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RECENT DEVELOPMENT IN TREATMENT FOR NON SMALL CELL LUNG CANCER A REVIEW

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ABSTRACT

The lungs are vital organs. Working with the heart and circulatory system, they provide life-sustaining oxygen and rid the body of carbon dioxide. Normal lungs have a great reserve capacity to meet the body's need for oxygen across a wide variety of circumstances. The same is true of the heart and circulatory system. This reserve capacity permits cancerous lung tumors to grow for years without compromising lung function. Furthermore, the lungs do not have many nerves to transmit pain messages. Therefore, a cancerous lung tumor can grow for many years without causing any symptoms. Lungs cancer is the fatal disease in worldwide. The prognosis of lungs cancer is generally favorable. Non small cell lungs cancer is regarded as life threatening disease occurred mostly than other types. Hence early diagnosis and quick treatment is essential. Normally surgery, radiation therapy and chemotherapy allow a good prognosis for non small cell lungs cancer.

Key Words:- Non small cell lungs cancer, Prognosis, Diagnosis.

INTRODUCTION

Normal body cells grow, divide into new cells, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

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Cancer (Hanahan *et al.,* 2000) begins when cells in a part of the body start to grow out of control. There are many kinds ofcancer, but they all start because of out-of-control growth of abnormal cells. Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer cells can also invade (grow into) other tissues, something that normal cells cannot do. Growing out of control and invading other tissues is what makes a cell a cancer cell. Cells become cancer cells because of damage to DNA. DNA is in every cell and directs all its actions. In a normal cell, when DNA gets damaged the cell either repairs the damage or the cell dies. In cancer cells, the

damaged DNA is not repaired, but the cell doesn't die like it should. Instead, this cell goes on making new cells that the body does not need. These new cells will all have the same damaged DNA as the first cell does. People can inherit damaged DNA, but most DNA damage is caused by mistakes that happen while the normal cell is reproducing or by something in our environment. Sometimes the cause of the DNA damage is something obvious, like cigarette smoking. But often no clear cause is found. In most cases the cancer cells form a tumor. Some cancers, like leukemia, rarely form tumors. Instead, these cancer cells involve the blood and blood-forming organs and circulate through other tissues where they grow. Cancer cells often travel to other parts of the body, where they begin to grow and form new tumors that replace normal tissue. This process is called metastasis. It happens when the cancer cells get into the bloodstream or lymph vessels of our body. No matter where a cancer may spread, it is always named (and treated) based on the place where it started. For example, breast cancer that has spread to the liver is still breast cancer, not liver cancer. Likewise, prostate cancer that has spread to the bone is still prostate cancer, not bone cancer.

Different types of cancer can behave very differently. For example, lung cancer and breast cancer are very different diseases. They grow at different rates and respond to different treatments. That is why people with cancer need treatment that is aimed at their particular kind of cancer. Not all tumors are cancerous. Tumors that aren't cancer are called benign. Benign tumors can cause problems – they can grow very large and press on healthy organs and tissues. But they cannot grow into (invade) other tissues. Because they can't invade, they also can't spread to other parts of the body (metastasize). These tumors are almost never life threatening. Lung cancers (Gould *et al.,* 2004) can start in the cells lining the bronchi and parts of the lung such as the bronchioles or alveoli. Lung cancers are thought to start as areas of pre-cancerous changes in the lung. The first changes in the genes (DNA) inside the lung cells may cause the cells to grow faster. These cells may look a bit abnormal if seen under a microscope, but at this point they do not form a mass or tumor. They cannot be seen on an x-ray and they do not cause symptoms. Over time, the abnormal cells may acquire other gene changes, which cause them to progress to true cancer. As a cancer develops, the cancer cells may make chemicals that cause new blood vessels to form nearby. These blood vessels nourish the cancer cells, which can continue to grow and form a tumor large enough to be seen on imaging tests such as x-rays. At some point, cells from the cancer may break away from the original tumor and spread (metastasize) to other parts of the body. Lung cancer is often a life-threatening disease (Alberg *et al.,* 2005) because it tends to spread in this way even before it can be detected on an imaging test such as a chest x-ray.

Anatomy of lungs

The lungs are two sponge-like organs found in chest. The right lung is divided into three sections, called lobes. The left lung has 2 lobes. The left lung is smaller because the heart takes up more room on that side of the body. When someone breathes in, air enters through the mouth or nose and goes into the lungs through the trachea (windpipe). The trachea divides into tubes called the bronchi (singular, bronchus), which enter the lungs and divide into smaller bronchi. These divide to form smaller branches called bronchioles. At the end of the bronchioles are tiny air sacs known as alveoli. Many tiny blood vessels run through the alveoli. They absorb oxygen from the inhaled air into the bloodstream and pass carbon dioxide from the body into the alveoli. This is expelled from the body when someone exhales. Taking in oxygen and getting rid of carbon dioxide are the lungs' main functions. A thin lining layer called the pleura surrounds the lungs. The pleura protect the lungs and help them slide back and forth against the chest wall as they expand and contract during breathing. Below the lungs, a thin, dome-shaped muscle called the diaphragm separates the chest from the abdomen. When someone breathes, the diaphragm moves up and down, forcing air in and out of the lungs (Gray 1918).

The lymph (lymphatic) system

The lymph system is one of the ways in which lung cancers can spread. This system has several parts:

- Lymph nodes are small, bean-shaped collections of immune system cells (cells that fight infections) that are connected by lymphatic vessels.
- Lymphatic vessels are like small veins, except that they carry a clear fluid called lymph (instead of blood) away from the lungs.
- Lymph contains excess fluid and waste products from body tissues, as well as immune system cells.

