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Overview of Lung Cancer, the Leading Cause of Cancer Deaths

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ABSTRACT
Lung cancer is one of the leading causes of death worldwide. In this paper, we address the details regarding lung cancer, one of the most prevalent types of cancer. Lung cancer is a type of cancer that originates in the lungs. Correspondingly, smokers have a higher chance than non-smokers of being afflicted. Diagnosis of lung cancer can be done through using tissue biopsy, whereas screening can be done through low-dose CT scan. Treatment however, is done differently depending on histology and which stage of lung cancer the patient is afflicted with. It is typically advised for individuals to avoid all types of smoking as basic prevention against lung cancer.

Keywords: Causes, Lung Cancer, Management, Non Small Cell Lung Cancer, Small Cell Lung Cancer, Smoking.

INTRODUCTION

One of the leading causes of death in the world, Cancer is reported to have caused over 9.6 million deaths in 2018 alone [1]. Cancer itself is a disease in which the cells of the body abnormally mutate and proliferate out of control. Often, these mutated cells join together and form lumps called tumors [2]. The severity of each patient is categorized based on how widespread the cancer is. For instance, cancer would be limited in one area for a patient at stage I. For a patient at stage IV, the cancer would have advanced to become advanced or metastatic cancer and has spread to many other parts of the patient's body [3].

Cancer is often categorized into many types depending on the source of its origin. Lung cancer, for instance, is a type of cancer that originates within the lungs and eventually forms tumors that hinders the patient's ability to breathe. As one of the most prevalent types of cancer, lung cancer accounts for 2.06 million deaths which is over 20 percent of all cancer deaths [1].

There are two distinct types of lung cancer: small cell lung cancer (SCLC), which always originates from the bronchus [4], and non-small cell lung cancer (NSCLC), which originate from lung tissues. Non-small cell lung cancer is comprised of three types of lung cancer, being adenocarcinomas, squamous cell carcinomas (epidermoid carcinomas, SqCC), and large cell carcinomas, and make up 80-85% of lung cancer cases [5]. Small cell lung cancer, though less common, making up 10-15% of lung cancer cases, is much more deadly and is mostly found in patients that smoke [4].

Adenocarcinoma is the most common type of lung cancer amongst non-smokers and smokers and amongst men and women of all ages, comprising of around 40% of all cancer types. It arises in small airway epithelial, or type II alveolar cells in charge of secreting mucus and other substances, and tends to occur in the periphery of the lung [6].

Squamous cell carcinoma arises from squamous cells in the airway epithelial cells in the bronchial tubes in the center of the lung and accounts for 25-30% of all cancer cases [6]. This subtype of NSCLC is found to be strongly correlated with heavy smoking [7].

Large cell carcinoma, on the other hand, is undifferentiated NSCLC without light microscopic evidence of squamous or glandular differentiation [8] and comprises of 5–10% of lung cancers [6].

ETIOLOGY

A majority of lung cancer cases (85% of NSCLC and 98% of SCLC) arise in smokers [2]. Factors such as the quantity of cigarette consumption, the age of onset of smoking, the degree of inhalation, the tar and nicotine content of cigarettes, and use of unfiltered cigarettes are found to be proportional to the risk of lung cancer [9]. Amongst 5,000 compounds present in cigarette smoke, 73 carcinogens in total are inducers of lung cancer [10]. The major carcinogens in tobacco smoke include polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, volatile nitrosamines, aromatic amines, aldehydes, volatile hydrocarbons such as benzene and 1,3-butadiene, miscellaneous other organic compounds, metals, and the radioelement ^{210}Po [11]. The metabolism of tobacco carcinogens is mainly catalyzed by the enzyme cytochrome P450, where the products covalently bind with deoxyribonucleic acid (DNA) and form DNA adducts in a process called metabolic activation.

