoms. Diagnosis mainly by chest radiographs and computed tomography (CT) scans. Lung cancers are classified according to histological type, staging uses TNM (tumor, lymph node and metastases) system. Management depends on cancer specific type, by surgery, radiotherapy and chemotherapy. In the U.S 16.8% survive for at least five years, in England overall five year survival less than 10%.Prevention, cessation of smoking, screening for lung cancer for those long smoking history and between 55 and 80 years. Long term intake of vitamin A,vitamin vitamin D,or vitamin E does not reduce risk of lung cancer. Higher intake of vegetables and fruit tend to lower risk. There is no clear association between diet and lung cancer.*

Keywords: *Lungcancer,Riskfactors,Smoking,Airpollution,Chemotherapy.*

I. Introduction

Lung cancer or lung carcinoma is a malignant lung tumor characterized by uncontrolled cell growth in the lung tissues [1,2].The highest rates are in North America, Europe, and East Asia, with over a one third of new cases in China. The rates in Africa and South Asia are much lower[3].Worldwide in 2012,lung cancer occurred in 1.8 million people and resulted in 1.6 million deaths[4].This makes it the most common cause of cancer related death in men and second most common in women after breast cancer[5].Malaysian National Cancer Registry(2007) ,reported 1865 lung cancer cases with male 70.8% and female 29.2%[6].Contributory factors include long- term tobacco smoking(85%)[1],10 to 15% of cases occurred in people who have never smoked[7].These cases are often caused by a combination of factors and exposure to random gas, asbestos, second- hand smoke, or other forms of air pollution[8].The two main types of(cancer) are small –cell lung carcinoma(SCLC) and non-small-cell lung carcinoma(NSCLC)[9].The most common clinical manifestations are coughing (including coughing of blood),weight loss, shortness of breath and chest pain[10].Diagnosis mainly by chest radiographs and computed tomography(CT)scans[1].The diagnosis is confirmed with biopsy by bronchoscopy or CT-guidance [11].Common treatment include surgery, chemotherapy, and radiography[1]NSCLC is sometimes treated with surgery, whereas SCLC usually respond to chemotherapy and radiotherapy[12].Prevention by avoiding risk factors including smoking and air pollution[13].The paper describes current literature, risk factors, and management of lung cancer.

II. History and Epidemiology

Lung cancers was uncommon before the advent of cigarette smoking it was not even recognized as a distinct disease until 1761[14].Different aspects of lung cancer were described further in 1810 [15].Malignant tumors made up only 1% of all cancers at autopsy in 1878,but has risen to 10-15% by early 1900s[16].Case reports in the medical literature numbered only 374 worldwide in 1912[17],but a review of autopsies showed the incidence of lung cancer had increased from 0.3% in 1852 to 5.66 in 1952[18].In Germany in 1929,physician Fritz Lickint recognized the link between smoking and lung cancer[16],which led to an aggressive antismoking campaign [19].British Doctors' Study published in the 1950s,was the first solid epidemiological evidence of the link between lung cancer and smoking[20].As a result,in 1964 the Surgeon General of the United States

recommended smokers should stop smoking[21]. The connection between radongases was first recognized among miners in the Ore Mountains near Schneeberg, Sxony. Silver has been mined there since 1470,and these mines rich in uranium, with its accompanying radium and radon gas[22].Miners developed a disproportionate amount of lung disease, eventually recognized as lung cancer in 1870s[23].Radon was confirmed as a cause of lung cancer in the 1960s[24].

The first successful pneumonectomy for lung cancer was performed in 1933[25].Palliative radiotherapy has been used since 1940s[26].In 1997 continuous hyper- fractionated accelerated radiotherapy was seen as an improvement over conventional radical radiotherapy[27].With small-cell lung carcinoma initial attempts in the 1960s at surgical resection and radical radiotherapy[28,29],were successful. In the1970s successful chemotherapy regimens developed [30].

Epidemiology

Worldwide lung cancer is the most common cancer among men in terms of both incidence and mortality and among women has the third highest incidence, and is second after breast cancer mortality. In 2012, there were 1.82 million new cases and 1.56 million deaths due to lung cancer, representing 1904% of all deaths from cancer [5].The population segment most likely to develop lung cancer is people over 50 who have history of smoking. In contrast to the mortality rate in men, which began declining more than 20 years ago, women's lung cancer mortality rates have been rising over the last decades, and are just recently beginning to stabilize[31].In the USA, the life time risk of developing lung cancer in 8% in men and 6% in women[10].