Lung cancer cells can enter lymphatic vessels and begin to grow in lymph nodes around the bronchi and in the mediastinum (the area between the 2 lungs). Once lung cancer cells have reached the lymph nodes, they are more likely to have spread to other organs of the body as well. The stage (extent) of the cancer and decisions about treatment are based in part on whether or not the cancer has spread to the nearby lymph nodes in the mediastinum.

Types of lung cancer

There are 2 major types of lung cancer:

- Small cell lung cancer (SCLC)
- Non-small cell lung cancer (NSCLC)

(If a lung cancer has some cells with characteristics of SCLC and other cells with characteristics of NSCLC it is called a combined small cell/non-small cell cancer. This is uncommon.)
These 2 types of lung cancer are treated very differently.

Non-small cell lung cancer
About 85% to 90% of lung cancers are non-small cell lung cancer (NSCLC). There are 3 main subtypes of NSCLC. The cells in these subtypes differ in size, shape, and chemical make-up when looked at under a microscope. But they are grouped together because the approach to treatment and prognosis (outlook) are often very similar(Horn *et al.,* 2014).

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Squamous cell (epidermoid) carcinoma
About 25% to 30% of all lung cancers are squamous cell carcinomas. These cancers start in early versions of squamous cells, which are flat cells that line the inside of the airways in the lungs. They are often linked to a history of smoking and tend to be found in the middle of the lungs, near a bronchus.

Adenocarcinoma
About 40% of lung cancers are adenocarcinomas. These cancers start in early versions of the cells that would normally secrete substances such as mucus. This type of lung cancer occurs mainly in current or former smokers, but it is also the most common type of lung cancer seen in non-smokers. It is more common in women than in men, and it is more likely to occur in younger people than other types of lung cancer. Adenocarcinoma is usually found in outer parts of the lung. It tends to grow slower than other types of lung cancer, and is more likely to be found before it has spread outside of the lung. People with a type of adenocarcinoma called adenocarcinoma in situ (previously called bronchioloalveolar carcinoma) tend to have a better outlook (prognosis) than those with other types of lung cancer.

Large cell (undifferentiated) carcinoma:
This type of cancer accounts for about 10% to15% of lung cancers. It can appear in any part of the lung. It tends to grow and spread quickly, which can make it harder to treat. A subtype of large cell carcinoma, known as large cell neuroendocrine carcinoma, is a fast-growing cancer that is very similar to small cell lung cancer.

Other subtypes:
There are also a few other subtypes of non-small cell lung cancer, such as adenosquamous carcinoma and sarcomatoid carcinoma. These are much less common.

Lung carcinoid tumors:
Carcinoid tumors of the lung account for fewer than 5% of lung tumors. Most are slow-growing tumors that are called typical carcinoid tumors. They are generally cured by surgery. Some typical carcinoid tumors can spread, but they usually have a better prognosis than small cell or non-small cell lung cancer. Less common are atypical carcinoid tumors. The outlook for these tumors is somewhere in between typical carcinoids and small cell lung cancer. For more information about typical and atypical carcinoid tumors, see the separate document Lung Carcinoid Tumor.

Cancers that spread to the lungs:
Cancers that start in other organs (such as the breast, pancreas, kidney, or skin) can sometimes spread (metastasize) to the lungs, but these are not lung cancers. For example, cancer that starts in the breast and spreads to the lungs is still breast cancer, not lung cancer. Treatment for metastatic cancer to the lungs is based on where it started (the primary cancer site).

Risk factors for non-small cell lung cancer
(Amos *et al.,* 2010,Moir *et al.,* 2008).

Tobacco smoke
Smoking is by far the leading risk factor for lung cancer. In the early 20th century, lung cancer was much less common than some other types of cancer. But these changed once manufactured cigarettes became readily available and more people began smoking. At least 80% of lung cancer deaths are thought to result from smoking. The risk for lung cancer among smokers is many times higher than among non-smokers. The longer is the smoking of more packs of cigarettes(Berthiller *et al.,* 2008) per a day, the greater is the risk. Cigar smoking and pipe smoking are almost as likely to cause lung cancer as cigarette smoking. Smoking low-tar or "light" cigarettes increases lung cancer risk as much as regular cigarettes. There is concern that menthol cigarettes may increase the risk even more since the menthol allows smokers to inhale more deeply.

Secondhand smoke:
The breathing in the smoke of others (called secondhand smoke or environmental tobacco smoke) can increase the risk of developing lung cancer by almost 30%. Workers who have been exposed to tobacco

(Pletcher *et al.*, 2012) smoke in the workplace are also more likely to get lung cancer. Secondhand smoke is thought to cause more than 7,000 deaths from lung cancer each year. Some evidence suggests that certain people are more susceptible to the cancer-causing effect of tobacco smoke than others.

Radon

Radon is a naturally occurring radioactive gas that results from the breakdown of uranium in soil and rocks. It cannot be seen, tasted, or smelled. According to the US Environmental Protection Agency (EPA), radon is the second leading cause of lung cancer in this country, and is the leading cause among non-smokers. Outdoors, there is so little radon that it is not likely to be dangerous. But indoors, radon can be more concentrated. When it is breathed in, it enters the lungs, exposing them to small amounts of radiation. This may increase a person's risk of lung cancer. The lung cancer risk from radon is much lower than that from tobacco smoke. However, the risk from radon is much higher in people who smoke than in those who don't. Radon levels in the soil vary across the country, but they can be high almost anywhere.

