Scientific Research Publishing

Journal of Cancer Therapy, 2022, 13, 450-463
https://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Non-Small Cell Lung Cancer: Treatment, Diagnosis, and Life after Treatment

Reethi Yadlapalli*, Eswar Kumar Adoni Valmiki, Terry Oroszi

Boonshoft School of Medicine, Wright State University, Dayton, OH, USA
Email: *yadlapalli.7@wright.edu

How to cite this paper: Yadlapalli, R., Valmiki, E.K.A. and Oroszi, T. (2022) Non-Small Cell Lung Cancer: Treatment, Diagnosis, and Life after Treatment. *Journal of Cancer Therapy*, **13**, 450-463.
https://doi.org/10.4236/jct.2022.137040

Received: May 3, 2022
Accepted: July 15, 2022
Published: July 18, 2022

Abstract

Lung cancer is becoming the most common cancer globally. In China, Lung cancer has become prevalent among preceding compared to present smokers. There are many treatments for lung cancer globally like Chemotherapy, Radiotherapy, Surgery, and Targeted therapy [1] [2]. Generally, lung cancer starts in the lungs. The spongy lungs in the chest inhale oxygen and exhale carbon dioxide. Those who smoke regularly have the highest risk of lung cancer than nonsmokers. This risk increases with an increase in length, time, and the number of cigarettes smoked. Immediate treatment will help in reducing the severity of cancer. The complications of lung cancer include shortness of breath, coughing up blood, pain, and fluid in the chest. Therefore, the primary step in preventing lung cancer is quitting smoking [3].

Keywords

Treatment, Lung Cancer, Non-Small Cell Lung Cancer, Diagnosis

1. Introduction

Treatment of Non-small cell lung cancer includes Anti-BRAF (V-RAF murine viral oncogene homolog B1) therapies, Surgery, Radiotherapy, Chemotherapy, and Targeted therapy. According to the reports, in 2019, approximately 16.9 million people worldwide have lung cancer. However, within ten years, this number has increased to 33%, of which 4% are adults. The main reason for lung cancer is smoking—other risk factors like exposure to asbestos, hereditary, toxic materials, and radon gas. There are many ways lung cancer is spread in the body. It starts from the cells of bronchi, bronchioles, or alveoli.

2. Pathology and Types of Lung Cancer

Lung cancer mainly includes two classes.

- Small-cell Lung Cancer
- Non-small Cell Lung Cancer

Lung cancer mainly depends on the measurements and location of the tumor, the spread of cancer into lymph nodes, and the spread of cancer into other parts of the body [4].

2.1. Small-Cell Lung Cancer

10% to 15% of lung cancers are small-cell lung cancers. Lung cancer can cure with treatments like chemotherapy. Radiotherapy is not severe compared to non-small cell lung cancer [5].

2.2. Non-Small Cell Lung Cancer

About 85% of Lung cancers are non-small cell lung cancers [6]. Small cell lung cancer is the most frequent type of lung cancer, and it further includes four subtypes.

1) Adenocarcinomas
2) Squamous cell carcinoma
3) Small cell carcinoma
4) Large cell carcinoma

Adenocarcinomas are peripheral masses that spread into the body in the form of Metastasis. Patients suffering from lung diseases are likely to get affected by this [7]. Squamous cell carcinomas are masses present in bronchi. These metastasize slowly. Small cell carcinomas are centrally located and clinically hostile. Large cell carcinomas are difficult to identify and are large peripheral masses [8].

3. Stages of Non-Small Cell Lung Cancer

They can determine lung cancer stages by looking at the tumor. The TNM system describes lung cancer stages. T represents Tumor size, N represents Node action, and M represents Metastasis. Stages of lung cancer are stages 0 to 4.

Occult Stage

It is otherwise named hidden cancer. Mucus gathers the lung cancer cells.

Stage 0: The size of the tumor is minute. Cells are not developed completely and have not expanded into the lungs.