For every 3-4 million cigarettes smoked, one lung cancer death occurs [32].The influence of "Big Tobacco "plays a significant role in the smoking culture[33].The role of passive smoking is increasingly being recognized as a risk factor for lung cancer[34].Emission from automobiles, factories, and power plants also pose potential risks[35].In the United States, black men and women have a higher incidence [36].Lung cancer rates are currently lower in developing countries[37]..With increased smoking in developing countries, the rates are expected to increase in next few years, notably in China and India [38,39].

In the United States military veterans have a 25-50% higher rate of lung cancer primarily due to higher rates of smoking [40].During the World War Two and the Korean War asbestos also played a part and Agent Orange may have caused some problems during the Vietnam War[41].Lung cancer is the second most common cancer in the UK(around 43,500 people were diagnosed with disease in 2011),and33,400 people died in 2012[42].From 1960s,the rates of lung adenocarcinoma started to rise relative to other types of lung cancer. This partly due to the introduction of filter cigarettes.The use of filters removes the larger particles from tobacco smoke, thus reducing deposition in larger airways. However smoker has to inhale more deeply to receive the same amount of nicotine, increasing particle deposit in small airways where adenocarcinoma tends to arise [43].The incidence of lung adenocarcinoma continues to rise [44].

III. Risk Factors

Cancer develops following genetic damage to DNA and epigenetic changes. These changes affect the normal functions of the cell, including cell proliferation, programmed cell death (apoptosis) and DNA repair. As more damage accumulates, the risk of cancer increases [45].

Smoking

Smoking, particularly of cigarettes, is far the main contributor to lung cancer [46].Cigarette smoke contains at least 73 known carcinogens, including benzo [α] pyrene [47,48].NNK,1,3-butadiene and a radioactive isotope of polonium,polonium-210[47].Across the developed world 90% of lung cancer deaths in men during the year 2000 were attributed to smoking(7)% for women)[49].Smoking accounts for 85% of lung cancer cases[1].Passive smoking-the inhalation of smoke from another's smoking is a cause of lung cancer in a nonsmokers. A passive smoker can be defined as someone living or working with a smoker. Studies from the US, Europe and UK[50,51,52]],have consistently shown a significant increased risk among those exposed to passive smoke[34].Those who live with someone who smokes have a 20-30% increase risk while those who work in an environment with secondhand smoke have 16-19% increase risk[53].Investigations of side stream smoke suggest it is more dangerous than direct smoke[54].Passive smoke causes about 3,400 deaths from lung cancer in the USA[50].Marijuana smoke contains many of the same carcinogens as those of tobacco smoke[55].However the effect of smoking cannabis on lung cancer is not clear[56].A 2014 review found that smoking cannabis doubled the risk of lung cancer[57].

Radon gas

Radon gas is a colorless and odorless gas generated by the breakdown of radioactive radium which in turn is the decay product of uranium, found in the Earth's crust. The radiation products ionize genetic material causing mutations that sometimes turn cancerous. Radon is the second-most common cause of lung cancer in the

USA[58],causing about 21,000 deaths each year[59].The risk increases 8-16% for every 100Bq/m^3 increase in the radon concentration[60].Radon gas levels vary by locality and the composition of the soil and rocks. About one in 15 homes has radon levels above the recommended guidelines of picocuries per liter(pCi/l)(148Bq/m^3)[61].

Air pollution and Asbestos

Outdoor air pollution has a small effect on increasing the risk of lung cancer[35].Fine particulates($PM_{2.5}$) and sulfate aerosols, which may be released in traffic exhaust fumes, are associated with highly increased risk[35].For nitrogen dioxide, an incremental increase of 10 parts per billion increases the risk of lung cancer by 14%[62].Outdoor air pollution is estimated to account for 1-2% of lung cancers[35].Tentative evidence supports an increased risk of lung cancer from indoor air pollution related to the burning of wood, charcoal, dung or crop residual for cooking and heating[63].Women are exposed to indoor coal smoke have twice the risk and number of the by-products of burning biomass are known or suspected carcinogens[64].The risk affects about 2.4 billion people globally[63],and is believed to account for 1.5% of lung cancer deaths[64].