Asbestos

Workplace exposure to asbestos fibers is an important risk factor for lung cancer. Studies have found that people who work with asbestos (in some mines, mills, textile plants, places where insulation is used, shipyards, etc.) are several times more likely to die of lung cancer. In workers exposed to asbestos who also smoke, the lung cancer risk is much greater than even adding the risks from these exposures separately. It's not clear to what extent low-level or short-term exposure to asbestos might raise lung cancer risk. Both smokers and non-smokers exposed to asbestos also have a greater risk of developing mesothelioma, a type of cancer (Veeramachaneni *et al.*, 2008) that starts in the pleura (the lining surrounding the lungs).

Other cancer-causing agents in the workplace

Other carcinogens (cancer-causing agents) found in some workplaces that can increase lung cancer risk include:

- Radioactive ores such as uranium
- Inhaled chemicals or minerals such as arsenic, beryllium, cadmium, silica, vinyl chloride, nickel compounds, chromium compounds, coal products, mustard gas, and chloromethyl ethers
- Diesel exhaust

This risk is far less than the risk caused by smoking, but some researchers estimate that worldwide about 5% of all deaths from lung cancer may be due to outdoor air pollution.

Radiation therapy to the lungs

People who have had radiation therapy to the chest for other cancers are at higher risk for lung cancer, particularly if they smoke; for example, people who have been treated for Hodgkin disease or women who get radiation after a mastectomy for breast cancer. Women who receive radiation therapy to the breast after a lumpectomy do not appear to have a higher than expected risk of lung cancer.

Marijuana smoking

Marijuana smoke contains tar and many of same cancer-causing substances that are in tobacco smoke. (Tar is the sticky, solid material that remains after burning, and is thought to contain most of the harmful substances in smoke.) Marijuana cigarettes (joints) are typically smoked all the way to the end, where tar content is the highest. Marijuana is also inhaled very deeply and the smoke is held in the lungs for a long time, which gives any cancer causing substances more opportunity to deposit in the lungs. And because marijuana is often an illegal substance, it may not be possible to control what other substances it might contain.

Talc and talcum powder

Talc is a mineral that in its natural form may contain asbestos. Some studies have suggested that talc miners and millers might have a higher risk of lung cancer and other respiratory diseases because of their exposure to industrial grade talc. But other studies have not found an increase in lung cancer rate. Talcum powder is made from talc. The use of cosmetic talcum powder has not been found to increase the risk of lung cancer.

Causes non-small cell lung cancer (Toloza *et al.*, 2003)

Smoking

Tobacco smoking is by far the leading cause of lung cancer. At least 80% of lung cancer deaths are caused by smoking, and many others are caused by exposure to secondhand smoke. Smoking is clearly the strongest risk factor for lung cancer, but it often interacts with other factors. Smokers exposed to other known risk factors such as radon and asbestos are at even higher risk. Not everyone who smokes gets lung cancer.

Lung cancer in non-smokers

Lung cancer in non-smokers can be caused by exposure to radon, secondhand smoke, air pollution, or other factors. Workplace exposures to asbestos, diesel exhaust, or certain other chemicals can also cause lung cancers in some people who do not smoke. A small

portion of lung cancers occur in people with no known risk factors for the disease. Lung cancers in non-smokers often have certain gene changes that are different from those in tumors from smokers. Gene changes that may lead to lung cancer Scientists now know how some of the risk factors for lung cancer can cause certain changes in the DNA of lung cells. These changes can lead to abnormal cell growth and, sometimes, cancer. Some genes contain instructions for controlling when cells grow, divide to make new cells, and die. Genes that help cells grow, divide, or stay alive are called oncogenes.Genes that slow down cell division or cause cells to die at the right time are called tumor suppressor genes. Cancers can be caused by DNA changes that turn on oncogenes or turn off tumor suppressor genes.

Inherited gene changes

Some people inherit DNA mutations (changes) from their parents that greatly increase their risk for developing certain cancers. But inherited mutations alone are not thought to cause very many lung cancers. Still, genes do seem to play a role in some families with a history of lung cancer. For example, some people seem to inherit a reduced ability to break down or get rid of certain types of cancer-causing chemicals in the body, such as those found in tobacco smoke. This could put them at higher risk for lung cancer. Other people may inherit faulty DNA repair mechanisms that make it more likely they will end up with DNA changes. Every time a cell divides into 2 new cells, it must make a new copy of its DNA. This process is not perfect, and copying errors sometimes occur.Cells normally have repair enzymes that proofread the DNA to help prevent this. People with repair enzymes that don't work as well might be especially vulnerable to cancer causing chemicals and radiation.

Acquired gene changes

Gene changes related to lung cancer are usually acquired during life rather than inherited. Acquired mutations in lung cells often result from exposure to factors in the environment, such as cancer-causing chemicals in tobacco smoke. But some gene changes may just be random events that sometimes happen inside a cell, without having an outside cause. Acquired changes in certain genes, such as the TP53 or p16 tumor suppressor genes and the K-RAS or ALK oncogenes, are thought to be important in the development of non small cell lung cancer. Changes in these and other genes may also make some lung cancers more likely to grow and spread than others.