Metabolic detoxification, on the other hand, involves converting carcinogens into harmless, readily excretable forms using the following enzymes: glutathione-S-transferases (GSTs), uridine-5′-diphosphate-glucuronosyltransferases (UGTs), epoxide hydrolases, and sulfatases. Cancer susceptibility is largely determined by one's balance between metabolic activation and metabolic detoxification. Hence, a higher risk of smoking-induced lung cancer is associated with high activation and detoxification capacity [12].

There are, however, almost 25 percent of never-smokers that developed lung cancer. The term never-smokers is defined by the U.S. Centers for Disease Control defines as someone who has smoked < 100 cigarettes per lifetime [13]. Due to its different tumorigenic pattern, clinicopathology, and history, lung cancer in never smokers is regarded as a separate entity from smoking-related lung cancer [14]. While SCLC and squamous cell carcinoma is more common in smokers, adenocarcinoma of the lung is more common in non-smokers (62% vs 18%, based on 5144 cases) [2,9].

Evidence gathered from multiple sources suggest a causal relationship between lung cancer and second hand smoke exposure, exposure to radon, indoor air pollution (combustion of coal or solid fuel for cooking), and other exogenous ionizing radiation exposures, as well [15].

The true cause of lung cancer, just like other types of cancer, is mutation in critical genes, specifically those that control cell growth and proliferation or the repair of damaged DNA. In 2010, The Cancer Genome Atlas (TCGA) initiated large-scale comprehensive molecular profiling of 230 cases of lung adenocarcinoma and 178 cases of squamous cell carcinoma using high-throughput sequencing techniques to identify detailed molecular profiles of lung cancer. High rate of somatic mutations in 18 oncogenes and tumor suppressor genes have been identified, including the following: TP53 (46%), KRAS (33%), KEAP1 (17%), STK11 (17%), EGFR (14%), NF1 (11%), BRAF (10%), SETD2 (9%), RBM10 (8%), MGA (8%), MET (7%), ARID1A (7%), PIK3CA (7%), SMARCA4 (6%), RB1 (4%), CDKN2A (4%), U2AF1 (3%), and RIT1 (2%). Approximately 75% of lung adenocarcinomas examined contained genetic alterations that promote the RTK/RAS/RAF signaling pathway. Of these cases, 62% display driver genetic alterations that promote the RTK/RAS/RAF pathway. Mutations in KRAS, EGFR, and BRAF comprised 32, 11, and 7.0% respectively out of the total driver genetic alterations. There are other genetic alterations that make up the rest of the driver genetic alterations, including the MET exon 14 skipping (4.3%), ERBB2 (or HER2) mutation (1.7%), ROS1 fusion (1.7%), ALK fusion (1.3%), MAP2K1 mutation (0.9%), RET fusion (0.9%), NRAS mutation (0.4%), and HRAS mutation (0.4%). As for the remaining 38% without driver genetic alterations, amplification of oncogenes in the RTK/RAS/RAF pathway such as ERBB2 amplification (0.9%) and MET amplification (2.2%) have been found to promote the RTK/RAS/RAF signaling pathway [16].

360 exonic mutations, 165 genomic rearrangements, and 323 segments of copy number alterations per tumor have been identified for the 178 cases of squamous cell carcinoma. This includes genetic mutations in TP53, CDKN2A, PTEN, PIK3CA, KEAP1, MLL2, HLA-A, NFE2L2, NOTCH1, RB1,

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and PDYN. TP53 mutations are the most common with the frequency of 90% [16].

Lastly, the genetic alteration in SCLC largely differs from NSCLC as they are highly complex. Comprehensive genomic analysis by Rudin et al. identifies SOX2 as a frequently amplified gene in small-cell lung cancer. In a sequencing project of 110 genomes, George et. al observes that almost all examined SCLCs involves bi-allelic inactivation of TP53 and RB1. C:G>A:T transversions found in 28% of all mutations on average indicates heavy smoking, which characterizes a trait of SCLC patients, as well [17,18].

