

Lung cancer screening methods and treatments

Ilma Meša^{1*}, Jasmin Šutković¹

¹Genetics and Bioengineering, International University of Sarajevo, Bosnia and Herzegovina

*Corresponding author: imesa@student.ius.edu.ba

© The Author

2021.

Published by
ARDA.

Abstract

For a very long time, lung cancer was a major health problem and the leading cause of death worldwide. Small cell lung cancer (SCLC) accounts for 15% of cases and non-small cell lung cancer (NSCLC) accounts for 85% of cases. Although many people believe that smoking is the primary cause of lung cancer, there are numerous other contributing factors as well. Nonsmokers have a higher risk of lung cancer from radon than smokers do. Smoke from household fuel, infections like Mycobacterium tuberculosis and the Human Papillomavirus, as well as inflammatory diseases like asthma and sarcoidosis, are additional risk factors for nonsmokers to develop lung cancer. Although radiotherapy is frequently underused, it has been shown to be one of the most effective methods for treating lung cancer. The advancement of technology has made it possible to better target radiotherapy at tumors and lessen the amount of radiation that is emitted to normal tissues around them. The most recent risk factors and characteristics of the disease, particularly in nonsmokers, as are novel treatment options, are outlined in this review.

Keywords: Lung cancer, SCLC, NSCLC, metastasis, radon, non-smokers, COVID-19, radiotherapy

1. Introduction

Any type of cancer arises from the mutation of healthy cells [1]. Although there are several variables that can cause this mutation, including chemical exposure, environmental conditions, and substance misuse, this process can occasionally be avoided. A mass of cancer cells known as a cancerous (malignant) tumor is capable of invading neighboring tissue and impacting negatively on it [2]. Additionally, it has the ability to "metastasize" to other body regions. Mutations that take place either within or on the exterior tissue of the lungs are the cause of lung cancer [3]. Lung cancer develops in lung cells and can spread to lymph nodes or other body organs. Naturally, inhaling dangerous substances is the primary way that lung damage manifests itself. However, even non-smokers going about their daily lives can acquire this illness. Non-small cell lung cancer and small cell lung cancer are the two subtypes of lung cancer that differ in the type of cell from which the cancer developed. Adenocarcinoma is the most common type of non-small cell lung cancer, and it mostly develops in the cells of the glands on the outside of the lung [2]. Squamous cells, which are flat, thin cells, also contain them. This type of cancer is known as squamous cell lung cancer because they line the bronchi, the large airways that connect the trachea to the lungs [4]. Large cell carcinoma is another type of these cells that occurs much less frequently. Sarcoma and sarcomatoid carcinoma are also members of this category [5]. Small-cell lung cancer, on the other hand, typically begins in the cells that line the bronchi in the middle of the lung. Small cell carcinoma and combined small cell carcinoma, also known as a mixed tumor with squamous or glandular cells [4], are the most common types of these cancers. Although they are not the same as primary lung cancer, other types of cancer can spread to the lungs.

Lung metastasis is the process by which cancer spreads from another part of the body to the lungs. Primary

lung cancer is treated and cured in a different way.

Lung cancer is the second most common type of tumor worldwide. A total of 19,292,789 new cases of cancer were recorded in 2020, according to the Global Cancer Observatory, a project developed by the International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO) [6]. Breast cancer accounted for 11.7% of these cases, followed by lung cancer (11.4%), which is more common in men (14.3%) [7]. Lung cancer is the leading cause of death worldwide in terms of mortality, accounting for 1,769,144 deaths in 2020 [6]. These data suggest that this disease has caused a serious health issue. Tobacco use is the primary risk factor for lung cancer, which accounts for between 80 and 90% of cases and most deaths [8].

Nonsmokers have a much lower prevalence of lung cancer, which accounts for 15 to 25% of all cases [9]. IARC has mentioned indoor radon, arsenic, chromium, air pollution, asbestos, diesel, nickel, and silicon dioxide as environmental carcinogens [10]. Chronic local inflammation and a lack of fresh fruit and vegetable consumption are additional risk factors. In 1987, the World Health Organization (WHO) and the Environmental Protection Agency (EPA) of the United States (EPA) both declared indoor radon to be carcinogenic to humans [11]. The World Health Organization (WHO) estimates that radon may be to blame for 3 to 14 percent of lung cancer cases—the leading cause among nonsmokers [11]. Radon is likewise answerable for roughly 21,000 malignant growth passages (2%) in Europe [12]. Small cell lung cancer (SCLC), which accounts for 15% of cases, and non-small cell lung cancer (NSCLC), which accounts for approximately 85%, are the two types of lung cancer [13]. Although NSCLC has a favorable survival prognosis when detected early, the majority of patients are already in advanced stages when the diagnosis is made, making survival more challenging and uncommon [14]. With a survival rate of about 5%, SCLC is significantly more aggressive than NSCLC [15]. When patients with stage I disease are identified early, surgery has a high chance of success as a treatment option, even though the scope of radical treatment is typically quite limited. Lung cancers are already in the metastatic stage IV when they are found. They spread through the blood vessels and lymphatic systems, where the lymphatic metastasis lasts longer than the time it takes to form distant metastases, whereas the spread through the blood vessels starts very early in distant metastases. The brain, bones, and adrenal glands are the most common peripheral sites for lung cancer metastases, but other organs can also be affected in advanced stages. In SCLC, liver metastases are more prevalent, while in adenocarcinoma and SCLC, brain metastases are more common. Cellular breakdown in the lungs is perhaps of the most forceful dangerous cancer, particularly SCLC. Chemotherapy and surgical resection are the primary treatments for lung cancer [16]. Patients with early-stage lung cancer typically receive chemotherapy, while those with advanced or metastatic disease typically receive surgery [17]. However, treatment approaches have also evolved over time. Lung cancer patients' survival is influenced by a number of factors, including age, sex, lung function, clinical and pathological stage, body constitution, comorbidity, and optimal treatment [18]. Tobacco use, which accounts for between 80 and 90 percent of lung cancer cases and the majority of deaths, is the primary risk factor [19]. Lung cancer, on the other hand, affects 15 to 25 percent of non-smokers and has a less well-understood epidemiology at this time. Lung cancer also has a poor prognosis and a very low 5-year survival rate [20]. This review provides a summary of the most recent disease's risk factors and characteristics, particularly in nonsmokers, as well as innovative treatment strategies. It also emphasizes the progress that has been made and the difficulties that can arise in the early detection of lung cancer.

1.1. Early lung cancer biology

Understanding changes in the environment of the lung itself during the early stages of cancer development may provide a novel method for the early detection of disease biomarkers. During the ventilation process, the lungs are frequently in contact with the outside world and must operate under extreme changes in local pressure. A complex epithelium of ciliated cells covers the branched airways, but there may also be a few distinct populations of secretory cells that act as progenitor cells during injury-induced airway repair [21]. 20% of cancers are linked to chronic inflammation, and there is a strong correlation between chronic inflammation and an increased risk of developing the disease [22]. Oncogenic changes may have triggered the induction of inflammatory pathways in both premalignant and malignant cells, indicating that inflammation can cause cancer as well as cancer [22]. Through inflammatory cells and mediators that are capable of acting in an autocrine and paracrine manner, the tumor microenvironment coordinates pro-inflammatory responses that affect both malignant and non-malignant cells [23]. Endothelial progenitor cells, tumor-associated fibroblasts, and inflammatory processes that invade the tumor make up the inflammatory microenvironment

[24]. The release of cytokines and chemokines from this microarray by tumor and host cells, stromal, endothelial, and immune cells enables the coordination of a self-limiting immune response. New biomarkers for the early detection of lung cancer could be discovered through numerous studies of preclinical disease models.