Signs and symptoms of non-small cell lung cancer

The most common symptoms of lung cancer are:

- A cough that does not go away or gets worse
- Chest pain that is often worse with deep breathing, coughing, or laughing
- Hoarseness
- Weight loss and loss of appetite
- Coughing up blood or rust-colored sputum (spit or phlegm)
- Shortness of breath
- Feeling tired or weak
- Infections such as bronchitis and pneumonia that don't go away or keep coming back
- New onset of wheezing

When lung cancer spreads to distant organs, it may cause:

- Bone pain (like pain in the back or hips)
- Neurologic changes (such as headache, weakness or numbness of an arm or leg, dizziness, balance problems, or seizures), from cancer spread to the brain or spinal cord
- Yellowing of the skin and eyes (jaundice), from cancer spread to the liver
- Lumps near the surface of the body, due to cancer spreading to the skin or to lymph nodes (collections of immune system cells), such as those in the neck or above the collarbone

Horner syndrome

Cancers of the top part of the lungs (sometimes called Pan coast tumors) may damage a nerve that passes from the upper chest into the neck. This can cause severe shoulder pain. Sometimes these tumors can affect certain nerves to the eye and part of the face, causing a group of symptoms called Horner syndrome:

- Drooping or weakness of one eyelid
- Having a smaller pupil (dark part in the center of the eye) in the same eye
- Reduced or absent sweating on the same side of the face

Conditions other than lung cancer can also cause Horner syndrome.

Superior vena cava syndrome

The superior vena cava (SVC) is a large vein that carries blood from the head and arms back to the heart. It passes next to the upper part of the right lung and the lymph nodes inside the chest. Tumors in this area may push on the SVC, which can cause the blood to back up in the veins. This can cause swelling in the face, neck, arms, and upper chest (sometimes with a bluish-red skin color). It can also cause headaches, dizziness, and a change in consciousness if it affects the brain. While SVC syndrome can develop gradually over time, in some cases it can

become life-threatening, and needs to be treated right away.

Paraneoplastic syndromes

Some lung cancers can make hormone-like substances that enter the bloodstream and cause problems with distant tissues and organs, even though the cancer has not spread to those tissues or organs. These problems are called paraneoplastic syndromes. Sometimes these syndromes may be the first symptoms of lung cancer. Because the symptoms affect organs besides the lungs, patients and their doctors may suspect at first that a disease other than lung cancer is causing them. Some of the more common paraneoplastic syndromes that can be caused by non-small cell lung cancer include:

- High blood calcium levels (hypocalcaemia), which can cause frequent urination, thirst, constipation, nausea, vomiting, belly pain, weakness, fatigue, dizziness, confusion, and other nervous system problems
- Excess growth of certain bones, especially those in the finger tips, which is often painful
- Blood clots
- Excess breast growth in men (gynecomastia)

Diagnosis of non-small cell lung cancer(Wang *et al.*, 1995).

Chest x-ray

This is the first test of doctor to look for any masses or spots on the lungs. Plain x-rays of the chest can be done at imaging centers, hospitals, and even in some doctors' offices.

Computed tomography (CT) scan

A CT (or CAT) scan is more likely to show lung tumors than routine chest x-rays. A CT scan(Glazer *et al.*, 1985) can also provide precise information about the size, shape, and position of any lung tumors and can help find enlarged lymph nodes that might contain cancer that has spread from the lung. This test can also be used to look for masses in the adrenal glands, liver, brain, and other internal organs that might be due to the spread of lung cancer. The CT scan uses x-rays to produce detailed cross-sectional images of the body. Instead of taking one picture, like a regular x-ray, a CT scanner takes many pictures as it rotates around the patient while lying on a table. A computer then combines these pictures into images of slices of the part of the body being studied. Unlike a regular x-ray, a CT scan creates detailed images of the soft tissues in the body. Before the CT scan, the patient may be asked to drink a contrast solution or may get an injection of a contrast solution through an IV (intravenous) line. This helps better outline structures in the patient's body. The contrast may cause some flushing (a feeling of warmth, especially in the face). Some people are allergic and get hives. Rarely, more serious reactions like trouble breathing or low blood pressure can occur.

CT-guided needle biopsy:

If a suspected area of cancer lies deep within the body, a CT scan can be used to guide a biopsy needle precisely into the suspected area. For this procedure, the patient stay on the CT scanning table, while the doctor advances a biopsy needle through the skin and toward the mass. CT scans are repeated until the doctor can see that the needle is within the mass. A biopsy sample is then removed and looked at under a microscope.

Magnetic resonance imaging (MRI) scan

MRI scans are most often used to look for possible spread of lung cancer to the brain or spinal cord. Like CT scans, MRI scans (Webb *et al.*, 1991) provide detailed images of soft tissues in the body. But MRI scans use radio waves and strong magnets instead of x-rays. The energy from the radio waves is absorbed and then released in a pattern formed by the type of body tissue and by certain diseases. A computer translates the pattern into a very detailed image of parts of the body. A contrast material called gadolinium is often injected into a vein before the scan to better see details.MRI scans take longer than CT scans (often up to an hour), and are a little more uncomfortable.

Positron emission tomography (PET) scan

A PET scan(Yasufuku *et al.*, 2006) can be a very important test if the patient appear to have early stage lung cancer. The doctor can use this test to help see if the cancer has spread to nearby lymph nodes or other areas, which can help determine if surgery may be an option for the patient. This test can also be helpful in getting a better idea whether an abnormal area on a chest x-ray or CT scan might be cancer.PET can reveal spread of cancer (Truong *et al.*, 2004)to the liver, bones, adrenal glands, or some other organs. It is not as useful for looking at the brain, since all brain cells use a lot of glucose. For this test, a form of radioactive sugar (known as fluorodeoxyglucose or FDG) is injected into the blood. (The amount of radioactivity used is very low and will pass out of the body over the next day or so.) Because cancer cells in the body are growing rapidly, they absorb more of the radioactive sugar. After about an hour, the patient will be moved onto a table in the PET scanner. The patient lie on the table for about 30 minutes while a special camera creates a picture of areas of radioactivity in the body. The picture is not finely detailed like a CT or MRI scan, but it

provides helpful information about your whole body(Gross *et al.*, 2011).

