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A Systematic Review on Lung Cancer and its Evolutionary Challenges in the Emerging Future

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ABSTRACT

Lung cancer incidence has dramatically risen in the past decades. It is one of the most common malignancies worldwide and a leading cause of cancer-related deaths both among men and women. Approximately 1.5 million people worldwide die from lung cancer every year. The disease has an extremely poor prognosis and there has been no noticed improvement in the 5-year survival rate in the last 30 years. Unfortunately currently available treatments do not prevent the progressiveness of the disease. There has been lack of optimism regarding treatment advances in the last ten years, and progress in treating or predicting the risk for lung cancer has been very slow. The present review discusses about the lung cancer, its stages and causes and the preventive steps to be taken to challenge the relentless progression of the disease.

Lung Cancer

Lung cancer is the leading cause of cancer death due to insufficient therapeutic options, which resulted in the equaling of morbidity with mortality rates and causing an unsolved health problem [1-3]. It is one of the most common malignancies in the US and worldwide and a leading cause of cancer-related deaths.

It is a disease that occurs due to unwanted growth in tissues of the lung. The growth which spreads beyond the lung is a process known as metastasis and it can also spread into other parts of the body [4,5]. Most cancers that begin its growth in lung are known as carcinomas and are derived from

epithelial cells. If uncontrolled growth can be detected successfully at early stages, it helps to proceed with many treatment options, which reduces risk of invasive surgery and increased survival rate [6-8]. Possible treatments of the disseminated disease include surgery, chemotherapy, and radiotherapy. Survival of the patient depends on stage, overall health, and other factors, but overall only 14% of people who are diagnosed with lung cancer can survive only for five years after their diagnosis [9].

Lung cancer basically consists of heterogeneous groups in terms of pathological features and is classified into two major types namely [10],

- Small Cell Lung Carcinoma (SCLC) and
- Non-Small Cell Lung Carcinoma (NSCLC).

NSCLC includes squamous cell carcinoma and adenocarcinoma. Vascular Endothelial Growth Factor (VEGF) and Basic Fibroblast Growth Factor (BFGF) produced by Non-Small Cell Lung Carcinoma (NSCLC) [11-13]. VEGF is known to promote the vascularization and growth of the tumor through mobilizing circulating endothelial cell precursors to the nascent blood vessels and plays a major role in establishing new metastatic foci. BFGF in addition to its involvement in tumor growth may have the potential to predict early-stage NSCLC recurrence following tumor resection [14-17].

Among the neuroendocrine tumors which constitute approximately 20% of lung cancers, SCLC comprises the majority of cases. It is a highly malignant tumor and originates from neuroendocrine cells (Amine Precursor Uptake and Decarboxylation/APUD cells) [18] of the bronchus called Feyrter cells and in addition to its rapid growth, early dissemination and progression to drug resistance after successful first-line therapy treatment of SCLC has very limited efficacy [19-22]. Lung cancer is the most preventable cancer worldwide owing to the fact that the fore-most and predominant risk factor is tobacco consumption and along with men, women are also increasingly being affected [23-25]. Non-neuroendocrine lung tumors which are known as non-SCLC (NSCLC), including adenocarcinoma, squamous cell carcinoma and large cell carcinoma, differ by a lower growth fraction and aggressiveness from SCLC [26-28].

Characterized Symptoms of Lung Cancer

Lung cancer is generally characterized and can be detected by some symptoms which include:

1. Coughing, especially if it persists or becomes intense
2. Pain in the chest, shoulder, or back unrelated to pain from coughing [30]
3. A change in color and volume of sputum
4. Shortness of breathing
5. Changes in the voice or hoarseness [31]
6. Harsh sounds with each breath (stridor)
7. Recurrence of lung problems, such as bronchitis or pneumonia
8. Coughing up phlegm or mucus, especially if it is with blood
9. Coughing up blood

The above symptoms are usually observed in the chest and the following symptoms may occur elsewhere in the body:

1. Loss of appetite or unexplained weight loss
2. Cachexia [33]
3. Fatigue
4. Headache, bone or joint pain
5. Bone fractures
6. Neurological symptoms [34], such as unsteady gait or memory loss
7. Neck or facial swelling
8. General weakness
9. Bleeding
10. Blood clots

Cancer Stem Cells- Origin

It is believed that the existence of Cancer Stem Cells (CSCs) [35-37] within the tumors is a responsible factor for the majority of biological characteristics that are associated with the severity of tumors/ cancer cells [38]. A CSC theory proposes that a tumor cell subpopulation has self-renewal capacity, cancer-initiating ability and multi-potent differentiation ability. In recent years, many experimental evidences came into prevalence in support of the role of CSCs [39]. There are many concepts in cancer which can be explained by the stem cell theory like tumor self-renewal, tumor heterogeneity, and tumor relapse after treatment and resistance to conventional chemotherapies. CSCs were firstly described in human hematopoietic cancer [40-42].

According to a debated concept, CSCs are generally known as rare population of undifferentiated cells driving tumor initiation, maintenance and spreading [43]. CSCs tend to have unlimited proliferation potential, self-renewal ability and capacity to generate a progeny of differentiated cells, responsible for the major tumor populations [44]. Cells which resemble CSCs' characteristics have been detected from leukemia, and a wide range of solid tumors, which include melanoma, breast, prostate, pancreatic, and colon carcinomas. These cells have the tendency to expand in vitro as tumor spheres, like mamma- and neurospheres, and produce original tumors in immunodeficient mice at lower cell numbers than the unfractionated tumor cell population [45-47]. Brain, hematopoietic, prostate and colon cancer CSCs feature the membrane antigen CD133, whose expression is shared by normal stem cells of different lineages [48].