Stage 1: Spread Cancer cells in tissues of the lungs except for lymph nodes.

Stage 2: Distribution of Cancer cells into lymph nodes.

Stage 3: Spread of the disease into the chest.

Stage 4: Spread of the disease throughout the body.

4. Risk Factors and Diagnosis

The critical risk factors for lung cancer are the following:

4.1. Smoking

Smoking is one of the primary risk factors for lung cancer. The mortality rate

increased at the beginning of the 20th century due to the overconsumption of tobacco, and smoke.

Released from tobacco contains toxic substances, carcinogens, and many harmful chemicals. Calculation of the smoking intensity is by the number of years and cigarettes smoked per day [9].

4.2. Electronic Cigarettes

The smoke of cigarettes contains nicotine in which. It got a patent in 1965. It became popular by 2003 and was almost available everywhere in 2005. There are 460 brands and 7700 flavors. Adults between 12 to 18 widely use these. In the USA, a survey done by national youth in 2017 reported that 20.8% of high school students and 4.9% of middle school students highly use e-cigarettes [10]. Studies show that vapor generated from e-cigarettes is harmful and shows long-term effects. But data suggests that e-cigarettes are less harmful than regular cigarettes [11].

4.3. Occupational Exposure

The cause of five to ten percent of lung cancer is occupational exposure to natural asbestos in rocks like altered ultramafic and mafic rocks. International Agency for Research on Cancer reported that occupational exposure. [12] includes exposure to chromium, arsenic, and cadmium. Studies conducted on people in Canada and Europe conclude that there is a rise in the risk of asbestos exposure by 12% in women and 24% in men [13].

4.4. Diet

Intake of foods that are rich sources of antioxidants, nutrients, and vitamins might decrease the cancer risk, but some studies proved that a high intake of antioxidants and Carotenoids, Preservation of Meat in salt like Sausages, pork, and Deep-fried recipes proved that these might increase the possibilities of lung cancer.

4.5. Alcohol Consumption

A study conducted on 399, 767 people and 3137 lung cancer patients showed high alcohol consumption.

4.6. Cannabis

Cannabis is the most common drug used other than tobacco. Approximately 7000 new people per day are smoking cannabis. The international lung cancer consortium conducted surveys on 2159 patients. They reported a slight indication that the effects of cannabis might be long-term [14]. Cannabis contains the same toxic chemicals that are present in tobacco.

4.7. Radon

Radon has no taste, odor, and color. It is a radioactive gas obtained from soil and

generated during the nuclear disintegration of uranium and thorium [15]. The next most common cause of lung cancer is Radon exposure in the United States. Because of radon gas, 3% to 14% of lung cancer patients are affected. However, we all believe radon mainly causes it, but it depends on the population [16].

4.8. Human Immunodeficiency Virus (HIV)

HIV is related to lung cancer. It is the most common death cause of cancer people [17]. Adults infected with HIV are more likely to smoke cigarettes than others. Studies also revealed that treatment for HIV may often reduce cancer risk.

4.9. Nonsmokers

25% of lung cancer patients in the world are nonsmokers [18]. Among them, 60% to 80% are females. Risk factors correlated with nonsmokers are cooking fumes, radon gas, and Hereditary. The cancer risk for nonsmokers has significantly increased over the decades [19]. **Diagnosis:** Diagnosis of Lung cancer by Weight loss, fatigue, cough, and chest pain. Diagnosis of lung cancer in the early-stage results in a high Survival rate and require high care by physicians even though they do not show any symptoms [20] (**Table 1**).

Table 1. Different methods of diagnosis of lung cancer.