Bone scan

A bone scan can help show if a cancer has spread to the bones. For this test, a small amount of low-level radioactive material is injected into a vein(intravenously, or IV). The substance settles in areas of bone changes throughout the entire skeleton over the course of a couple of hours. The patient then lie on a table for about 30 minutes while a special camera detects the radioactivity and creates a picture of the patient's skeleton. Areas of active bone changes attract the radioactivity and show up as hot spots. These areas may suggest metastatic cancer, but arthritis or other bone diseases can also cause the same pattern. Bone scans aren't needed very often because PET scans, which are often done in patients with non-small cell lung cancer, can usually show if cancer has spread to the bones. Bone scans are done mainly when there is reason to think the cancer may have spread to the bones (because of symptoms such as bone pain) and other test results aren't clear.

Tests to diagnose lung cancer

Symptoms and the results of certain tests may strongly suggest that a person has lung cancer, but the actual diagnosis of non-small cell lung cancer is made by looking at lung cells under a microscope. The cells can be taken from lung secretions (sputum or phlegm), found in fluid removed from the area around the lung (thoracentesis), or removed from a suspicious area using a needle or surgery (known as a biopsy). The choice of which test(s) to use depends on the situation.

Sputum cytology

A sample of sputum (mucus you cough up from the lungs) is looked at under a microscope to see if it contains cancer cells. The best way to do this is to get early morning samples from you 3 days in a row. This test is more likely to help find cancers that start in the major airways of the lung, such as most squamous cell lung cancers. It may not be as helpful for finding other types of non-small cell lung cancer.

Thoracentesis

If there is a buildup of fluid around the lungs (pleural effusion), doctors can perform thoracentesis to find out if it was caused by cancer spreading to the lining of the lungs (pleura). The buildup might also be caused by other conditions, such as heart failure or an infection. For this procedure, the skin is numbed and a hollow needle is inserted between the ribs to drain the fluid. (In a similar test called pericardiocentesis, fluid is removed from within the sac around the heart.) The fluid is checked under a microscope for cancer cells. Chemical tests of the fluid are also sometimes useful in telling a malignant (cancerous) pleural effusion from a benign (non-cancerous) one. If a malignant pleural effusion has been diagnosed, thoracentesis may be repeated to remove more fluid. Fluid buildup can keep the lungs from filling with air, so thoracentesis can help the patient breathe better.

Needle biopsy

Doctors can often use a hollow needle to get a small sample from a suspicious area (mass). In a fine needle aspiration (FNA) biopsy (Herth *et al.*, 2003), the doctor uses a syringe with a very thin, hollow needle (thinner than the ones used for blood tests) to withdraw (aspirate) cells and small fragments of tissue. In a core biopsy, a larger needle is used to remove one or more small cylinders (cores) of tissue. Core biopsies provide a larger sample than FNA biopsies, so they are often preferred. An advantage of needle biopsies is that they don't require a surgical incision. The drawback is that they remove only a small amount of tissue. In some cases (particularly with FNA biopsies), the amount of tissue removed might not be enough to both make a diagnosis and to classify DNA changes in the cancer cells that can help doctors choose anticancer drugs. If the suspected tumor is in the outer portion of the lungs, either kind of biopsy needle can be inserted through the skin on the chest wall. This is called a transthoracic needle biopsy. The area where the needle is to be inserted may be numbed with local anesthesia first. The doctor then guides the needle into the area while looking at the lungs with either fluoroscopy (which is like an x-ray, but creates a moving image on a screen rather than a single picture on film) or CT scans. Unlike fluoroscopy, CT doesn't give a constant picture, so if CT is used, the needle is inserted toward the mass (tumor), a CT image is taken, and the direction of the needle is guided based on the image. This is repeated a few times until the needle is within the mass. A possible complication of this procedure is that air may leak out of the lung at the biopsy site and into the space between the lung and the chest wall.

This can cause part of the lung to collapse and may cause trouble breathing. This complication, called a pneumothorax, often gets better without any treatment. If not, it is treated by putting a small tube into the chest space and sucking out the air over a day or two, after which it usually heals on its own. An FNA biopsy may also be done to check for cancer in the lymph nodes

between the lungs:Transtracheal FNA or transbronchial FNA is done by passing the needle through the wall of the trachea (windpipe) or bronchi (the large airways leading into the lungs) during bronchoscopy or end bronchial ultrasound .In some cases an FNA biopsy is done during endoscopic esophageal ultrasound by passing the needle through the wall of the esophagus (Yasufuku *et al.,* 2004).

Bronchoscopy

Bronchoscopy can help the doctor find some tumors or blockages in the larger airways of the lungs which can often be biopsied during the procedure. For this exam, a lighted, flexible fiber-optic tube (called a bronchoscope) is passed through the mouth or nose and down into the windpipe and bronchi. The mouth and throat are sprayed first with a numbing medicine. The patient may also be given medicine through an intravenous (IV) line. Small instruments can be passed down the bronchoscope to take biopsies (samples of tissue). The doctor can also sample cells from the lining of the airways with a small brush (bronchial brushing) or by rinsing the airways with sterile saltwater (bronchial washing).These tissue and cell samples are then looked at under a microscope (Leong *et al.,* 2012).