1.2. Tumor growth and cell movement

Tumor cells must restrict the vascular supply for nutrition and oxygen uptake in order to encourage growth. Tumor cells must adapt to the migratory cell structure in order to migrate and avoid being attacked by lymphocytes in order to move within the stroma. Communication with the microenvironment's macrophages, fibroblasts, lymphocytes, and dendritic cells begins when nodules form within the stroma. Tumor cells can either begin to cooperate with macrophages, which release angiogenic growth factors, or directly release angiogenic factors (such as vascular endothelial growth factors, VEGF) with the intention of directly stimulating the formation of new blood vessels to facilitate angiogenesis [25]. The vascular form of squamous cell dysplasia is an excellent illustration of angiogenesis induced by tumor cells, whereas in adenocarcinomas, angiogenesis is dependent on macrophage cooperation [26].

1.2.1. Hypoxia's role in the migration and metastasis of tumor cells

As the essential cancer develops, it prompts the difficulty of framing fresh blood vessels, which brings about hypoxia. Tumor cells are confronted with this issue and attempt to evade hypoxia-induced apoptosis. Growth factors (IGF and EGF), which are also induced by hypoxia, can inhibit apoptosis [27]. In hypoxic environments, cancer cells reduce metabolism and cell division to avoid apoptosis and cell death [28]. In order to create a stroma that is suitable for the invasion and migration of tumor cells or the inhibition of their migration, macrophages collaborate with fibroblasts and myofibroblasts. Myofibroblasts, on the other hand, cooperate with tumor cells, while fibroblasts in scars do not [29]. Myofibroblasts, also known as tumor-associated fibroblasts, are distinct from normal fibroblasts in the lungs in that they express distinct proteins and genes related to their role in the development of cancer. Tumor cell migration is also influenced by changes in the orientation and composition of matrix proteins. These proteins are explicit on the grounds that they can control the strength of the stroma by their coordinated testimony, as well as by making an organization through cross-connecting. In the event of Intratumoral hypoxia and acidity in non-small cell lung cancer, cells of the tumor stroma selectively synthesize osteonectin [30]. Immunohistochemistry demonstrates that osteonectin favors cancer cell invasion and migration. The orientation and makeup of the matrix proteins are another crucial aspect. While organized directed deposition and high levels of collagen encourage tumor cell migration, high levels of elastin encourage resistance to the migration of tumor cells [31]. The tumor suppressor gene, RBM5 (RNA-binding protein 5), which is deleted in most cases of lung cancer, also has an impact on matrix protein deposition. Apoptosis and cell cycle arrest are both triggered by the encoded protein. Cell movement is facilitated by the regulation of β -catenin, collagen, and laminin that results from RBM5 deletion [32]. Thusly, Rac1 and β -catenin decidedly correspond with lymph hub metastases in cellular breakdown in the lung's patients [33]. There are other matrix proteins, but not enough research has been done on them in this field.

1.3. The migration of tumor cells

Tumor cells must undergo changes in order to migrate to distant locations and thus establish metastases after establishing the primary tumor, organizing nutrition, and protecting themselves from immune cells' attacks. Migration is much simpler for individual cells than it is for small clusters because individual cells are better able to adapt, allowing for better movement. In carcinosarcomas, high-grade adenocarcinomas, and SCLC, tumor cells decrease or eliminate cytokeratin filaments during migration and increase de novo expression of α -actin and vimentin. A poor prognosis was observed for lung adenocarcinomas that expressed a lot of the smooth muscle actin gene ACT2, which is associated with increased distant metastases [34]. Adenocarcinoma's in vitro migration, invasion, and clonogenicity were reduced by downregulation of this gene without affecting proliferation. Since it appears that different genes control how tumor cells move, it is assumed that there is no one mechanism that works for each type of tumor. Instead, it is assumed that tumor cells each adapted different migration protocols and used them during carcinogenesis [35].

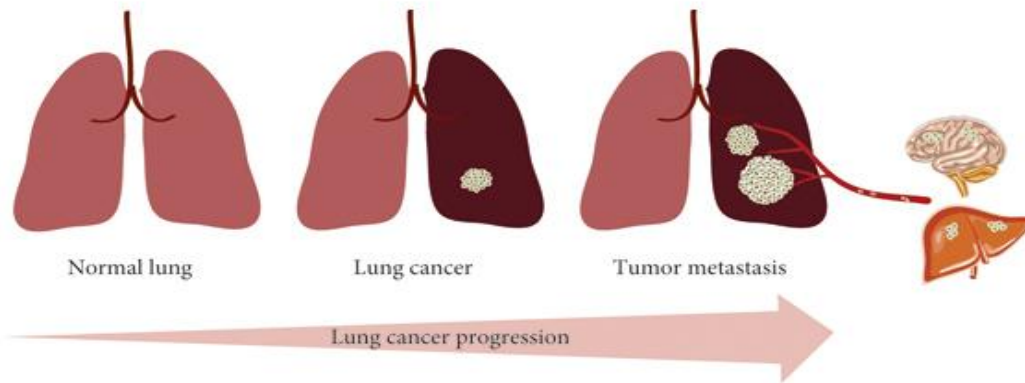


Figure 1. Lung cancer progression [36]

2. Radon: What is it?

The well-known radioactive gas radon-222 is produced naturally as a byproduct of the decay of uranium-238. Its concentration is related to the amount of uranium found in cracks in the earth's crust beneath residential structures [37]. It can diffuse through the soil and into the air for 3.8 days due to its short half-life, which allows it to decay into a series of short-lived radioactive products by emitting alpha particles. About half of all-natural radiation to which people are exposed comes from indoor radon [38]. The European Code Against Cancer is increasingly recommending lower radon concentrations in enclosed spaces [39]. National authorities must use tools and methods to prevent radon exposure and identify the population that is exposed to high concentrations of radon indoors and is at risk of developing lung cancer in order to reduce radon-related diseases. Based on WHO data from 1987, radon in closed spaces was declared carcinogenic to humans [40]. In 1913, a hypothesis was put forth that radon and its derivatives cause a high incidence of lung cancer among silver and uranium miners in Germany [41]. In 2003, Pavia et al. published the first meta-analysis on the association of indoor radon and lung cancer [42]. This meta-analysis included 17 case-control studies and found that patients exposed to more than 150 Bq/m³ had a 24% increased risk of developing lung cancer [42]. Other studies and results indicate that radon increases the risk of lung cancer without a threshold and can be carcinogenic at any level, depending on an individual's sensitivity, the number of years of exposure, the amount of exposure during childhood, tobacco use, pollution, and asbestos. In addition, very little information is currently available regarding the clinical characteristics of radon-related lung cancer patients. The majority of studies on radon and lung cancer were conducted on current and former smokers; however, some studies only included nonsmokers and demonstrated an increased risk of lung cancer in patients who lived in apartments with high radon levels. As a result, Lorenzo-Gonzalez gathered all of the research data on radon-induced lung cancer, including data from nonsmokers, and discovered a relevant risk of 1.1 to 1.73, with no negative association in any study [43].