Diagnostic method	sensitivity	specificity	Indication	Comments
Sputum cytology	Central 71% Peripheral <50%	99%	Central and hemoptysis	Non-invasive
Thoracentesis	80%	>90%	Pleural effusion	-
Excisional biopsy	-	-	Palpable lymphadenopathy	-
Flexible bronchoscopy	Central tumors 88%	90%	Central or peripheral tumor	Transbronchial inspiration increases sensitivity in peripheral tumors
Transthoracic needle aspiration	Peripheral tumors 90%	97%	Peripheral tumor in non-surgical patients is inconclusive	Transbronchial inspiration increases sensitivity in peripheral tumors
Video-assisted thoracotomy	-	-	Small peripheral tumors (<2 cm in diameter)	Do not need thoracotomy
Thoracotomy	-	-	It cleans resectable tumors	Treatment is necessary

Reference: [16].

Generally, the Usage of CT scans to diagnose Lung cancer. There are several ways for tissue evaluation like bronchoscopy, thoracentesis, and mediastinoscopy. The minimal, confined approach is to choose the highest yield method. EBUS-TBNA is the most used method for central tumors in the body. They gave tissue diagnoses to patients suffering from non-small cell lung cancer. There are many ways lung cancer occurs when disease severity is less [21] [22]. Some include flexible bronchoscopy, sputum cytology, and thoracic needle aspiration. Sputum cytology is to detect centrally located tumors in the body. It notices 71% of central and 50% of peripheral tumors. Using flexible bronchoscopy is to see 88% of central tumors. Bleeding and pneumothorax are severe injuries of transbronchial needle aspiration [23]. Transthoracic needle aspiration seems to be effective compared to bronchoscopy. The most challenging part of this is the insertion of the needle into the chest tube. Video-assisted thoracoscopy is to detect small peripheral tumors [24].

5. Treatment for Non-Small Cell Lung Cancer

Treatments for non-small cell carcinoma include molecularly Targeted therapy, Surgery, Immunotherapy, chemotherapy, and Radiotherapy (**Table 2**).

Table 2. Treatment of lung cancer according to stage.

Stage	Primary Treatment	Adjuvant therapy	Five-year survival rate (%)
Non-small cell carcinoma			
I	Resection	Chemotherapy	60 to 70
II	Resection	Chemotherapy with or without radiotherapy	40 to 50
IIIA-Resectable	Resection with or without preoperative chemotherapy	Chemotherapy with or without radiotherapy	15 to 30
IIIA-Unresectable	Chemotherapy with concurrent or subsequent radiotherapy	None	10 to 20
IIIB-Pleural effusion	Chemotherapy with concurrent or subsequent radiotherapy	None	10 to 15
Small cell carcinoma			
Limited disease	Chemotherapy with concurrent radiotherapy	None	15 to 25
Extensive disease	Chemotherapy	None	<5

Reference: [16].

6. Recommended Treatments

6.1. Surgery

Surgery is not suitable for all patients. It is only recommended for patients with stage One to stage Three A. Surgery is one of the best methods to cure lung cancer. But for surgery, the patient must agree to the intervention of surgery. Recently, changes to surgical eligibility, including lobectomy [17] [25]. In the beginning, many surgeries focused on increasing the selection criteria for surgical incisions of lung cancer in people on the edge of operation [26].

Initially, verification of writings on whether lobectomy is needed or not for minor lumps [27] does not have proof due to combined reports. Most of them are from little reminiscence series, and the lobectomy method will be the primary standard method for the surgical department of NSCLC.

6.2. Targeted Therapy

Changing cell signaling and regulatory pathways that pathways can inactivate, resulting in lung cancer treatment. So, this kind of method is in receptor tyrosine kinases. Most of the patients are with inactivated NSCLS and EGFR carrying. There advanced many different EGFR inhibitors long ago. Gefitinib is the first lung cancer drug that FDA approved. However, during phase 3 clinical trials, Gefitinib failed to report the endurance of their drug test.

6.3. Molecularly Targeted Therapy

Almost 10% - 30% of tumors activate the tyrosine kinase domain in the EGFR gene. Osimertinib is the 3rd generation EGFR TKI in front-line therapy. Based on the research studies, contrast Osimertinib with the first-generation Patients with EFGR TKI who developed a superior median OS of Osimertinib for 38.6 months.