End bronchial ultrasound

Ultrasound is a type of imaging test that uses sound waves to create pictures of the inside of the patient's body. For this test, a small, microphone-like instrument called a transducer gives off sound waves and picks up the echoes as they bounce off body tissues. The echoes are converted by a computer into a black and white image on a computer screen. For end bronchial ultrasound (Herth *et al.,* 2004), a bronchoscope is fitted with an ultrasound transducer at its tip and is passed down into the windpipe. This is done with numbing medicine (local anesthesia) and light sedation. The transducer can be pointed in different directions to look at lymph nodes and other structures in the mediastinum (the area between the lungs). If suspicious areas such as enlarged lymph nodes are seen on the ultrasound, a hollow needle can be passed through the bronchoscope and guided into these areas to obtain a biopsy. The samples are then sent to a lab to be looked at under a microscope (Gu *et al.,* 2009).

Endoscopic esophageal ultrasound

This test is like end bronchial ultrasound, except the doctor passes an endoscope (a lighted, flexible scope) down the throat and into the esophagus (the tube connecting the throat to the stomach). This is done with numbing medicine (local anesthesia) and light sedation. The esophagus lies just behind the windpipe and is close to some lymph nodes inside the chest to which lung cancer may spread. As with end bronchial ultrasound, the transducer can be pointed in different directions to look at lymph nodes and other structures inside the chest that might contain lung cancer. If enlarged lymph nodes are seen on the ultrasound, a hollow needle can be passed through the endoscope to get biopsy samples of them. The samples are then sent to a lab to be looked at under a microscope.

Mediastinoscopy and mediastinotomy(Ginsberg *et al.,* 1987)

These procedures may be done to look more directly at and get samples from the structures in the mediastinum (the area between the lungs). They are done in an operating room while patients are under general anesthesia (in a deep sleep). The main difference between the two is in the location and size of the incision.

Mediastinoscopy (Sortini *et al.,* 1994)

A small cut is made in the front of the neck and a thin, hollow, lighted tube is inserted behind the sternum (breast bone) and in front of the windpipe to look at the area. Instruments can be passed through this tube to take tissue samples from the lymph nodes along the windpipe and the major bronchial tube areas. Looking at the samples under a microscope can show whether cancer cells are present.

Mediastinotomy (Carlens et al., 1959, Annema et al., 2010)

The surgeon makes a slightly larger incision (usually about 2 inches long) between the left second and third ribs next to the breast bone. This lets the surgeon reach some lymph nodes that cannot be reached by mediastinoscopy.

Thoracoscopy

Thoracoscopy can be done to find out if cancer has spread to the spaces between the lungs and the chest wall, or to the linings of these spaces. It can also be used to sample tumors on the outer parts of the lungs as well as nearby lymph nodes and fluid, and to assess whether a tumor is growing into nearby tissues or organs. This procedure is not often done just to diagnose lung cancer, unless other tests such as needle biopsies are unable to get enough samples for the diagnosis. Thoracoscopy is done in the operating room while you are under general anesthesia (in a deep sleep). A small cut (incision) is made in the side of the chest wall. (Sometimes more than one cut is made.) The doctor then inserts a thin, lighted tube with a small video camera on the end through the incision

to view the space between the lungs and the chest wall. Using this, the doctor can see potential cancer deposits on the lining of the lung or chest wall and remove small pieces of tissue to be looked at under the microscope. (When certain areas can't be reached with thoracoscopy, the surgeon may need to make a larger incision in the chest wall, known as a thoracotomy).Thoracoscopy can also be used as part of the treatment to remove part of a lung in some early-stage lung cancers. This type of operation, known as video-assisted thoracic surgery (VATS).

Immunohistochemistry

For this test, very thin slices of the sample are attached to glass microscope slides. The samples are then treated with special proteins (antibodies) designed to attach only to a specific substance found in certain cancer cells. If the patient's cancer cells contain that substance, the antibody will attach to the cells. Chemicals are then added so that antibodies attached to the cells change color. The doctor who looks at the sample under a microscope can see this color change.

Molecular tests

Blood tests

Blood tests are not used to diagnose lung cancer. But they can help to get a sense of a person's overall health; for example, to see if a person is healthy enough to have surgery. A complete blood count (CBC) determines whether your blood has normal numbers of various cell types. For example, it can show if patient is anemic (have a low number of red blood cells), if patient could have trouble with bleeding (due to a low number of blood platelets), or if patient is at increased risk for infections (because of a low number of white blood cells). This test will be repeated regularly if patient is treated with chemotherapy, because these drugs can affect blood-forming cells of the bone marrow. Blood chemistry tests can help spot abnormalities in some of patient's organs, such as the liver or kidneys. For example, if cancer has spread to the liver and bones, it may cause abnormal levels of certain chemicals in the blood, such as a higher than normal level of lactate dehydrogenase (LDH).

Pulmonary function tests

Pulmonary function tests (PFTs) are often done after lung cancer is diagnosed to see how well patients lungs are working . This is especially important if surgery might be an option in treating the cancer.Surgery to remove lung cancer may mean removing part or all of a lung, so it's important to know how well the lungs are working beforehand. Some people with poor lung function (like those with lung damage from smoking) don't have enough lung reserve to withstand removing even part of a lung. These tests can give the surgeon an idea of whether surgery is a good option, and if so, how much lung can safely be removed. There are different types of PFTs, but they all basically have you breathe in and out through a tube that is connected to a machine that measures airflow. Sometimes PFTs are coupled with a test called an arterial blood gas. In this test, blood is removed from an artery (most blood tests use blood removed from a vein) to measure the amount of oxygen and carbon dioxide that it contains.

Staging of non-small cell lung cancer (AJCC 2010, Groome *et al.*, 2007, Kameyama *et al.*, 2009).

The TNM staging system

The system used to describe the growth and spread of NSCLC is the American Joint Committee on Cancer (AJCC) TNM staging system. Numbers or letters appear after T, N, and M to provide more details about each of these factors. The numbers 0 through 4 indicate increasing severity. The TNM staging system is complex and can be hard for patients to understand.