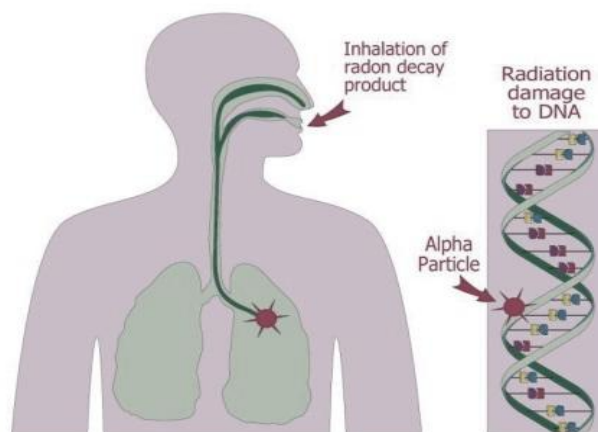


Figure 2. How radon causes lung cancer? [44]

Despite everything, despite the fact that numerous studies show that radon has no effect on lung cancer, there is sufficient preclinical and clinical evidence to suggest that radon is a carcinogen of the first group and a risk factor for lung cancer today, after smoking tobacco. There has been a lot of talk about the link between radon exposure and lung cancer. The combination of radon and tobacco smoke is thought to be more of a synergy than an additive, increasing the risk of dying from lung cancer in smokers exposed to radon above 200 Bq/m³ by 20 to 25 times [45]. In the early stages of the carcinogenic process, radon and tobacco smoke function as cocarcinogens. Both produce reactive oxygen species (ROS) that interact with DNA hydroxyl radical attack and radiolysis, resulting in bulky DNA adducts, saturation of the DNA repair pathway, and increased apoptosis [46]. DNA damage and high genomic tumor instability are caused by radon, but the mechanism of its carcinogenesis and connection to lung cancer are still a mystery.

3. Utilizing circulating microRNAs to detect lung cancer

Through translational inhibition or degradation of target messenger RNAs (mRNAs), microRNAs (miRNAs) are critical regulators of gene expression [47]. The majority of cancers are caused by changes in miRNA expression. Lung cancer tissue has lower levels of the Let7 miRNA, but when it is overexpressed, it starts to stop the growth of the lung cancer cell line [48]. On the other hand, lung cancer tissue and cell lines both overexpress miRNA-21 [49]. Patients with lung cancer and healthy controls both have circulating miRNAs in their blood. They are utilized as diagnostic biomarkers because of their high resistance to RNase [50]. Additionally, it was suggested that miRNA analysis could boost the efficiency of lung cancer screening programs. In order to identify differentially expressed miRNA prior to the development and diagnosis of lung cancer, the researchers analyzed the expression of miRNA in the plasma of patients participating in the LDCT lung screening study [51]. Consequently, when combined with LDCT, it reduced the rate of false positives by five times, but clinical-pathological staging in predicting prognosis was still not improved. Although additional research is required, the use of circulating miRNAs appears promising for the early detection of NSCLC [52].

4. Lung cancer in non-smokers

Carcinogens released by smoking tobacco are linked to between 80 and 90 percent of lung cancer cases worldwide. A critical extent of cellular breakdown in the lung's cases are analyzed in patients who won't ever smoke [53]. An expansion in the quantity of cellular breakdown in the lungs patients was seen in non-smokers, contrasted with smokers. Other risk factors play a significant role in the carcinogenesis of lung cancer in nonsmokers who are diagnosed. It has already been mentioned that soil radon is the second most significant risk factor for lung cancer, after smoking (10 percent of cases) [54]. Additionally, asbestos exposure is currently the most significant occupational exposure and is the third most common cause of lung cancer worldwide [55]. Arsenic, chromium, and ionizing radiation, which are found in workers in the pesticide application, stainless steel production, and welding industries, as well as mining workers, are additional occupational determinants of lung cancer with a high level of evidence that promotes causation [56]. Electricians, masons, and carpenters are also included in this. Additionally, in addition to being a significant risk factor for lung cancer, secondhand smoke is ranked as the ninth leading cause of disability-adjusted life years and the tenth leading cause of death worldwide. The Worldwide Organization for Exploration on Disease has characterized the utilization of coal for cooking or warming as cancer-causing group 1, while biomass is delegated group 2 [57]. It is common knowledge that carcinogenesis is accompanied by chronic inflammation as a secondary infection. Among chronic infections, pulmonary tuberculosis caused by *Mycobacterium tuberculosis*, an intracellular pathogen, has a latency period and increases the risk of lung cancer regardless of smoking status [58]. Infection with the bacterium *Helicobacter pylori* (Hp) [59] as well as the human papillomavirus (HPV) are both regarded as risk factors for lung cancer. Asthma and other inflammatory diseases also have a connection to lung cancer. Patients with or without a history of smoking were found to have this connection [60].