Asbestos can cause a variety of lung diseases; including lung cancer. Tobacco smoking and asbestos have a synergistic effect on the formation of lung cancer[8].In smokers who work with asbestos, the risk of lung cancer is increased 45-fold compared to general population[65].Asbestos can also cause cancer of the pleura, called mesothelioma-which is different from lung cancer[66].

Genetics and miscellaneous risk factors

About 8% of lung cancer is due to inherited factors [67].In relatives of people with lung cancer, the risk is doubled. This is likely due to a combination of genes [68]. Polymorphism on chromosomes 5, 6, and 15 are known to affect the risk of lung cancer [69].Numerous other substances, occupations, and environmental exposures have been linked to lung cancer. The International Agency for Research on Cancer(IARC) states there is "sufficient evidence" to show the following are carcinogenic in the lungs[70]:

a) Metals-i.e., aluminumproduction, cadmium and cadmium compounds, chromium(VI) compounds, beryllium and berylliumcompounds,iron and steelfounding, nickelcompounds, arsenic and inorganic arsenic compounds, underground hematite mining.
b) Combustion products, incomplete combustion, coal(indoor emission from household coal burning)coal gasification, coal-tar pitch, coke production,soot,diesel engine exhaust)
c) Ionizing radiation (X-radiation, gammaradiation, plutonium).
d) Toxic gases (methyl ether(technical grade),Bis(chloromethyl) ether, sulfur mustard, MOPP(vincristine-prednisone –nitrogen n=mustard-procarbazine mixture)fumes from painting).
e) Rubber production and crystalline silica dust.

IV. Pathogenesis

Pathogenesis in lung cancer is similar to other cancers, lung is initiated by activation of oncogenes or inactivation of tumor suppressor genes[71].Carcinogens cause mutations in these genes which induce the development of cancer[72].Mutations in the *K-ras* proto-oncogene are responsible for 10-30% of lung adenocarcinomas[14].About 4% of non-small cell lung carcinomas involve an EML4-ALK tyrosine kinase fusion gene [73].Epigenetic changes-such as alteration of DNA methylation, histone tail modification, or micro RNA regulation-may lead to inactivation of tumor suppressor genes[74].

Epidermal growth factor receptor(EGFR) regulates cell proliferation, apoptosis, angiogenesis, and tumor invasion[14].Mutations and amplification of EGFR are common in non-small –cell lung carcinoma and provide the basis for treatment with EGFR-inhibitors,Her2/neu is affected less frequently[73].Other genes that are often mutated or amplified are c-MET,NKX2-1,LKBI,PIK3CA,and BRAF[14].

The cell lines of origin are not fully understood [10].The mechanism may involve abnormal activation of stem cells. In proximal airways, stem cells that express keratin 5 are more likely to be affected, typically leading to squamous-cell lung carcinoma. In middle airways, implicated stem cells include club cells and neuroepithelial cells that express club cell secretory protein. Small –cell lung carcinoma may be derived from these cell lines[75],or neuroendocrine cell[10],and may express CD44[76].Metastasis of lung cancer requires transition from epithelial to mesenchymal cell type. This may occur through activation of signaling pathways such as Akt/GSK3Beta,MEK-ERK,Fas and Par6 [76].

V. Clinical Manifestations

Clinical manifestations which may suggest lung cancer include: Respiratorysymptoms: coughing, coughingblood, wheezing sound or shortness of breath. Systemicsymptoms: weight loss,weakness, fever, or clubbing of the fingernails. Symptoms due to the cancer mass pressing or adjacent structures: chestpain, bonepain, superior vena cava obstruction, or difficulty in swallowing [10].If the cancer grows in the airways; it

may obstruct airflow, causing breathing difficulties. The obstruction can lead to accumulation of the secretions behind the blockage, and predispose pneumonia [10]. Depending on the type of tumor, paraneoplastic phenomena-symptoms not due to the local presence of cancer-may initially attract attention to the disease[77].In lung cancer, these phenomena may include hypercalcemia, syndrome of inappropriate antidiuretic hormone(SIADH,abnormally concentrated urine and diluted blood),ectopic ACTH production, or Lambert-Eaton myasthenia syndrome(muscle weakness due to autoantibodies).Tumors in the top of the lung know as Pancoast tumors, may invade the local part of the sympathetic nervous system, leading to Horner's syndrome(dropping of the eyelid and small pupil on that side),as well as damage to the bronchial plexus[10].