Tumor (T) categories for lung cancer

TX: The main (primary) tumor can't be assessed, or cancer cells were seen on sputum
cytology or bronchial washing but no tumor can be found.

T0: There is no evidence of a primary tumor.

Tis: The cancer is found only in the top layers of cells lining the air passages. It has not
invaded into deeper lung tissues. This is also known as carcinoma in situ.

T1: The tumor is no larger than 3 centimeters (cm)—slightly less than 1¼ inches—across, has not reached the membranes that surround the lungs (visceral pleura), and does not affect the main branches of the bronchi. If the tumor is 2 cm (about 4/5 of an inch) or less across, it is called **T1a**.

If the tumor is larger than 2 cm but not larger than 3 cm across, it is called **T1b**.

T2: The tumor has 1 or more of the following features:

- It is larger than 3 cm across but not larger than 7 cm.
- It involves a main bronchus, but is not closer than 2 cm (about ¾ inch) to the carina (the point where the windpipe splits into the left and right main bronchi).
- It has grown into the membranes that surround the lungs (visceral pleura).
- The tumor partially clogs the airways, but this has not caused the entire lung to collapse or develop pneumonia.

If the tumor is 5 cm or less across, it is called **T2a**. If the tumor is larger than 5 cm across (but not larger than 7 cm), it is called **T2b**.

T3: The tumor has 1 or more of the following features:

- It is larger than 7 cm across.
- It has grown into the chest wall, the breathing muscle that separates the chest from the abdomen (diaphragm), the membranes surrounding the space between the two lungs (mediastinal pleura), or membranes of the sac surrounding the heart (parietal pericardium).
- It invades a main bronchus and is closer than 2 cm (about ¾ inch) to the carina, but it does not involve the carina itself.
- It has grown into the airways enough to cause an entire lung to collapse or to cause pneumonia in the entire lung.
- Two or more separate tumor nodules are present in the same lobe of a lung.

T4: The cancer has 1 or more of the following features:

- A tumor of any size has grown into the space between the lungs (mediastinum), the heart, the large blood vessels near the heart (such as the aorta), the windpipe (trachea), the tube connecting the throat to the stomach (esophagus), the backbone, or the carina.
- Two or more separate tumor nodules are present in different lobes of the same lung.

Node(N) categories for lung cancer

NX: Nearby lymph nodes cannot be assessed.

N0: There is no spread to nearby lymph nodes.

N1: The cancer has spread to lymph nodes within the lung and/or around the area where the bronchus enters the lung (hilar lymph nodes). Affected lymph nodes are on the same side as the primary tumor.

N2: The cancer has spread to lymph nodes around the carina (the point where the
windpipe splits into the left and right bronchi) or in the space between the lungs
(mediastinum). Affected lymph nodes are on the same side as the primary tumor.

N3: The cancer has spread to lymph nodes near the collarbone on either side, and/or spread to hilar or mediastinal lymph nodes on the side opposite the primary tumor.

Metastasize(M) categories for lung cancer

M0: No spread to distant organs or areas. This includes the other lung, lymph nodes further away than those mentioned in the N stages above, and other organs or tissues such as the liver, bones, or brain.

M1a: Any of the following:

- The cancer has spread to the other lung.
- Cancer cells are found in the fluid around the lung (called a malignant pleural effusion).
- Cancer cells are found in the fluid around the heart (called a malignant pericardial effusion).

M1b: The cancer has spread to distant lymph nodes or to other organs such as the liver, bones, or brain.

Stage grouping for lung cancer

Once the T, N, and M categories have been assigned, this information is combined to assign an overall stage of 0, I, II, III, or IV. This process is called stage grouping. Some stages are subdivided into A and B. The stages identify cancers that have a similar outlook (prognosis) and thus are treated in a similar way. Patients with lower stage numbers tend to have a better outlook.

Treatment of non-small cell lung cancer

Depending on the stage of the disease and other factors, the main treatment options for people with non-small cell lung cancer (NSCLC) can include:

- Surgery
- Radiofrequency ablation
- Radiation therapy
- Chemotherapy
- Targeted therapies
- Palliative procedures can also be used to help with symptoms.

Types of lung surgery (Posther *et al.,* 2006)

These operations require general anesthesia (where you are in a deep sleep) and are usually done through a surgical incision between the ribs in the side of the chest (called a thoracotomy).

- **Pneumonectomy:** an entire lung is removed in this surgery.
- **Lobectomy:** an entire section (lobe) of a lung is removed in this surgery.
- **Segmentectomy or wedge resection:** part of a lobe is removed in this surgery.

Another type of operation, known as a **sleeve resection**, may be used to treat some cancers in large airways in the lungs. The type of operation your doctor recommends depends on the size and location of the tumor and on how well your lungs are functioning. People whose lungs are healthier can withstand having more lung tissue removed. Doctors often prefer to do a more extensive operation (for example, a lobectomy instead of a segmentectomy) if a person's lungs are healthy enough, as it may provide a better chance to cure the cancer.

Video-assisted thoracic surgery:

Some doctors now treat some early stage lung cancers near the outside of the lung with a procedure called video-assisted thoracic surgery (VATS), which requires smaller incisions than a thoracotomy.During this operation, a thin, rigid tube with a tiny video camera on the end is placed through a small cut in the side of the chest to help the surgeon see inside the chest on a TV monitor. One or two other small cuts are created in the skin, and long instruments are passed through these cuts to do the same operation that would be done using an open approach (thoracotomy). One of the incisions is enlarged if a lobectomy or pneumonectomy is done to allow the specimen to be removed. Because usually only small incisions are needed, there is less pain after the surgery and a shorter hospital stay usually 4 to 5 days. Possible complications during and soon after surgery depend on the extent of the surgery and the person's health beforehand. Serious complications can include excess bleeding, wound infections, and pneumonia. While it is rare, in some cases people may not survive the surgery, which is why surgery isn't a good idea for everyone.