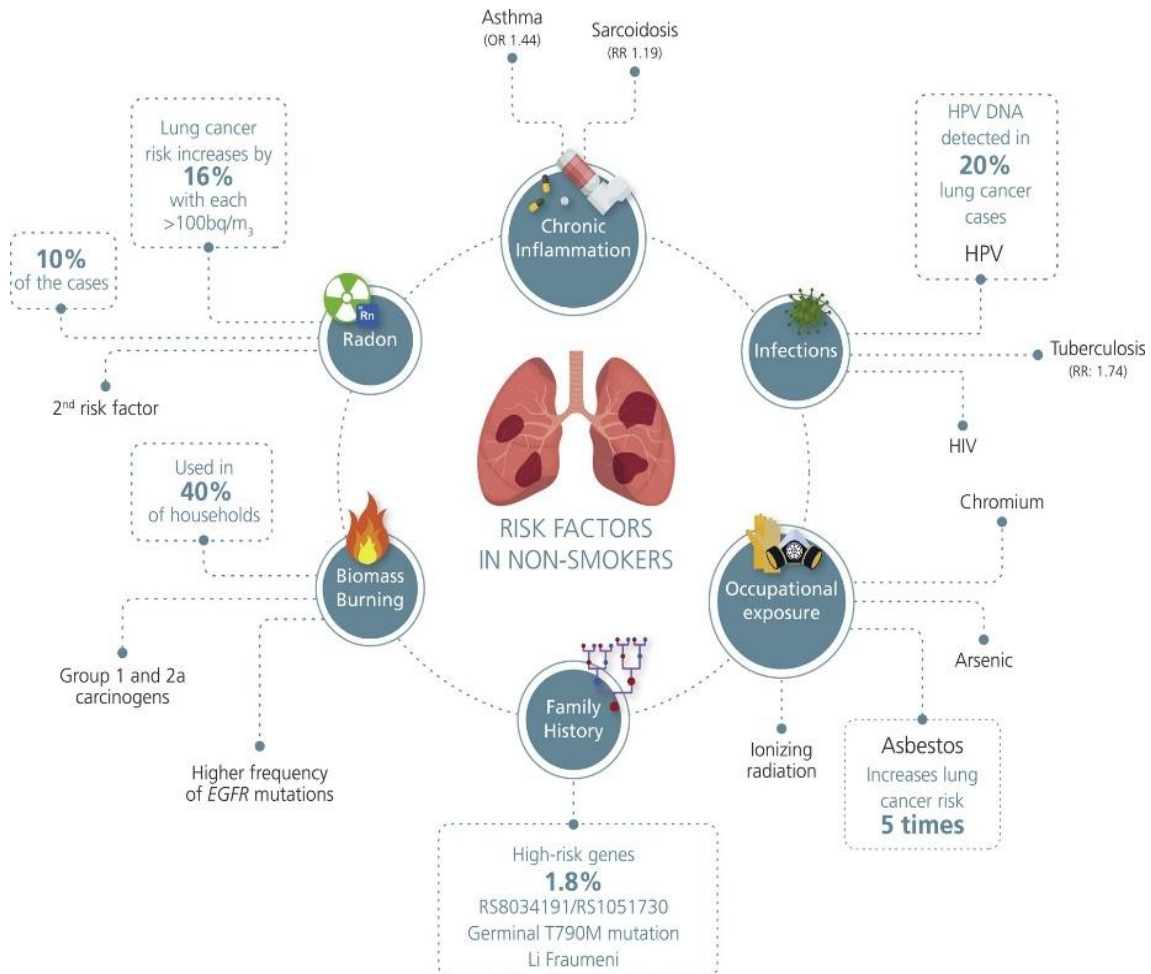


Figure 3. Risk factors for lung cancer in nonsmokers [61]

In many countries, women are more likely than men to smoke, but this gap has begun to close. Women account for the majority of lung cancer diagnoses in patients who have never smoked, but their mortality rates from the disease are very similar. As to contrasts in cellular breakdown in the lungs patients who never smoked, the discoveries were problematic. Histology of adenocarcinoma tumors is typically seen in nonsmoking lung cancer patients. Adenocarcinoma is the most common histology in patients who have never smoked, despite the fact that numerous studies report variations in this frequency ranging from 85 to 100 percent [61]. Patients who have never smoked are thought to have a much lower incidence of squamous cell histology—less than 5% of cases. A patient with small cell lung cancer who has never smoked is extremely uncommon, but this frequency can vary.

5. Lung Cancer and the COVID-19 Pandemic

Patients with cancer, particularly lung cancer patients, have stated on numerous occasions that they experience significantly worse outcomes from the coronavirus disease 2019 (COVID-19), including higher rates of hospitalization and death [62]. It is not entirely clear whether the individual is already predisposed to significant symptoms of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or whether it is lung cancer itself [63]. Other factors that may predispose an individual to this condition include age, genetic variations in immunity, a history of smoking, and treatment for cancer. The analyses revealed that patients with lung cancer experience a more severe course of COVID-29 infection. Despite the fact that COVID-19 was only responsible for a small percentage of lung cancer deaths during that time period, it was responsible for the deaths of a quarter of all patients tested for the disease. One third of the 102 patient tested experienced a milder outpatient course, two thirds required hospitalization, and one fourth died [64]. Basic clinical characteristics, such as smoking, age, hypertension, and chronic obstructive pulmonary disease (COPD), are linked to the diversity of these COVID-19 phenotypes. The findings suggest that rather than the cancer itself or cancer-targeted treatment, the primary drivers of the severity of COVID-19 disease in lung

cancer patients are risk factors for lung cancer and related chronic health conditions [65]. The biological basis of the immune response of the SARS-CoV-2 host virus is related to the severity of COVID-19. Because HLA class I alleles are responsible for determining the quantity and quality of COVID-19 antigens presented to the adaptive immune response, which influences the effectiveness of T cells' acute and memory responses, the impact of HLA alleles on COVID-19 severity was investigated [66]. However, additional samples are required to precisely define the effect of HLA alleles on COVID-19 severity. Over half of the COVID-19 patients recovered from their lung cancer, including a small number of those who initially required intubation or invasive mechanical ventilation, despite the disease's severity [67]. Predictors of recovery included a lower number of years of smoking and the absence of COPD [68]. This information depicts cardiopulmonary sickness and additionally its gamble factors that lopsidedly lead to more regrettable results of Coronavirus in unselected patient populaces, driven by different elements including age, hidden organ injury, direct SARS-CoV-2 attack, and hyperinflammation [69]. The vulnerability of lung cancer patients during the pandemic and the ongoing critical need to continue and drive improvements in optimal cancer care are highlighted by these data, which characterize COVID-19 in patients with lung cancer.

6. Methods of treatment

Systemic therapies (chemotherapy, immunotherapy, and targeted drugs), interventional radiology, and palliative care are all common components of lung cancer treatment, which is a complicated process that frequently involves multiple treatment modalities. Radiotherapy is the main technique for treatment for which there are signs in all phases of the sickness, yet additionally in all classes of the patient's ailment. At some point in their cancer journey, 77% of all lung cancer patients have an evidence-based reason to receive radiotherapy [70]. In any case, radiotherapy remains underutilized in many regions of the planet. The ideal utilization of radiotherapy can bring about an expansion in the endurance pace of 4% [71]. Late advances in radiotherapy have brought about better results in the therapy of cellular breakdown in the lungs.

6.1. Lung cancer treatment with radiotherapy

The rapid development of radiotherapy enables treatments that are quicker, more precise, and free of side effects. Four-dimensional computed tomography (DCT), which makes it easier to check the position of the tumor before and during treatment, is the primary factor in the accuracy of radiotherapy [72]. The use of stereotactic body ablative radiotherapy (SBRT) was made possible by this technology. The delivery of large ablative doses of radiotherapy in smaller, geometrically precise portions is referred to as SBRT [73]. As a result, it reduces the toxicity of radiotherapy and its impact on the normal tissues that surround it. Multiple unevenly intensified beams of intensity are directed toward the tumor in intensity modulated radiotherapy (IMRT), which allows for more conformity in the treatment and lower doses for normal tissue [74]. The role of modern radiotherapy in enhancing outcomes for all stages of lung cancer has been expanded by these technologies.

An exciting area of research is the combination of immunotherapy and radiotherapy. The tumor microenvironment is reprogrammed, cytokines and chemokines are released, leukocytes are infiltrated, and tumor cells are more sensitive to immunogenic cell death as a result of radiotherapy [75]. Because it can increase danger signals, ionizing radiation will increase immunogenicity and, in some patients, become an extremely effective individualized vaccine in situ, enhancing immunotherapy's effects [76]. These preclinical findings, in which patients who received radiotherapy prior to immunotherapy observed improved OS, have been supported by recent clinical studies [77]. All of this suggests that checkpoint inhibitor immunotherapy and radiotherapy might work together in a beneficial and potentially synergistic way.