PATHOPHISIOLOGY

Lung cancer is caused by carcinogen presence in the lungs, followed by the progression and spread of the cancer [19]. First, the cancer cell mutates. These mutated cells then form lumps of mass called tumors, neoplasms, or lesions. These can be separated into the two aforementioned types SCLC and NSCLC depending on the morphology or histology. The former usually form in central tumors while the latter form both peripheral and central tumors.

Cancer then spreads to other parts of the body through a process called metastasis. While SCLC undergoes metastasis at a faster rate than NSCLC, both do so in similar fashion. The lung cancer first metastasizes to lymph nodes around the lungs near the mutated cell. Then, it may spread to other parts of the body such as the brain, liver, and bone through the bloodstream [20,21].

The extent of this spread may be measured through tumor, node, and metastasis (TNM) staging. The T in TNM indicates the area of the cancer and the size of the tumor. This is measured in five categories from T0 - T4 where T0 indicates no cancer cells are found, T1 indicates that the cancer has only infected the lungs. T2 indicates that the cancer either has a radius of 3 - 5 cm, infects the main bronchus or the visceral pleura, and/or shows an atelectasis or obstructive pneumonitis that extends to the hilum. T3 indicates that the cancer has a radius of 5 to 7 cm, has two or more tumors in the same lung lobe, invades the chest wall, invades the pericardium, invades the phrenic nerve, and/or shows one or more satellite nodules in the same lung lobe. T4 indicates that the cancer has a radius over 7 cm or has spread to places other than the initial lobe [22].

N-staging, on the other hand, describes whether the cancer has spread to lymph nodes or not [21]. N1 nodes represent ipsilateral nodes within the lung up to hilar nodes; N2 nodes represent ipsilateral mediastinal or subcarinal lymphadenopathy, and N3 nodes represent contralateral mediastinal, contralateral hilar lymphadenopathy, scalene or supraclavicular nodes.

Lastly, M staging describes whether the cancer has spread to a different part of the body. M0 indicates that there is no distant metastasis, while M1 indicates that there is distant metastasis. M1 is divided into three categories, with M1a indicating regional metastatic disease (malignant pleural or pericardial effusion/nodules and contralateral or bilateral pulmonary nodules), M1b indicating solitary extrathoracic metastasis, and M1c indicating multiple extrathoracic metastases [22, 23].

SCREENING

Lung screening is advised for patients at risk of being afflicted with lung cancer. These patients include people who are heavy smokers, have been smoking for a prolonged period of time [24], or those who are frequently exposed to second hand and third hand smoking.

In the past, lung cancer screening can be done through CT (Computerized Tomography) scan. It must be noted however, that using CT screening for lung cancer is not guaranteed to be effective. In fact, a study done by Richard Saitz records that the risk for a false-positive result was 33% for those undergoing CT group. In total, only one to two percent of all participants in the study had positive results [25].

Therefore, the technique of low-dose CT was developed. Investigation should include helical low-dose computed tomography (also called LDCT), where an x-ray machine scans the body in a spiral path and uses low doses of radiation to produce detailed pictures of the lungs [26]. Compared to a conventional chest CT scan, LDCT proves to be more effective in terms of detecting lung cancer and exposes the patient to less radiation within a shorter time period [23]. If a nodule, or a small, approximately spherical, circumscribed focus of

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abnormal tissue, then further examination may be recommended upon the doctor's consideration [27].

The landmark trial of lung cancer screening is the National Lung Screening Trial (NLST), which is a randomized multicenter study conducted to compare the effects of screening for lung cancer using LDCT and chest radiography. This trial was launched in September 2002, involving 53,456 participants who were deemed eligible based on the criteria of being around 55-74 years, being a former smoker who quit smoking within the past 15 years, having more than 30 or more pack-years of cigarette smoking history, and having the ability to lie on the back with arms raised over the head [28]. After participants were randomly assigned to undergo three annual screenings with either low-dose CT (26,722 participants) or single-view posteroanterior chest radiography (26,732 participants), data was collected on the cases of lung cancer and the number of deaths from lung cancer until December 2009. It was concluded that LDCT indeed lowered the mortality rate of lung cancer by 6.7 % in comparison to the chest radiography group [29].

