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# Stem Cell Therapies for Lung Cancer Patients with a History of Tobacco Use

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**Abstract**

Lung cancer is the most commonly diagnosed cancer in both men and women. There are two main types of lung cancer, small cell carcinoma, and non-small cell carcinoma. Non-small cell carcinoma is more common and less aggressive than small cell carcinoma. Lung cancer is more commonly diagnosed in its later stages, making it harder to treat in the long run. The leading cause of small cell carcinoma is smoking and using tobacco products. The current treatments generally do not have a high success rate, specifically for patients with small cell lung cancer. A new treatment method that can change the course of cancer treatment in the future: stem cell therapy. Stem cell therapy can repair the lungs of small cell carcinoma patients and provide them with the needed cells for their lungs to return to normal function. The stem cells would be removed from the skin or blood of the patient and genetically transformed into embryonic stem cells, which provide more utility for the stem cells in the body. Once they are modified, these stem cells can be transferred to the body through in vitro scaffolds, tissue-engineered scaffolds, and local injections. After the transfer has occurred, the stem cells would be able to rebuild the lungs and help the body return to normal conditions.

*Keywords: Lungs, Cancer, Stem Cells, Tobacco, Smoking*

## 1. Introduction/Background

Lung cancer is caused by a malignant tumor that is formed in the bronchi, bronchioles, or alveolus of the lung. Many lung cancer patients experience symptoms in the later stages of the disease's development and may experience perpetual coughing with blood and phlegm along with a lack of energy and constant fatigue. For over 70 years, lung cancer has been the most common cancer between both women and men, with breast cancer being the most frequently diagnosed cancer among women and prostate cancer being common among men. Once diagnosed with this cancer, only 40% of patients survive for a year or more and only 15% are able to survive for 5 years or more (American Cancer Society, 2022). This is because lung cancer is more commonly diagnosed in the later stages of development, making it harder to treat. In 2022, there are estimated to be 236,740 more cases of lung cancer and 130,180 deaths from lung cancer in the United States. As shown in Figure 1, lung cancer makes up 25% of all cancer deaths, being higher than the breast, colon, and prostate cancer deaths combined. Lung cancer is more frequently diagnosed in patients that are 65 years old and older. (American Cancer Society, 2022).

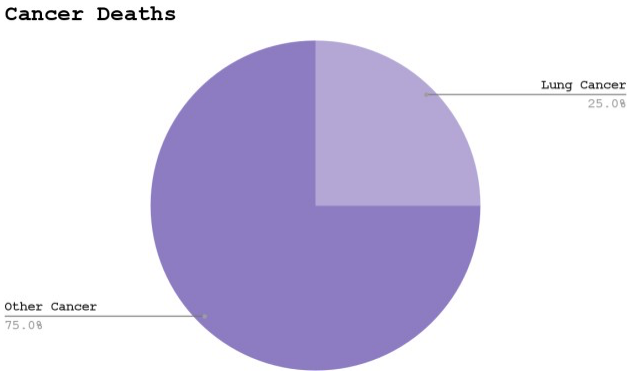


Figure 1. This image models the percentage of cancer deaths that are associated with lung cancer compared to other cancers.

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### 1.1 Types of Lung Cancer

There are two main types of lung cancer, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Small cell lung cancer, or small cell carcinoma, begins in the bronchi, where it rapidly grows and spreads throughout the entire body. On the other hand, non-small cell lung cancer is usually less aggressive than small cell carcinoma and is divided into three main groups, adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (Spiro and Silvestri, 2005). All three types of non- small cell lung cancer spread moderately compared to small cell lung cancer and occur in different parts of the lung. While non-small cell carcinoma can occur to anyone, small cell carcinoma is caused from smoking and is in more need of a cure due to its aggressive nature. This review will focus on the treatment of small cell carcinoma, as it is directly connected with smoking and has a high mortality rate.

### 1.2 Smoking and its Impacts

Smoking is known to be the main cause of small cell carcinoma because of the many carcinogens, or cancer-causing agents, located inside a single cigarette. There is a total of 7,000 chemicals found in one cigarette, with 70 of these chemicals known to be carcinogens. Examples of such carcinogens are benzene, aldehydes, ethylene oxide, aromatic amines, and N-nitrosamines. When these chemicals are inhaled into the body and transported through the lungs, they can damage the epithelial cells located in the lungs and lead to cell mutations that form into cancerous cells. These cancerous cells can mutate and form tumors that lead to small cell carcinoma.