Radiotherapy innovations have progressed altogether throughout the course of recent many years, bringing about more noteworthy reasonableness for treatment, decreased harmfulness, and further developed endurance results. New technologies include the MRI-line, which makes it possible to see the tumor while it is being treated [78]. This lets the treatment be changed right away in response to changes in the tumor or normal tissues. Although SBRT-based radiotherapy has limited clinical benefit for peripheral tumors, it improves the therapeutic ratio for central tumors by ensuring adequate tumor coverage with the radiotherapy dose [79]. Lung cancer outcomes will continue to improve as a result of current research using immunotherapy, improved imaging for real-time tumor targeting, and machine learning from big data.

7. Lung cancer screening methods

In asymptomatic at-risk populations, the efficacy of lung cancer screening with Chest x-rays (CXR) or computed tomography (CT) has been investigated. In the past, the final outcome was a change in the disease's stage; however, the reduction in mortality is the gold standard indicator of screening's effectiveness [80]. This strategy necessitates focusing on people who pose the greatest risk. Plain CXR and sputum cytology were used to detect early lung cancer in some 1970s trials [81]. Although only 20% of diagnoses were made, sputum cytology alone identified more than 80% of lung cancers that could be surgically removed, as majority of squamous cell carcinomas in their early stages [82]. When cytological screening was added, there was no difference in mortality, as was observed. CXR screening also found 60% of lung cancers that came up during the screening period, half of which were staged diseases [83]. Since CT can provide more detailed images of the chest than CXR, it is better suited for cancer diagnosis. It is common knowledge that the radiation dose, which is 100 times higher than that of CXR, is too high to justify the benefits of early diagnosis over the dangers of radiation exposure [84]. As a result, interest in lung cancer screening only emerged when CT was confirmed with low radiation doses [85]. Low dose computed tomography, known as LDCT, is performed at settings to minimize radiation exposure compared to a standard chest CT. The effective radiation dose of Low dose computed tomography (LDCT) is 22% lower than that of standard CT [86]. As a result, a modification to the protocol was proposed to lessen the use of Positron emission tomography (PET) CT in screening trials in order to lower the risk of radiation exposure. The diagnosis of lung cancer can be easily made with the assistance of LCDT, but there is no benefit in terms of mortality. Lung cancer-specific mortality (20%) and all-cause mortality (6.7%) have been found to be significantly lower in the LDCT group [87]. Additionally, there was a lower rate of late-stage diagnoses, which indicates that the disease's early stages were successfully identified and treated. Lung cancer screening does not appear to be beneficial for nonsmokers. Lung cancer detection rates differ significantly between current and former smokers, according to additional analyses [88].

7.1. Bronchoscopy

Due to its significance in the early detection of lung cancer and its use in the nodal stage of the disease thanks to the introduction of endobronchial ultrasound, bronchoscopy holds a special place in diagnostics [89]. In contrast to the screening of patients at risk for lung cancer, where the sensitivity can be quite low, the sensitivity for detecting lung cancer in patients is variable, ranging from 34 to 88 percent depending on the size and position of the tumor [90]. To work on the responsiveness of bronchoscopy in the analysis of cellular breakdown in the lungs, researchers broke down the RNA articulation of histologically ordinary bronchial epithelium, which was acquired at the hour of bronchoscopy in patients associated with having cellular breakdown in the lungs. With a sensitivity of 80% and a specificity of 84%, the experiment was carried out on 77 patients, both those who had and those who did not have lung cancer [91]. The blend of bronchoscopy and this classifier prompted a complete responsiveness of 97% for the finding of cellular breakdown in the lungs. There is no precise evidence of how this would function in the context of screening due to the high nature of this population, which includes more than 70% lung cancer patients [92].

8. Conclusions

The leading cause of cancer-related death worldwide is lung cancer, which is a public health issue. Nonsmokers have seen an increase in cancer cases in recent years, most of which are linked to radon, one of the main risks of lung cancer. DNA damage and high genomic tumor instability are brought on by radon. If we want to reduce lung cancer mortality, early detection of the disease is critical. New treatments like stereotactic body ablative radiotherapy (SABR) are showing promising results in treating patients with early-stage lung cancer who are inoperable. This directly means that more patients could benefit from early detection through screening, even though some patients have other comorbidities that could prevent surgery. New cancers were found with the help of LDCT, but there were also a lot of false positive results. As a result, additional complementary tests are needed to reduce the number of false positive results and catch aggressive cancers early. Patients at risk would be better identified and fewer would require screening as a result of this. Plasma microRNA tests and antibodies were found to have the appropriate specificity for resolving the high LDCT false positive rate in the search for biomarkers. When combined with LDCT, plasma microRNA predicts a five-fold decrease in the rate of false positives; however, despite their reasonable sensitivity, they have not been tested for the diagnosis of aggressive cancers missed by LDCT. Lung cancer can benefit greatly from radiotherapy, which can be used at any stage of the disease. As its development has progressed, its

indications and outcomes have expanded, leading to increased survival and decreased toxicity. Lung cancer treatment outcomes will continue to improve as a result of immunotherapy and radiotherapy. All of this necessitates additional tests, particularly those aimed at the early detection of aggressive tumors.