6.4. Chemotherapy

Patients with significant lung cancers are present at the time of treatment. The primary use of chemotherapy is for patients whose disease is advanced [28]—treatment of Stages from IIA through IIIA NSCLC patients with adjuvant chemotherapy. Typically, chemotherapy is pretty much better for lung cancer patients. However, still, there is an insight thought about using the standard traditional therapeutic agents [29]. All these years, there has been an increase in cancer biology studies. These studies have opened several helpful therapeutic strategies, including EGFR, Signal transduction, and Angiogenesis pathways. Certain lung cancer patients with high-risk diseases might have a chance to welcome back the condition. In 1995 an excellent data analysis took place on 52 different patients in the clinical trials and compared the results after the surgery; in this analysis, a 5-year-old who lived through the chemotherapy saw significant results because he received platinum-based chemotherapy.

One thousand eight hundred sixty-seven subjects enrolled in international

adjuvant lung cancer trials, and these patients are from Stage One to Stage Three cancer. Besides, these different patients also receive platinum-based chemotherapy [30]. Under observation for five years, relic advantage was 4.1%, and the chance of dying went down to 14%. Four hundred eighty-two subjects in Stage Two cancer from Stage One got enrolled in the national cancer institute of Canada and inter-group study.

6.5. Radiotherapy

The veteran's administration of lung cancer study group conducted the first radiation therapy clinical trial for lung cancer patients. This study group has segregated the patients regarding small cell and extensive cell diagnoses usually given to receive a thoracic artery [31]. Hadron is a minute particle affected by nuclear force. These hadrons carry major biologic validness and can quickly transfer their energy where there is low oxygen. However, the main problem with this Hadron therapy is that it is costly with the systemic network. Nevertheless, many things have helped patients survive lung cancer, which are nothing but cell differentiation, maintaining a proper diet, changing the markers of molecules, and quitting smoking. There is a hospital with 5018 beds with 712 patients. On top of that, these patients survived due to the changes in age, treatment type, and quitting smoking.

6.5.1. Advances in Radiotherapy

Radiotherapy has become one of the most popular treatments for lung cancer. Radiotherapy techniques are precise with fewer reactions—the primary use of radiotherapy is to diagnose tumors. The most advanced method of Radiotherapy techniques was Four-dimensional Computed tomography. Computed tomography is to identify the tumors in any case site. The cone beam's design quality recognizes the Tumor site before and during operation. They are merging these techniques with high-quality methods of immobilization of the victim. In addition, they proved the capacity to process Stereotactic Ablative Body Radiotherapy. SABR is the transfer of high doses in small fragments and geometric accuracy.

There is an alternative technique to the movement of tumors called respiratory gating. In this process, the ray of radiotherapy is active based on the tumor's location [32]. Achievement of Gating is by the breath-hold method of patients. Where the patients hold their breath during which treatment during that short time, this process is challenging for patients with lung diseases.

6.5.2. KRAS Mutations

KRAS mutations are nothing but unregulated KRAS genes that takes towards the GTP-bound state. Smoking caused by tobacco activates KRAS mutations in lung cancer. On examining the patient's NSCLC and 30% went up. An extensive study on these mutations found that the codon variant is the most common variant found in the protein. These proteins are inside the amino acid glycine and

cystine. Even though there is excellent work behind finding and developing targeted therapies, there are no certain drugs that deal with KRAS mutations [33].

For the last 40 years, KRAS has been the main thing to study and develop the drugs. However, five years ago, many scientists thought that dealing with KRAS mutations was a considerable challenge [34] in scientific history because of its complex structure.

The treatment of non-small cell lung cancer involves evolving selected agents for cancers protecting gene mutations. Many somatic driver mutations were mentioned, with the frequencies and spectrum of mutations varying among squamous cell carcinoma and adenocarcinoma. Regular testing of genes for somatic mutations from the biopsy is going towards the standard of excellent patient care—recognizing specific mutations in ALK & EGFR, which used FDA-approved selected treatments to deliver medical advantages. The finding of other gene mutations can easily allow patients and doctors towards specific clinical trials along with freshly chosen agents. At present several treatments are under the expansion of selected receptor tyrosine kinases which are activated.