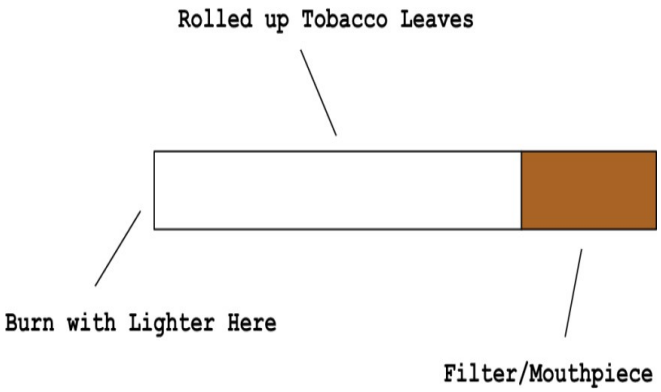


Figure 2. This is a model of the specific parts of a cigarette. It showcases how a person would use a cigarette and where the tobacco is located

There are multiple devices that an individual can use to smoke and consume tobacco. The most common throughout history has been cigarettes. When a cigarette is lit, the tobacco is burned and travels through the cigarette, where the tobacco leaves are filtered, and the smoke enters the mouth of the consumer. Figure 2 shows the specific parts of a cigarette. E-cigarettes and vapes have been more commonly used today. E-cigarettes contain a battery-powered heating device that vaporizes the chemicals in the device for aerosol to be produced. This aerosol is then inhaled by the smoker.

### 1.3 Current Treatments for Cancer

Currently, there are three main treatments for cancer, surgery, radiation therapy, and chemotherapy. Surgery removes the tumor from the affected location to prevent cancer from spreading. This has its drawbacks, as it is only beneficial for patients with tumors close to the skin and with cancer that has not likely spread. There is also a high mortality rate for the surgery and the median survival rate post-surgery is only around 3 years. Radiation therapy uses extreme amounts of radiation to target and kills the cancer cells to shrink the tumor. The radiation targets the DNA of the cancer cells and alters the sequence, which leads to apoptosis. Radiation can be harmful to the body if exposed for too long, which can lead to hair loss, problems in the heart and brain, and trouble with speech and memory. Similar to radiation therapy, chemotherapy uses specific anti-cancer chemicals that can kill cancer cells to diminish the tumor.

Chemotherapy also has a low success rate of 16% when used by itself, but does have a higher success rate of 35% when paired with radiation therapy. The current treatments for cancer are not sustainable for patients with small cell carcinoma as they only extend their lives by 1-4 years and leave the patients with many side effects from the treatments.

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### 1.4 What is Stem Cell Therapy?

There is a possible treatment method that can potentially change treatment methods for small cell carcinoma. This method is stem cell therapy. Stem cells are unspecialized cells located in specific parts of the body. The stem cells can then be used to build tissues in the body and maintain needed functions for survival. There are two main types of stem cells, embryonic stem cells and adult stem cells. Embryonic stem cells are the stem cells during the developmental processes of an embryo. They can become specialized into any cells for function in a newborn baby (Lo and Parham, 2009). On the other hand, adult stem cells have specific functions they will end up performing, meaning they will become specialized into cells based on their location. For instance, if a stem cell was located in the brain, it would only be able to become a brain cell. Stem cell therapy, also known as regenerative medicine, uses the idea of stem cells to replace cancerous cells with functioning stem cells to rebuild the organ and treat the patient (Lo and Parham, 2009). This way of treatment would be beneficial as it provides patients with the needed cells to rid the body of cancer as quickly as possible. It also allows the body to rebuild the damaged organ and get back its original structure and functions.

There was a main ethical concern regarding the use of stem cell therapy. Because it was hard to obtain specific stem cells for different kinds of cancer, scientists would use the stem cells from unused embryos in order to find stem cells that could be used for any part of the body. Many people were concerned with this way of extraction and with using embryos from in vitro fertilization (Lo and Parham, 2009). Luckily, in 2012, this problem was solved when Shinya Yamanaka and John Gurdon were awarded the Nobel Peace Prize for their influential discovery in this matter. Yamanaka and Gurdon were able to reprogram adult stem cells into embryonic stem cells using important genes in the cells (Gurdon and Yamanaka, 2019). This discovery was extremely important because scientists are now able to extract stem cells from the blood of the patient and reprogram the blood stem cells into embryonic stem cells, where they can be used for various treatments for any of their disorders.