References

- [1] "What is Lung Cancer?," Lung Cancer Center, 2021. [Online]. Available: <https://www.lungcancercenter.com/lung-cancer/>.
- [2] "What is Lung cancer?," Canadian Cancer Society, May 2020. [Online]. Available: <https://cancer.ca/en/cancer-information/cancer-types/lung/what-is-lung-cancer>.
- [3] Hassan Lemjabbar-Alaoui, Omer Hassan, Yi-Wei Yang and Petra Buchanan, "Lung cancer: biology and treatment options," *ncbi*, vol. 1856, no. 2, pp. 189-210, 2015.
- [4] Ming-Yue Li, Li- Zhong Liu and Ming Dong, "Progress on pivotal role and application of exosome in lung cancer carcinogenesis, diagnosis, therapy and prognosis," *Molecular Cancer*, p. 20, 2021.
- [5] Win Sen Heng, Frank A.E. Kruij and Shiau-Chuen Cheah, "Understanding Lung Carcinogenesis from a Morphostatic Perspectivr: Prevention and Therapeutic Potential of Phytochemicals for Targeting Cancer Stem Cells," *Int. J. Mol. Sci.*, vol. 11, p. 5697, 2021.
- [6] Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin D.M., Pineros M., Znaor A. and Bray F., "Estimating the Global Cancer Incidence and Mortality in 2018: GLOBOCAN Sources and Methods," *Int. J. Cancer*, vol. 144, pp. 1941-1953, 2019.
- [7] Alberg A.J., Brock M.V., Ford J.G., Samet J.M. and Spivack S.D., "Epidemiology of Lung Cancer: Diagnosis and Management of Lung Cancer, 3rd Ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines," *Chest*, vol. 143, pp. e1S-e29S, 2013.
- [8] R. Doll and R. Peto, "Mortality in Relation to Smoking: 20 Years' Observations on Male British Doctors," *Br. Med. J*, vol. 2, pp. 1525-1536, 1976.
- [9] Brenner D.R., Boffetta P., Duell E.J., Bickeböllner H., Rosenberger A, McCormack V., Muscat J.E., Yang P., Wichmann E.-E. and Brueske-Hohlfeld I, "Previous Lung Diseases and Lung Cancer Risk: A Pooled Analysis From the International Lung Cancer Consortium," *Am. J. Epidemiol.*, vol. 176, pp. 573-585, 2012.
- [10] Kaufman E.L., Jacobson J.S., Hershman D.L., Desai M. and Neugut A.I., "Effect of Breast Cancer Radiotherapy and Cigarette Smoking on Risk of Seconf Primary Lung Cancer," *J. Clin. Oncol*, vol. 26, pp. 392-398, 2008.
- [11] WHO, Handbook on Indoor Radon: A Public Health Perspective, Geneva, Switzerland: World Health Organization, 2009.
- [12] Darby S, Hill D, Auvinen A, Barros-Dios J.M., Baysson H., Bochicchio F., Deo H., Falk R., Forastiere F. and Hakama M., "Radon in Homes and Risk of Lung Cancer: Collaborative Analysis of Individual Data from 13 European Case-Control Studies," *BMJ*, vol. 330, p. 223, 2005.
- [13] Herbst RS, Heymach JV and Lippman SM, "Lung cancer," *N. Engl. J. Med.*, vol. 359, pp. 1367-1380, 2008.
- [14] Shah R, Sabanathan S, Richardson J, Mearns AJ and Goulden C, "Results of stage I and II lung cancer," *J. Cardiovasc. Surg.*, vol. 37, pp. 169-172, 1996.
- [15] H. K. al., "Small cell lung cancer doublinh time and its effect on clinical presentation: a concise review," *Clin. Med. Insights Oncol.*, vol. 6, pp. 199-203, 2012.
- [16] Shin D.Y., Na I. I., Kim C. H., Park S., Beak H. and Yang S. H., "EGFR mutation and vrain metastasis in pulmonary adenocarcinomas," *Journal of Thoracic Oncology*, vol. 9, pp. 195-199, 2014.
- [17] Islam KM, Jiang X, Anggondowati T, Lin G and Ganti AK, "Comorbidity and survival in lung cancer patients," *Cancer Epidemiol Biomarkers Prev.*, vol. 24, no. 7, pp. 1079-1085, 2015.
- [18] D. C. CS, Tanoue LT and Matthay RA, "Lung cancer: epidemiology, etiology, and prevention," *Clin Chest Med.*, vol. 32, no. 4, pp. 605-644, 2011.
- [19] A. Alberg, B. M.V., F. J.G., S. J.M. and S. S.D., "Epidemiology of lung cancer: diagnosis and

- management of lung cancer, 3rd ed: american college of chest and physicians evidence-based clinical guidelines," *Chest*, vol. 143, pp. e1S-e29S, 2013.
- [20] P. R. Doll R, "Mortality in Relation to Smoking: 20 Years observations on Male British doctors," *Br. Med. J.*, vol. 2, pp. 1525-1536, 1976.
- [21] H. B. al., "Repair and regeneration of the respiratory system: complexity, plasticity, and mechanisms of lung stem cell function," *Cell Stem Cell*, vol. 15, pp. 123-138, 2014.
- [22] B. F. Crusz SM, "Inflammation and cancer: advances and new agents," *Nat. Rev. Clin. Oncol.*, vol. 12, pp. 584-596, 2015.
- [23] Mantovani A, Allavena P, Sica A and Balkwill F, "Cancer-related inflammation," *Nature*, vol. 454, pp. 436-444, 2008.
- [24] K. M. Yang L, "Roles of tumor suppressors in regulating tumor-associated inflammation," *Cell Death Differ*, vol. 21, pp. 1677-1686, 2014.
- [25] Niethammer, A.G., Xiang, R., Becker, J.C., Wodrich, H., Pertl, U., Karsten, G., Eliceiri, B.P. and Reisfeld, R.A., "A DNA vaccine against VEGF receptor 2 prevents effective angiogenesis and inhibits tumor growth," *Nature Medicine*, vol. 8, pp. 1369-1375, 2002.
- [26] Xiang, R., Luo, Y., Niethammer, A.G. and Reisfeld, R.A., "Oral DNA vaccines target the tumor vasculature and microenvironment and suppress tumor growth and metastasis," *Immunology Reviews*, vol. 222, pp. 117-128, 2008.
- [27] Gharib, T.G., Chen, G., Huang, C.C., Misek, D.E., Iannettoni, M.D., Hanash, S.M., Orringer, M.B. and Beer, D.G., "Genomic and proteomic analyses of vascular endothelial growth factor and insulin-like growth factor-binding protein 3 in lung adenocarcinomas," *Clinical Lung Cancer*, vol. 5, pp. 307-312, 2004.
- [28] S. & E. S. Brader, "Phosphoinositide 3-kinase signalling pathways in tumor progression, invasion an angiogenesis," *Tumori*, vol. 90, pp. 2-8, 2004.
- [29] Kawashiri, S., Tanaka, A., Noguchi, N, Hase, T., Nakaya, H., Ohara, T., Kato, K. and Yamamoto, E., "Significance of stromal desmoplasia and myofibroblast appearance at the invasive frnt in squamous cell carcinoma of the oral cavity," *Head and Neck*, vol. 31, pp. 1346-1353, 2009.
- [30] Koukourakis, M.I., Giatromanolaki, A., Brekken, R.A., Sivridis, E., Gatter, K.C., Harris, A.L. and Sage, E.H., "Enhanced expression of SPARC/osteonectin in the tumor-associated stroma of non-small cell lung cancer is correlated with marker of hypoxia/acidity and with poor prognosis of patients," *Cancer research*, vol. 63, pp. 5376-5380, 2003.
- [31] Coulson-Thomas, V.J., Coulson-Thomas, Y.M., Gesteria, T.F., de Paula, C.A., Mader, A. M., Waisberg, J., Pinhal, M.A., Friedl, A., Toma, L. and Nader, H.B., "Colorectal cancer desmoplastic reaction up-regulates collagen synthesis and restricts cancer cell invasion," *Cell and Tissue Research*, vol. 346, pp. 223-236, 2011.
- [32] Oh, J.J., Taschereau, E.O., Koegel, A.K., Ginther, C.L., Rotow, J.K., Isfahani, K.Z. and Slamon, D.J., "RBM5/H37 tumor suppressor, located at the lung cancer hot spot 3p21.3, alters expression of genes involved in metastasis," *Lung Cancer*, vol. 70, pp. 253-262, 2010.
- [33] Soltermann, A, Tischler, V., Arbogast, S., Braun, J., Probst-Hensch, N., Weder, W., Moch, H. and Kristiansen, G., "Prognostic significance of epithelial-mesenchymal and mesenchymal-epithelial tansition protein expression in non-small cell lung cancer," *Clinical Cancer Research*, vol. 14, pp. 7430-7437, 20008.
- [34] Lee, H.W., Park, Y.M., Lee, S.J., Cho, H.J., Kim, D.H., Lee, J.I., Kang, M.S., Seol, H.J, Shim, Y.M., Nam, D.H., Kim, H.H. and Joo, K.M., "Alpha-smooth musle actin (ACTA2) is required for metastatic potential of human lung adenocarcinoma," *Clinical Cancer Research*, vol. 19, pp. 5879-5889, 2013.
- [35] Narita K, Matsuda, Y., Seike, M., Naito, Z., Gemma, A. and Ishiwata,T., "Nestin regulates proliferation, migration, invasion and stemness of lung adenocarcinoma," *International Journal of Oncology*, 2014.
- [36] Yuan-Xiang Shi, De-Qiao Sheng, Lin Cheng and Xin-Yu Song, "Current Landscape of Epigenetics in Lung Cancer: Focus on the Mechanism and Application," *Journal od Oncology*, p. 11, 2019.
- [37] T. J., Noble Gases, New York, NY, USA: Cavendish Square Publishing, 2012.