Many of the symptoms of lung cancer(poor appetite, weight loss ,fever, fatigue)are not specific[11].In many people, the cancer has already spread beyond the original site by the time they have symptoms and seek medical attention[78].Symptoms that suggest the presence of metastatic disease include weight loss, bone pain and neurological symptoms(headaches, fainting, convulsions, or limb weakness)[10].Common sites of spread include the brain ,bone, adrenal glands, opposite lung,liver,pericardium,and kidneys [78].About 10% of people with lung cancer do not have symptoms at diagnosis; these cancers are incidentally found on routine chest radiography[79].

VI. Diagnosis

Chest radiograph is one of the first investigative steps if a person reports symptoms that may suggest lung cancer. This may reveal an obvious mass, widening of the mediastinum (suggestive of spread to lymph nodes there), atelectasis (collapse), consolidation (pneumonia)or pleural effusion [1].CT imaging is typically used to provide more information about the type and extent of disease. Bronchoscopy or CT-guided biopsy is often used to sample the tumor for histopathology [79].Lung cancer often appears as a solitary pulmonary nodule on a chest radiograph. Many other disease can also give this appearance, including metastatic cancer, hamartomas, and infectious granulomas such as tuberculosis, histoplasmosis and coccidioidomycosis[80].Lung cancer can also be an incidental finding as a solitary pulmonary nodule on a chest radiograph or CT scan done for an unrelated reason[81].

Bai and associates concluded that tuberculosis in Asia favors lesser reliance on PET(position emission tomography) scanning and greater use of non-surgical biopsy over surgical diagnosis and surveillance[82].Chang and colleagues concluded that 90% of the screening-detected pure focal ground-glass opacity(GGO) lung nodules did not grow during long term follow-up in subjects with history of malignancy and most growing nodules had an indolent clinical course[83].The definitive diagnosis of lung cancer is based on histological examination of the suspicious tissues[10],in the context of the clinical and radiological features[11].Clinical practice guidelines recommend frequencies for pulmonary nodule surveillance[84]. CT imaging should be used for longer or more frequently than indicated as extended surveillance exposes people to increased radiation [84].

Lung cancer classification

Lung cancers are classified according to histological type[11].For therapeutic purposes, two broad classes are distinguished: non-small-cell lung carcinoma and small-cell lung carcinoma[85].The three main subtypes NSCLC are adenocarcinoma, squamous-cell carcinoma and large cell carcinoma[10,].Nearly 40% of lung cancers are adenocarcinoma, which usually originates in peripheral ling tissue[11].

Lung is a common place for spread of tumors from other parts the body. Secondary cancers are classified by the site of origin;e.g.,breast cancer that has spread to the lung is called metastatic breast cancer. Metastases often have a characteristic round appearance on chest radiograph [86].

Lung cancer staging

Lung cancer staging is an assessment of the degree of spread of the cancer from its original source [87].It is one of the factors affecting the prognosis and potential treatment of lung cancer[10].The evaluation of non-small-cell lung(NSCLC) staging uses the TNM(Tumor, lymph node, metastases).This is based on the size of the primary tumor, lymph node involvement and distant metastasis[10].Using the TNM descriptors, a group is assigned, ranging from occult cancer ,through stages 0,IA(one-A),IB,IIA,IIB,IIIA,III B,and IV9four).This stage group assists with choice of treatment and estimation of prognosis[88].For both NSCLC and SCLC,the two general types of staging evaluation are clinical and surgical staging. Clinical staging is performed prior to definitive surgery. It is based on the results of imaging studies (Such as CT scans and PET scans), and biopsy results. Surgical staging is evaluated either during or after the operation, and is based on the combined results of surgical and clinical findings, including surgical sampling of thoracic lymph nodes [[11].

VII. Management

Treatment for lung cancer depends on the cancer's specific type, how far it has spread, and the person's performance status. The common treatments include palliative care, surgery, chemotherapy, and radiation therapy[89,10].Targeted therapy of lung cancer is growing in importance for advanced lung cancer[90].