### 1.5 Purpose

The hypothesis made is that stem cell therapy can be used as a potential cure for small cell carcinoma patients with a history of tobacco use. The purpose of this review is to prove whether or not this theory is true. Small cell carcinoma is largely associated with smoking, but with an increase in the variety of tobacco products, more people are developing addictions to cigarettes. Because of this, there is no known method to prevent people from smoking, and as small cell carcinoma cases arise, finding the best treatment possible will help reduce the deaths that are caused by smoking. This review showcases a treatment method that has been proven to be successful for other diseases, and developments will be made on whether or not scientists should experiment with stem cell therapy as a treatment method.

## 2. Stem Cell Therapies

There are four types of stem cell therapies, hematopoietic stem cells (HSCs), skin stem cells (SSCs), neural stem cells (NSCs), and mesenchymal stem cells (MSCs). HSCs are stem cells that are able to develop into any kind of blood cells, such as white blood cells, red blood cells, and platelets. They are most commonly found in the blood and bone marrow. SSCs are adult stem cells that are present in the skin. They are able to differentiate into multiple cell types of the skin and can be used for skin renewal and repair. NSCs are multipotent cells that form the radial glial progenitor cells. These cells create neurons and glia that help the nervous system function during the development of the embryo. Finally, MSCs are stem cells that are found in the bone marrow. They are important for the maintenance of the skeletal system, such as bone, fat, and cartilage.

The most common kinds of stem cell therapies are the use of HSCs and MSCs. For HSCs, the blood is removed from the body, the stem cells are extracted from the blood sample, and the blood is returned back to the body for normal function. In order to stimulate the growth of more stem cells, many patients take medications, such as filgrastim, to increase the bone marrow stem cell count days before the extraction is completed. Stem cell treatment

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is also commonly used with chemotherapy in order to remove cancerous cells from the body while providing the organ with new and healthy stem cells. Once the stem cells are retrieved from the patient, the adult stem cells have to be reprogrammed into embryonic stem cells in order to be able to be beneficial for the treatment of the patient. In order to do so, scientists most commonly inject the stem cells with viruses that contain four specific genes, SOX2, Oct4, KLF4, and cMyc. These genes modify the stem cells in order for them to obtain the characteristics of an embryonic stem cell without raising any ethical concerns. Finally, the stem cells are transferred back to the body using three common delivery methods: local injections, in vitro scaffolds, and tissue-engineered scaffolds. Many studies have been conducted in order to test the effectiveness of each kind of delivery method on patients with different disorders.

Local injections are usually conducted in a region close to the affected area of the patient. The treatment process is commonly split into three injection rounds in a span of 2-5 days. The first injection is a solution of simple sugars called dextrose that prepares the body for the stem cells to enter. The second injection is done with the extracted stem cells for them to travel to the region that needs to be treated. The final injection is platelets that will allow the stem cells to function in the body. Multiple studies have been conducted to show the effectiveness of local injection stem cell therapy.

In one study, done by Saieh Hajighasemlou et al., scientists conducted stem cell treatment through local injections on patients with hepatocellular carcinoma (HCC), the most common form of liver cancer. The cells derived from the bone marrow (MSCs) are used for treatment. Hajighasemlou et al. conducted this treatment on 18 nude mice with HCC and split them into 6 groups, chemotherapy, stem cells through intravenous therapy (IV), stem cells through local injection, chemotherapy and stem cells through IV, chemotherapy and stem cells through IV, and no treatment. The results were able to showcase that using a local injection rather than an IV worked better for the treatment of nude mice. The tumor was also able to be diminished with a combination of chemotherapy and stem cell treatments using the mesenchymal cells under a local injection. This is because the chemotherapy treatment kills the cancerous cells and leaves more room for the stem cells to help treat the patient.

Another study, conducted by Jignesh Dalal et al., discusses the benefits of mesenchymal stem cells on patients with Crohn's disease. Crohn's disease is a type of inflammatory bowel disease that occurs in the lining of the digestive tract. It commonly causes abdominal pain, diarrhea, fatigue, and weight loss. Patients with Crohn's disease also may experience perianal fistula, an infected tunnel between the skin and anus, or enterocutaneous fistula, an infected tunnel between the skin and stomach. Dalal et al. were able to explain how mesenchymal stem cells are able to be used as a treatment for Crohn's disease and suppress the rapid growth of the affected cells using local injections. In order to test this theory, they derived MSCs from 9 patients with perianal fistulas and 1 patient with enterocutaneous fistulas. The injections were done every 4 weeks until there was a response in the body. The results showcased a benefit in the fistulizing lesions with the use of local injections as the cells were shown to have had a major contribution to the repair process of the lesions.