6.5.3. EGFR

EGFR mutations aid in the critical signaling of EGFR, which are present in the tyrosine kinase domain. PI3K-AKT and RAS-MEK-ERK pathways play a crucial role in the development and shifting of cancer cells, existence. Mutant EGFR activates these. Lung cancers associated with EGFR mutations are incredibly delicate with EGFR tyrosine kinase inhibitors. These used alterations in EGFR for genetic screening to find stage 4 patients who accept EGFR TKIs in a First-line setting [35]. The present investigation concentrates on enhancing time and successful methods to focus on resistance mechanisms during development. One of the familiar resistance mechanisms is EGFR T790M in resistant tumors (~50%).

6.5.4. ALK

The merging of EML 4 and ALK is occurred by the transposition of chromosome 2. Chromosome results in the encoding of a fusion protein. ALK signaling activates the growth and cell proliferation of RAS-ME-ERK, PI3K-AKT, and JAK3-STAT3 pathways. Relocating of ALK in non-small cell lung cancer is correlated with the patient's age, smoking history, and morphology of signet ring cell. The restraining of ALK and many kinases are by crizotinib; they exhibited a 57% response rate in patients with ALK translocations [18].

6.5.5. ROS1

The relocation of chromosomes by the involvement of the ROS1 and recognition gene in1.5% of lung adenocarcinomas. Most of the ROS1 in nonsmokers, young people, and people are affected by adenocarcinoma. Patients with translocations of RO1 respond to Crizotinib [18].

6.5.6. KRAS

Generally, the Alteration of KRAS occurs in lung cancer people. Usually, the re-

port shows ~25% of adenocarcinomas in lung cancer patients. KRAS mutations restrain codons 12 and 13. These are unique to patients' EGFR, ALK, and Smoking history. KRAS mutations relate to EGFR TK1 therapy. At present, there are no medications that straightly target EGFR mutations. [18].

6.5.7. PI3K

PIK3CA is gathered at two main sites, exon 9 and 20, which encodes the kinase and helical domains of the protein. It affects the increase in lipid kinase activity and signaling of PI3K-AKT. Several PI3k inhibitors are under origination which varies from inhibition of PI3K-AKT to pan-PI3K to Selective PI3K inhibitors. Preclinical data suggest that PI3K mutations are highly delicate to one agent of PI3K inhibitors [18].

6.5.8. FGFR1

It is the possible target in squamous cell lung cancer. Initiation of FGFR1 leads to downstream signaling identification of ~20% of squamous cell lung cancer. Prevention of FGFR1 in both cancer cells and mouse models results in retardation of growth and cell death. They also slow down tyrosine kinases [18].

6.5.9. PDGFRA

It is visible mainly in squamous cell lung cancer. The slowdown of PDGFRA through shRNA damages cell growth and harbor-free growth. Different inhibitors of PDGFRA are under clinical development. These also control multiple kinases.

6.5.10. DDR2

It merges with collagen and produces cell transfer, rapid cell growth, and survival. Squamous cell lung cancer has DDR2. Prevention of DDR2 results in the slowdown of cell growth. DDR2 mutant Ectopic expression results in the transformation of cells. Even though different mutations contain different transformative capacities, it proves that these mutations are oncogenic, and cancers with DDR2 mutations are delicate to DDR2 inhibitors.

6.5.11. BRAF

Identification of these mutations in 1% to 3% of non-small cell lung cancer patients. The action of V600E in BRAF mutant is unknown.