Management after nodule detection is determined by categorization of the nodule, which includes two main types: solid or subsolid nodule, the latter further subdivided into semi-solid and ground glass nodule. Solid nodules have 7 – 11% chance of malignancy, semi-solid nodule a 48 – 63% chance of malignancy, and ground glass nodule an 18 – 59% chance of malignancy [30].

MANAGEMENT

A treatment option for lung cancer includes surgery, chemotherapy, targeted therapy, radiation treatments, and immunotherapy. With regards to lung cancer, the details on each of the aforementioned treatment are as listed below [31].

Surgery - Treatment involves making incisions to remove cancer cells. There are many types of surgery such as pneumonectomy which removes the entire lungs, lobectomy, which removes one of the five lobes of the lungs, and segmentectomy, where only part of a lobe is removed.

Chemotherapy - Treatment includes injecting or ingesting drugs, targeted at cancer, which enter the bloodstream and goes throughout the body. Drugs such as cisplatin, carboplatin, docetaxel, nab-paclitaxel, gemcitabine, pemetrexed, and paclitaxel are often used for chemotherapeutic treatment of NSCLC [32]. The specific regimen depends on the setting of the treatment, as chemotherapy is further subdivided into neoadjuvant chemotherapy (delivered before primary treatment), adjuvant chemotherapy (delivered after primary treatment) and palliative chemotherapy (common in stage IV cancer).

Radiation Therapy - Treatment attempts to use high frequency and energy rays to eliminate cancer cells.

Depending on the stage and type, treatment options for lung cancer may include one or a combination of these different methods.

For **stage 1** NSCLC patients, part of the lung may be removed through sleeve resection, segmentectomy, wedge resection, or one lobe with the tumor may be removed through lobectomy with lymph node dissection. Adjunctive Chemotherapy may also be recommended depending on the risk of recurrence [33].

For **stage 2** NSCLC patients, surgery is done to remove any lymph nodes at risk if the patient is healthy enough, or the entire lung may be removed (pneumonectomy). The tissue removed is then checked to see if there are any signs of cancer spreading in areas not removed.

For **stage 3A** NSCLC patients, a combination of surgery, chemotherapy, and radiation treatments may be needed. However, if the patient has stage 3B lung cancer, they cannot be treated through surgery as the cancer has spread to important lymph nodes in the neck or chest. Radiotherapy then becomes the preferred treatment.

For **stage 4** NSCLC patients, treatment includes chemotherapy, radiation therapy, and medicine which targets the blood vessels and blocks the growth of cancer cells is applied [34].

Besides from the use of empirical chemotherapy with a platinum-doublet as the standard treatment method, **targeted therapy** is also currently used and developed in hopes of improving NSCLC patient outcomes and quality of life. Identification and inhibition of signaling pathways triggered by mutations in oncogenic drivers, epigenetic mutations, and tumor-suppressor-gene inactivation has proved to be an effective focus for successful targeted therapy

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[45]. For this reason, patients are screened for biomarkers that could serve as potential molecular targets in tumors. Two of the common agents are mutations in EGFR and ALK genes. Epidermal growth factor receptor, or EGFR, is a cell-surface tyrosine receptor which, when overexpressed, can result in carcinomas and accelerated tumor progression [36]. Tyrosine kinase inhibitors, such as gefitinib, afatinib, erlotinib, may be used to inhibit mutant EGFR at the intracellular domain, whereas monoclonal antibodies may be used to inhibit EGFR at the extracellular domain. Anaplastic lymphoma kinase (ALK) rearrangements, on the other hand, can be inhibited using crizotinib, ceritinib, and alectinib [37]. Angiogenesis, or the formation of new blood vessels in order to transport nutrients and oxygen to the tumor, may also be inhibited with targeted therapy drugs. Benvacizumab and Ramucirumab, for example, inhibit Vascular Endothelial growth factor (VEGF), which stops the growth of blood vessels to feed the tumor [38].