Surgery

In most cases of early-stage NSCLC,removal of a lobe of lung (lobectomy) is the surgical treatment of choice. In people who are unfit for a full lobectomy, a smaller sub lobarexcision (wedge resection) may be performed. Radioactive iodine brachytherapy at the margins of wedge excision may reduce the risk of recurrence. Rarely, removal of a whole lung (pneumonectomy) is performed [91].Video-assisted thoracoscopysurgery(VATS) and VATs lobectomy us a minimal invasive approach to lung cancer surgery[92].

Radiotherapy and Chemotherapy

Radiotherapy is often given together with chemotherapy, and may be used with curative intent in people with NSCLC who are not eligible for surgery. This form of high-intensity radiotherapy is called radical radiotherapy[93].A refinement of this technique is continuous hyper- fractionated accelerated radiotherapy(CHART), in which a high dose of radiotherapy is given in a short time period[94].Prophylactic cranial irradiation (PCI) is a type of radiotherapy to the brain, used to reduce the risk of metastasis[95].For both NSCLC and SCLC patients, smaller doses of radiation to the chest may be used for symptom control(palliative radiotherapy)[96].

Chemotherapy

Chemotherapy regimen depends on the tumor type[[11].Small-cell lung cancer(SCLC),even relatively early stage disease, is treated primarily with chemotherapy and radiation[97].In SCLC,cisplatin and etoposide are most commonly used [98].In advanced non-small-cell lung cancer(NSCLC),chemotherapy improves survival and is used as first-line treatment, provided the person is well for the treatment[99].Chemotherapy may be combined with palliative care in the treatment of the NSCLC. In advanced cases, appropriate chemotherapy improves average survival over supportive care alone, as well as improving quality of life [100].In targeted therapy, several drugs that target molecular pathways in lung cancer are available, especially for the treatment of advanced disease. Some of the drugs used in targeted therapy may be useful in the treatment of bone metastases [90].

VIII. Prognosis And Prevention

Of all people with lung cancer in the US,16.8% survive for at least five years after diagnosis[101].In England, between 2005 and 2009,overall five- year survival for lung cancer was less than 10%[102].Outcomes are generally worse in the developing world[103]. Prognostic factors in NSCLC include presence of pulmonary symptoms, large tumor size(>3cm),non-squamous cell type(histology),degree of spread(stage) and metastases to multiple lymph nodes, and vascular invasion. For people with inoperable disease, outcomesare worse in those with poor performance status and weight loss more than 10%[104].Prognostic factors in small cell lung cancer include performance status, gender, stage of disease, and involvement of the central nervous system or liver at the time of diagnosis[105].

Prevention

Smoking prevention and smoking cessation are effective ways of preventing the development of lung cancer [106].Policy interventions to decrease passive smoking in public areas such as restaurants and workplaces have become more common in many Westerncountries [107].The World Health Organization has called for governments to institute a total ban on tobacco advertisement to prevent young people from taking up smoking. They assess that such bans have reduced tobacco consumption by 16% where instituted [108].

Screening for lung cancer

For individuals with high risk of developing lung cancer computed tomography(CT) screening can detect cancer and give a person options to respond to it in a way that prolongs life[84].This form of screening reduces the chance of death from lung cancer by an absolute amount of0.3%(relative amount of 20%)[109].High risk people are those age 55-74 who have smoked equivalent of a pack of cigarettes daily for 30 years including time within the past years[84].CT screening is associated with a high rate of falsely positive tests which may result in unneeded treatment[110]. The U.S Preventive Services Task Force (USPSTF) recommends yearly screening using low- dose computed tomography in those who have a total smoking history of 30 pack-years and are between 55 and 80 years old until a person has not been smoking for more than 15 years[111].

Miscellaneous preventive measures

Long term use of supplemental vitamin A, vitamin C,vitamin D or vitamin E does not reduce the risk of lung cancer[112,113].Some studies suggest that people who eat diets with a higher proportions of vegetables and fruit tend to have lower risk[50],but this may be due to confounding-with the lower risk actually due to the association of a high fruit/vegetables diet with less smoking[114].More rigorous studies have not demonstrated a clear association between diet and lung cancer[10].

IX. Conclusions

Lung cancer is prevalent worldwide, and with high mortality. Smoking is the main risk factor. Prevention by avoiding risk factors, smoking and air pollution. Early detection has better outcomes.

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