6.6. Prevention

Many lung cancers can be easily avoided by quitting smoking. Since 1960, the smoking people ratio has been slightly reduced. In 2016 United States government conducted a survey, and in the survey, they came to know that 50.5% of smoking cigarettes came from adults. Even though many smoking companies have mentioned that smoking is harmful to health and can cause cancer and death [36]. Early findings are the only choice to find people suffering very highly. Globally, lung cancer will be the most significant health problem in this 21st century due to its rapid advances in diagnosis, risk assessment, and early detec-

tion. Treatment will be critical and prevent advances in disease.

6.7. Apoptosis and Autophagy

These play a significant part in the process of lung cancer. Autophagy is also called self-eating. This late endosome is present in autophagy. Alternatively, it can be either shifted or merged with the lysosome to produce autolysosome.

Apoptosis is otherwise known as cell death. Intracellular or extracellular signals are prominent by a morphological change in cell death. Autophagy can function as positive and negative in encouraging apoptosis in non-small cell lung cancer. Autophagy and apoptosis get alerted under the stress of cells. Generally, autophagy leads to apoptosis, supporting the homeostasis of cells.

Many results show that autophagy is also called Autophagic cell death. The deficiency of chromatin condensation identifies it. LC3 Lipidation and independent apoptosis by inhibiting the pathway of autophagy or autophagy genes.

ADC contains several methods of cell death. The caspases and apoptotic processes of autophagy-related proteins are part of cell death. Recent studies proved that caspases play a role in autophagy regulation. The activated caspases prevent autophagy, in which caspases collapse the proteins that are associated with autophagy. For example, caspase eight is popularly known for preventing pro-autophagy. Inhibition of caspase eight results in hyperactive autophagy of T cells. Whereas Caspase 9 is a protein related to the production of the apoptosome and apoptotic pathways intrinsic. It represents those caspases that are activated execute synonyms as well as strengthen autophagy [37].

6.8. Advanced Treatments

The exponential growth of selected remedies with a progressive and robust group of drugs and portrayal of the mechanism of obtained resistivity confirmed the character for repeated genomic profiling during Tumor development, mainly in cases with EGFR mutations. T790M, the most common root of resistance, is fortunately treated with Osimertinib. The continuous study of the Genomic index is carried out by numerous biopsies. It leads to many complications. The alternative is to utilize plasma genotyping along with sequencing circulating tumor DNA. The study conducted on 216 patients with plasma genotyping and central tissue showed 70% of plasma genotyping. Tissue negative results patients identified with 31% plasma EGFR mutations. The reason was that the medication of Osimertinib and ORR and PFS resulted in equal T790M. Treatment of continuous biopsy for patients with negative plasma results. Due to rare gene alterations, applying many types of research on non-small cell lung cancer is problematic. Enrolling patients to conduct studies has become difficult. So innovative master protocols are invented to check this issue [38].

7. Life after Treatment

Even after lung cancer treatment, patients are likely to suffer from symptoms

associated with lung cancer. Since it depends on several factors, in the case of surgery, there is evidence and data that support patients will lead an everyday life after the surgery. There are no good reasons to prove that patients will return to daily life in treatments other than surgery. However, as technology increases, advanced methods might prove this wrong. Suppose the disease is detected in an early stage and given proper treatment. In that case, the quality of life is better when compared to the disease diagnosed lately performing the Studies on people who have undergone lung cancer treatment. QOL (Quality of life) levels at Six to Nine. In case of surgery, QOL results in six months to One year for better recovery [32].

8. Conclusion

Being diagnosed with lung cancer is a horrifying situation. With advances in treatments, more people live longer and live well with lung cancer. There are ways to make positive lifestyle changes to improve the quality of life. Even after many treatments and techniques, lung cancer has become a severe issue. A plan with proper diagnosis and treatment plays a crucial role in cancer control to control cancer. The significant achievement of this plan is to cure cancer and extend the patient's life span. This disease reached its peak mainly in china. The survival rate depends on several factors—treatment in the early stages of lung cancer results in high chances of survival rate. The advances in radiotherapy are trending due to the increased survival rate.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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