Immunotherapy also proves to be another option for those with advanced NSCLC, as it is used to stimulate a person's own immune system to recognize and destroy cancer cells. Drugs such as Nivolumab (Opdivo) and pembrolizumab (Keytruda) are used to block PD-1, a protein which normally prevents T cells from attacking other body cells, whereas drugs like Atezolizumab (Tecentriq) are used to block PD-L1, a protein that is found on tumor and immune cells, to boost immune response [39].

Treatment for SCLC is similar to NSCLC in many aspects, but different in that it is highly aggressive and is typically characterized by a high proliferation rate and early metastasis [40]. The two main categorization includes Limited Disease (LD), which is made up of TNM stages I, II, and III and Extensive Disease (ED), which is made up of stage IV.

Treatment of **LD (stages I, II, and III)** involves a combination of chemotherapy and thoracic irradiation rather than the typical unimodal chemotherapy, as it diminishes local relapse and improves overall survival (OS) [41, 42, 43, 44]. Various studies support this and show how concurrent chemo-radiation combined followed by an early start of radiotherapy (after the first or second cycles), serves as a better disease control than the sequential modality [40]. One downfall of this bimodal treatment model is the development of chemo-resistant and radiation-resistant clones, which could consequently lead to an increase in tumor cell population [45]. The recommended regimen usually includes 4 cycles of platinum-based chemotherapy, with Cisplatin administered when possible. If the patient is not a candidate for Cisplatin, Carboplatin is another available option [46].

Treatment of **ED (stage IV)** typically includes the use of systemic chemotherapy with palliative intent [47]. 4-6 cycles of platinum-based chemotherapy, such as Cisplatin and Etoposide, are recommended.

There is a high chance of patients relapsing even after an effective platinum-based first line. Usually, the efficacy of second line treatment depends on the time of relapse and progression, which is <10% response for three months interval or less and 25% response for over three months.

PREVENTION

As the majority of lung cancer cases stem from smoking [1], not engaging cigarette smoking or similar inhalation practices (marijuana, hookahs, cigars, etc.) is a good first step in preventing the formation of lung tumors. This, however, is not limited to just firsthand smoking. Second hand smoking is just as dangerous as first hand smoking, as essentially the same chemicals are being inhaled by both people [48]. Third hand smoking, though not as damaging, can still increase the chances of developing cancer [49]. As such, it is best to avoid all forms of smoking, whether intentional or inadvertent.

Additionally, overexposure to various carcinogens also carry a chance of developing cancer. Currently, there are 150 substances classified as known or probable carcinogens, with 8 of them being identified as lung-targeting carcinogens (arsenic, asbestos, beryllium, cadmium, chromium, diesel fumes, nickel and silica) [23]. Additionally, other chemicals such as radon are also known to be carcinogenic, and with radon being in a gaseous state, there is a threat of causing lung cancer [50]. Carcinogens can be generally described as an agent that can cause cancer in humans [51]. Though chemicals like arsenic and radon are usually low in quantity, it is commonly advised to check for these carcinogens in one's house and workplace.

CONCLUSION

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Despite advancements in medical technology and new techniques such as immunotherapy and targeted therapy, curing lung cancer still proves to be a challenge. This is especially so at the later stages. In order to best combat lung cancer, one should instead attempt to lower the probability of being afflicted through prevention methods such as refraining from smoking. Nevertheless, medical technology is progressing rapidly and progress is being made with cancer research. Combined with adequate awareness campaigns, the current problem on lung cancer can be alleviated.

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