-
- [38] "National Council of Radiation Protection and Measurements (NCRP) Report No. 160," 2015.
- [39] WHO, Handbook on Indoor Radon: A Public Health Perspective, Geneva, Switzerland: World Health Organization, 2009.
- [40] Lubin, J.H., Boice J.D., Edling C., Hornung R.W., Howe G.R., Kunz E., Kusiak R.A., Morrison H.I., Radford E.P. and Samet J.M., "Lung cancer n Radon-exposed miners and estimation of risk from indoor exposure," *JNCI J. Natl. Cancer Inst*, vol. 87, pp. 817-827, 1995.
- [41] S. I. Greenberg M., "Lung cancer in the Schneeberg Mines: A reappraisal of the data reoorted by harting and hesse in 1879," *Ann Occup Hyg*, vol. 37, pp. 5-14, 1993.
- [42] Pavia M., Bianco A., Pileggi C. and Angelillo I.F., "Meta-Analysis of residential exposure to radon gas an lung cancer: Bull," *World health organ*, vol. 81, pp. 732-738, 2003.
- [43] Gonzalez M.L., Ruano-Ravina A., Torres-Duran M., Kelsey K.T., Provencio M., Parente-Lamelas I., Leiro-Fernandez V., Vidal-Garcia I., Castro-Anon O. and Martinez C., "Lung cancer and residential radon in never-smokers: a pooling study in the northwest of spain," *Environ Res*, vol. 172, pp. 713-718, 2019.
- [44] "Radon Gas and Lung Cancer," Utah Radon Services, 28 June 2017. [Online]. Available: <https://www.utahradonservices.com/radon-gas-and-lung-cancer/>.
- [45] Prak E.J., Lee H., Kim H.C., Sheen S.S., Koh S.B., Park K.S., Cho N.H., Lee C.-M. and Kang D.R., "Residential radon exposure and cigarette smoking in association with lung cancer: a matched case-control study in Korea," *Int. J. Environ. Res. Public Health*, vol. 17, p. 2946, 2020.
- [46] Bohm R., Sedlak A., Bulko M. and Holy K-, "Use of Threshold-Specific Energy model for the prediction of effects of smoking and radon exposure on the risk of lung cancer," *Radiat. Dosim*, vol. 160, pp. 100-103, 2014.
- [47] P. P. L. S. Hayes J, "MicroRNAs in cancer: biomarkers, functions and therapy," *Trends Mol. med.*, vol. 20, pp. 460-469, 2014.
- [48] T. J. e. al, "Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival," *Cancer Res.*, vol. 64, pp. 3753-3756, 2004.
- [49] W. H. L. J. W. Z. Liu ZL, "MicroRNA-21 (miR-21) expression promotes growth, metastasis, and chemoradioresistance in non-small cell lung cancer cells by targeting PTEN," *Mol. Cell. Biocehm.*, vol. 372, pp. 35-45, 2013.
- [50] S. J. e. al, "Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers," *Nat. Cell Biol.*, vol. 10, pp. 1470-1476, 2008.
- [51] B. M. e. al, "MicroRNA signatures in tissues and plasma predict development and prognosis od computed tomography detected lung cancer," *Proc. Natl Acad. Sci. USA*, vol. 108, pp. 3713-3718, 2011.
- [52] S. S. e. al, "Circulating microRNA signature as liquid-biopsy to monitor lung cancer in low-dose computed tomography screening," *Oncotarget*, vol. 6, pp. 32 868-32 877, 2015.
- [53] R. Doll, "Smoking and carcinoma of the lung," *Acta Unio Int. Contra Cancrum*, vol. 9, no. 3, pp. 495-506, 1953.
- [54] Krewski, D., Lubin, J.H., Zielinski, J.M., Alavanja, M., Catalan, V.S., Field, R.W., Klotz, J.B., Letourneau, E.G., Lynch, C.F., Lyon, J.I., Sandler, D.P., Schoenberg, J.B., Steck, D.J., Stolwijk, J.A., Weinberg, C. and Wilcox, H.B., "Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies," *Epidemiology*, vol. 16, no. 2, pp. 137-145, 2005.
- [55] Albeg, A.J., Brock, M.V., Ford, J.G., Samet, J.M. and Spivack, S.D., "Epidemiology of lung cancer: diagnosis and management of lung cancer, rrd ed: american college of chest physicians evidence-based clinical practice guidelines," *Chest*, vol. 143, no. 5 Suppl, pp. e1S-e29S, 2013.
- [56] Shankar, A., Dubey, A., Saini, D., Singh, M., Prasad, C.P., Roy, S., Bharati, S.J., Rinki, M., Singh, N., Seth, T, Khanna, M, Sethi, N, Kumar, S., Sirohi, B, Mohan, A, Guleria, R and Rath, G.K., "Environmental and occupational determinants of lung cancer," *Transl. Lung Cancer Res*, vol. 8, no. Suppl 1, pp. S31-S49, 2019.
- [57] J. Balmes, "Household air pollution from domestic combustion of soild fuels and health," *J. Allergy Clin. Immunol.*, vol. 143, no. 6, pp. 1979-1987, 2019.
-