The origin of CSCs is still a hot topic which is widely being discussed. One theory is the malignant transformation of normal stem cells particularly in rapidly dividing tissues, where the stem cell is available throughout life and it might undergo different mutations [49].

In a combined model of complex tumor development integrating the stochastic and CSC model, genetically distinct CSCs are known to exist on top of each heterogenous tumor subclone [50, 51]. Most therapies are targeted at the bulk of rapidly dividing tumor cells but not the slowly dividing CSCs. CSCs are well-resistant to both radiation therapy and chemotherapy, and, therefore, this subpopulation persists following therapy being responsible for relapses which occur in some cases [52-55]. The CSCs' resistance to therapy is a complex, multistep process that occurs with the short-term, inherent plasticity of subpopulations of cancer cells. The cytotoxic stimuli which results from inhibiting a target can result in enhanced expression/activity of stemness factors in the persisting subpopulations of cells [56-58]. These stemness factors results in genetic plasticity that allows these cells to remain in a dormant, drug-tolerant state. Since the role of CSCs is still not well established, these cells are also alluded to as tumor initiating cells [TICs], cancer initiating cells [CICs] and tumor propagating cells [TPCs] [59,60].

Recently, independent studies using lineage-tracing technique in mouse models have proposed the existence of CSCs in brain, skin and intestinal tumors [61-64]. Eradicating CSCs, in addition or instead of the fast growing tumor mass seems to constitute a promising approach to achieve a long-lasting response and thereby improving cancer therapy. Therefore, studies looked at the cell response to injury as a means to find if the stem cell characteristics can be characterized [65-68].

Stem cell populations are established in niches, which resemble the microenvironment that interacts with stem cells to regulate stem cell self-renewal and differentiation [69]. It remains unexplained whether CSCs form their own microenvironment/niches or depend on the pre-existing tissue environment. The solid microenvironment is composed of different mesenchymal cell types which are recruited by cancer cells to enhance their survival, growth, invasion and dissemination [70,71]. These include endothelial cells of the blood and lymphatic circulation, inflammatory cells, fibroblasts and others. Fibroblasts produce different chemokines that modulate tumor expansion, invasion, angiogenesis, and activation of extracellular matrix associated cytokines and growth factors. Some of them are commonly associated with self-renewal [72-75].

Lung Cancer- Diagnosis and Treatment

Computed tomography (CT) and Positron Emission Tomography (PET) are able to define the level of the disease, both anatomically & functionally. PET and CT are the two medical imaging techniques which are used to find out affected part in accurate manner [76-79].

The existing system shows how PET/CT was used to detect the lung cancer and various ways for managing the respiratory motion in medical manner [80]. It also explains the workflow of the imaging technique. Algorithms are not used in the existing system. Two concepts are combinedly integrated into patient-specific workflows i.e. are PET/CT guided radiotherapy and motion managed radiotherapy [81-83]. A scanned image of PET/CT is shown in the figure 1 for example [84]. Imaging with PET/CT becomes a standard care in the lung cancer staging, but it is still underused in its direct integration to therapy planning. The most frequent application of PET and CT to lung cancer patient care is used for diagnosis and also to know the stages of the disease in accurate and precise manner [85-87].

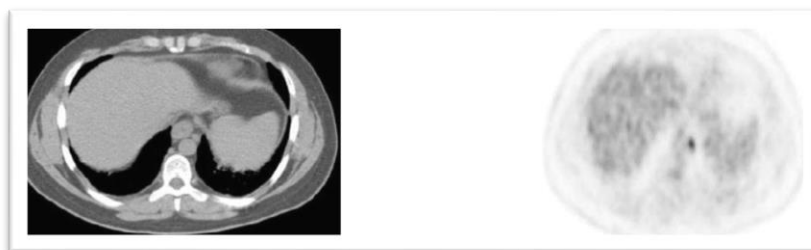


Figure 1: CT and PET scan image

In patients with SCLC, combination chemotherapy produces results that are clearly superior to single-agent treatment with objective response rates of 65 to 90% and total response rates ranging from 45 to 75% [88-90]. A combination of etoposide and cisplatin/carboplatin chemotherapy with concurrent chest irradiation is standard and achieves median survivals of 18 to 24 months and 40% to 50% ranging of 2-year survival with less than a 3% treatment-related mortality [91-93]. The prognosis for patients with relapsing SCLC is exceedingly poor, with expected survival between 2 to 3 months. Topotecan [94] is the sole approved chemotherapeutic drug for second line treatment of SCLC prolonging live for several months. In summary, the treatment of SCLC is characterized by extremely short survival rates in advanced disease, that have been not seen much improvement in the past years [95,96].

Patients are currently diagnosed with lung cancer when their disease is fairly in an advanced stage, a condition where they begin to experience symptoms. Unfortunately, at this stage, surgery or radiotherapy is usually not viable options, and chemotherapy is usually commenced. The importance of prediction of lung cancer at an early stage is therefore of utmost and primary importance. Other potential targeted therapies are under investigation which includes BRAF, HER-2, c-KIT and EML4-ALK [97]. Emerging genetic markers of lung cancer risk have also been reported. From the numerous studies that have emerged over the past decade, a Single Nucleotide Polymorphism (SNP) at chromosome 13q31.3, and Endothelial Growth Factor, EGF=61 A>G polymorphisms [98] have emerged as promising markers of NSLC risk, but further studies are required. To offer the most effective targeted therapy for the lung cancer, it is now essential to sub-classify NSLC and perform molecular analyses. In terms of the rapid recurrence of SCLC after primary therapy 99, this tumor entity is ideally suited to test clinical efficacy of CSC-directed therapies [100] in combination with the elimination of the tumor bulk using conventional chemotherapy.

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