Because of the shown effectiveness of locally injected stem cells for patients with hepatocellular carcinoma and Crohn's disease, this method of treatment can also be a beneficial treatment for patients with small cell carcinoma. The lungs, intestines, and liver all play extremely crucial roles in the human body and need proper treatments for them to function well. The human body would not be able to survive without these vital organs. If stem cells have advantages for the treatment of liver cancer and the lesions formed by the fistulas, they can play a large role in the treatment of small cell carcinoma and other cancers in the future. More research and experiments can be done to prove this theory.

Another method of stem cell treatment is scaffolding. A scaffold is a medical technique in which a framework has been produced in order to create an environment that helps with the formation of desired tissue for patients with degenerative diseases. The new tissue can then be introduced back into the patient to help the region that was impacted. In order to do so, stem cells (programmed to become lung cells) are placed on the scaffolds to be guided in their growth of new tissue. There are two types of scaffolding techniques, in vitro scaffolds and tissue-engineered scaffolds. In vitro scaffolds are done in Petri dishes to help initiate the growth of tissue. Tissue-engineered scaffolds use materials such as collagen and polylactic acid to create an environment for new tissue to grow. Many studies have been conducted in order to test the effectiveness of in vitro scaffolds on patients with tissue degenerative

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diseases.

One study, done by Andrew W. Holle et al., explains the general pattern of growth that has been experienced in the treatment of cancers in the body due to in vitro models. Holle et al. discuss specific drugs located in the cells that are more efficient in in vitro scaffolding methods, making their research more accurate and reliable. He also explains that since new methods for culturing cancer cells in scaffolds have been created, there are more areas in the future that can use this testing to their advantage. The researchers were able to conclude that the technique of scaffolding can be significant in the future treatment of cancer as they were able to help detect and reduce cancer cell tumors created in the body.

The use of scaffolding can also help with the growth of drug discoveries in this field of work to expand treatment methods to more than chemotherapy and radiation therapy.

Another study, conducted by Yongxiang Luo et al., analyzes bifunctional scaffolds as a potential treatment for breast cancer. The researchers decided to perform this experiment because scaffolding showcased similar results to the function and look of normal breast tissue, as it was very flexible and had similar behaviors to breast tissue. They build a scaffold using synthetic materials to create better results for treatment. The scaffold was able to show positive effects for cancer therapy and did match the properties of the tissue very well. The scaffold also was able to continue mitosis in the breast tissue to help the tissue maintain its health and overall well-being. All in all, the scaffold was shown to be a great option for the treatment of breast cancer and for the repairing of damaged tissues in the body.

The general methods that have been created for scaffolding show major advantages that can be used to determine how it can treat small cell carcinoma. Using the scaffolding technique with stem cells can also be used to help find more treatments for small cell carcinoma using different types of stem cells and different drugs. Scaffolds also have the ability to act similarly to normal breast tissue, making them beneficial for the treatment of breast cancer. The lung tissue also has to be flexible in order to contract and relax during inspiration and expiration. This means that the scaffolding technique can also be used for treating small cell carcinoma and can help continue the growth of the tissue to maintain a healthy lung.

More research is currently being conducted to test the effect of scaffolding on patients with more invasive forms of cancer.

## 3. Conclusion

The first and most beneficial way to avoid developing small cell carcinoma is to quit or avoid smoking entirely. By doing so, the lungs won't be easily damaged and have as high of a chance of developing any sort of lung cancer. It also avoids the possibility of developing any other kinds of lung diseases, such as emphysema, damaged air sacs, and chronic obstructive pulmonary disease (COPD), the blockage of the airways. However, with the increase in tobacco use across the country, it is becoming harder to stop people from smoking and increasing their risk for developing lung cancer. Finding the most beneficial treatment method will help limit the number of deaths associated with smoking and small cell carcinoma.

This review helped prove that stem cell therapy can extremely beneficial in the treatment of this disease. Stem cells can be used to initiate the growth of new tissue and also quicken the recovery process of small cell carcinoma patients. When paired with chemotherapy, the chemicals from the chemotherapy can help diminish the tumor and prevent the growth of cancerous cells while stem cell therapy can help initiate the development of healthy cells to quicken the healing process. Future research can be done to test this theory and discover the true potential of stem cell therapy for small cell carcinoma with a history of tobacco use.

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