-
- [58] Brenner, D.R., McLaughlin, J.R. and Hung, R.J., "Previous lung diseases and lung cancer risk: a systematic review and meta-analysis," *PLoS One*, vol. 6, no. 3, p. e17479, 2011.
- [59] Deng, B, Li, Y, Zhang, Y, Bai, L and Yang, P, "Helicobacter pylori infection and lung cancer: a review of an emerging hypothesis," *Carcinogenesis*, vol. 34, no. 6, pp. 1189-1195, 2013.
- [60] Qu, Y.L., Liu, J., Zhang, L.X., Wu, C.M., Chu, A.J., Wen, B.L., Ma, C., Yan, X.Y., Zhang, X, Wang, D.M., Lv, X. and Hou, S.J, "Asthma and the risk of lung cancer: a meta-analysis," *Oncotarget*, vol. 8, no. 7, pp. 11614-11620, 2017.
- [61] Luis Corrales, Rafael Rosell, Andres F. Cardona, Claudio Martin, Zyanya Lucia Zatarain-Barron and Oscar Arrieta, "Lung cancer in never smokers: The role of different risk factors other than tobacco smoking," *science direct*, p. 8, 2020.
- [62] Dai M, Liu D and Liu M, "Patients with cancer appear more vulnerable to SARS-COV-2: a multi-center study during the COVID-19 outbreak," *Cancer Discov*, 2020.
- [63] Liang W, Guan W and Chen R, "Cancer patients in SARS-CoV2-infection;a nationwide analysis in China," *Lancet Oncol* , vol. 21, pp. 335-337, 2020.
- [64] P. B. F. N. e. a. Sidney J, "HLA class I supertypes: a revised and updated classification," *BMC Immunology*, vol. 9, p. 1, 2008.
- [65] W. D. R. S. e. a. Grifoni A, "Targets of T cell responses to SARS-COV-2 coronavirus in humans with COVID-19 disease and unexposed individuals," *Cell* , 2020.
- [66] L. Y.-H. G. X.-H. e. a. Zhu F-C, "Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open label, non-randomised, first-in-human trial," *The Lancet*.
- [67] H. E. G. C. e. a. Docherty AB, "Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study," *BMJ*, vol. 369, p. m1985, 2020.
- [68] P. J. R. J. e. a. Clerkin KJ, "COVID-19 and Cardiovascular Disease," *Circulation*, vol. 141, pp. 1648-1655, 2020.
- [69] K.-W. H. S. S. e. a. Hoffmann M, "SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor," *Cell*, vol. 181, pp. 271-280, 2020.
- [70] B. M. Delaney GP, "Evidence-based estimates of the demans for radiotherapy," *Clin. Oncol.*, vol. 27, pp. 70-6, 2015.
- [71] Shafiq J, Hanna TP, Vinod SK, Delaney GP and Barton MB, "A population-based model of local control and survival benefit of radiotherapy for lung cancer," *Clin. Oncol*, vol. 28, pp. 627-38, 2016.
- [72] Giraud P, Morvan E, Claude L, Mornex F, Le Pechoux C, Bachaud J-M, Boisselier P, Beckendorf V, Morelle M and Carrere M-O, "Respiratory gating techniques for optimization of lung cancer radiotherapy," *J. Thorac. Oncol.*, vol. 6, pp. 2058-68, 2011.
- [73] E. H. Shalini K. Vinod, "Rdiotherapy treatment for lung cancer: Current status and future directions," *wiley online library*, 2020.
- [74] Shimizu S, Shirato H, Igura S, Akita-Dosaka H, Kitamura K, Nishioka T, Kagei K, Nishimura M and Miyasaka K, "Detection of lung tumor movement in real-time tumor-tracking radiotherapy," *Int. J. Radiat. Oncol. Biol. Phys.*, vol. 51, pp. 304-10, 2001.
- [75] Liu Y, Dong Y, Kong L, Shi F, Zgu H and Yu J, "Abscopal effect of radiotherapy combined with imune checkpoint inhibitors," *J. Hematol. Oncol.* , vol. 11, p. 104, 2018.
- [76] Rodriguez-Ruiz ME, Vanpouille-Box C, Melero I, Formenti SC and Demaria S, "Immunological mechanisms responsible for radiation-induced abscopal effect," *Trends Immunol*, vol. 39, pp. 644-55, 2018.
- [77] Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, Garon EB and Lee P, "Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial," *Lancet Oncol.*, vol. 18, pp. 895-903, 2017.
- [78] Henke LE, Olsen JR, Contreras JA, Curcuru A, DeWees TA, Green OL, Michalski J, Mutic S, Roach
-

- MC and Bradley JD, "Stereotactic online adaptive radiation therapy (SMART) for ultracentral thorax malignancies: result of a phase 1 trial," *Adv. Radiat. Oncol.*, vol. 4, pp. 201-9, 2018.
- [79] Finazzi T, Palacios MA, Haasbeek CJA, Admiraal MA, Spoelstra FOB, Bruynzeel AME, Slotman BJ, Lagerwaard FJ and Senan S, "Stereotactic MR-guided adaptive radiation therapy for peripheral lung tumors," *Radiatother. Oncol.*, vol. 144, pp. 46-52, 2020.
- [80] Hestbech MS, Siersma V, Dirksen A, Pedersen JH and Brodersen J, "Participation bias in a randomised trial of screening for lung cancer," *Lung Cancer*, vol. 73, pp. 325-331, 2011.
- [81] Fontana RS, Sanderson DR, Woolner LB, Miller WE, Bernatz PE, Payne WS and Taylor WF, "The Mayo lung project for early detection and localization of bronchogenic carcinoma: a status report," *Chest*, vol. 67, pp. 511-522, 1975.
- [82] Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE and Muhm JR, "Lung cancer screening: the Mayo program," *J. Occup. Med.*, pp. 746-750, 1986.
- [83] Oken MM et al, "Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial," *JAMA*, vol. 306, pp. 1865-1873, 2011.
- [84] Zhang Y, Li X, Segars WP and Samei E, "Comparison of patient specific dose matrices between chest radiography, tomosynthesis, and CT for adult patients of wide ranging body habitus," *Med. Phys.*, vol. 41, p. 023901, 2014.
- [85] Naidich DP, Marshall CH, Gribbin C, Arams RS and McCauley DI, "Low-dose CT of the lungs: preliminary observations," *Radiology*, vol. 175, pp. 729-731, 1990.
- [86] Larke FJ, Kruger RL, Cagnon CH, Flynn MJ, McNitt-Gray MM, Wu X, Judy PF and Cody DD, "Estimated radiation dose associated with low-dose chest CT of average-size participants in the National Lung Screening Trial," *AJR Am. J. Roentgenol.*, vol. 197, pp. 1165-1169, 2011.
- [87] N. L. S. T. R. T., "Reduced lung-cancer mortality with low-dose compound tomographic screening," *N Engl. J. Med.*, vol. 365, pp. 395-409, 2011.
- [88] Tammemagi MC et al, "Evaluation of the lung cancer risks at which to screen ever- and never- smokers: screening rules applied to the PLCO and NLST cohorts," *PLoS Med.*, vol. 11, p. e1001764, 2014.
- [89] N. N. e. al., "Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration compared with conventional approaches: an open-label, pragmatic, randomised controlled trial," *Lancet Respir. Med.*, vol. 3, pp. 282-289, 2015.
- [90] Rivera MP, Mehta AC and Wahidi MM, "Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines," *Chest*, vol. 143 (5 Suppl), p. e142S, 2013.
- [91] W. D. e. al., "Derivation of a bronchial genomic classifier for lung cancer in a prospective study of patients undergoing diagnostic bronchoscopy," *BMC Med. Genomics*, vol. 8, p. 18, 2015.
- [92] S. G. e. al, "A bronchial genomic classifier for the diagnostic evaluation of lung cancer," *N Engl. J. Med.*, vol. 373, pp. 243-251, 2015.