Radiofrequency ablation (RFA) for non-small cell lung cancer

This technique might be an option for some small lung tumors that are near the outer edge of the lungs, especially in people who can't tolerate surgery. It uses high-energy radio waves to heat the tumor. A thin, needle-like probe is placed through the skin and moved along until the end is in the tumor. Placement of the probe is guided by CT scans. Once it is in place, an electric current is passed through the probe, which heats the tumor and destroys the cancer cells.RFA is usually done as an outpatient procedure, using local anesthesia (numbing medicine) where the probe is inserted. Major complications are uncommon, but they can include the partial collapse of a lung (which often resolves on its own) or bleeding into the lung. Radiation therapy for non-small cell lung cancer Radiation therapy uses high-energy rays (such as x-rays) or particles to kill cancer cells. There are 2 main types of radiation therapy external beam radiation therapy and brachytherapy (internal radiation therapy).

External beam radiation therapy

External beam radiation therapy (EBRT) focuses radiation from outside the body on the cancer. This is the type of radiation therapy most often used to treat a primary lung cancer or its spread to other organs. Before your treatments start, the radiation team will take careful measurements to determine the correct angles for aiming the radiation beams and the proper dose of radiation. Treatment is much like getting an x-ray, but the radiation dose is stronger. The procedure itself is painless. Each treatment lasts only a few minutes, although the setup time getting you into place for treatment – usually takes longer. Most often, radiation treatments to the lungs are given 5 days a week for 5 to 7 weeks, but this can vary based on the type of EBRT and the reason it's being given. Standard (conventional) EBRT is used much less often than in the past. Newer techniques help doctors treat lung cancers more accurately while lowering the radiation exposure to nearby healthy tissues. These techniques may offer better success rates and fewer side effects. Most doctors now recommend using these newer techniques when they are available.

Three-dimensional conformal radiation therapy (3D-CRT):

3D-CRT uses special computers to precisely map the location of the tumor(s). Radiation beams are shaped and aimed at the tumor(s) from several directions, which makes it less likely to damage normal tissues.

Intensity modulated radiation therapy (IMRT):

IMRT is an advanced form of 3D therapy. It uses a computer-driven machine that moves around you as it delivers radiation. Along with shaping the beams and aiming them at the tumor from several angles, the intensity (strength) of the beams can be adjusted to limit the dose reaching the most sensitive normal tissues. This technique is used most often if tumors are near important structures such as the spinal cord. Many major hospitals and cancer centers now use IMRT.

Stereotactic body radiation therapy (SBRT):

SBRT, also known as stereotactic ablative radiotherapy (SABR), is sometimes used to treat very early stage lung cancers when surgery isn't an option due to issues with a patient's health or in people who do not want surgery. Instead of giving small doses of radiation each day for several weeks, SBRT uses very focused beams of high-dose radiation given in fewer (usually 1 to 5) treatments. Several beams are aimed at the tumor from different angles.

Stereotactic radiosurgery (SRS):

SRS is a type of stereotactic radiation therapy that is given in only one session. It can sometimes be used instead of or along with surgery for single tumors that have spread to the brain. In one version of this treatment, a machine called a Gamma Knife® focuses about 200 beams of radiation on the tumor from different angles over

a few minutes to hours. Your head is kept in the same position by placing it in a rigid frame. In another version, a linear accelerator (a machine that creates radiation) that is controlled by a computer moves around your head to deliver radiation to the tumor from many different angles. These treatments can be repeated if needed.

Brachytherapy (internal radiation therapy)

In people with lung cancer, brachytherapy is sometimes used to shrink tumors in the airway to relieve symptoms. But it is used less often for lung cancer than for other cancers such as head and neck cancers. For this type of treatment, the doctor places a small source of radioactive material (often in the form of small pellets) directly into the cancer or into the airway next to the cancer. This is usually done through a bronchoscope, but it may also be done during surgery. The radiation travels only a short distance from the source, limiting the effects on surrounding healthy tissues. The radiation source is usually removed after a short time. Less often, small radioactive seeds are left in place permanently, and the radiation gets weaker over several weeks.

Use of radiation therapy

Radiation therapy might be given at different times, depending on the purpose:

- As the main treatment of lung cancer (sometimes along with chemotherapy), especially if the lung tumor cannot be removed by surgery because of its size or location, if a person's health is too poor for surgery, or if a person does not want surgery.
- After surgery (alone or along with chemotherapy) to try to kill any small deposits of cancer that surgery may have missed.
- Before surgery (usually along with chemotherapy) to try to shrink a lung tumor to make it easier to operate on.
- To relieve (palliate) symptoms of advanced lung cancer such as pain, bleeding, trouble swallowing, cough, or problems caused by spread to other organs such as the brain. For example, brachytherapy is most often used to help relieve blockage of large airways by cancer.

Possible side effects of radiation therapy (Wender *et al.*, 2013)

Common side effects depend on where the radiation is aimed and can include:

- Fatigue
- Nausea and vomiting
- Loss of appetite and weight loss
- Skin changes in the area being treated, which can range from mild redness to blistering and peeling
- Hair loss where the radiation enters the body Often these go away after treatment. When radiation is given with chemotherapy, the side effects are often worse.

Radiation therapy to the chest may damage your lungs and cause a cough, problems breathing, and shortness of breath. These usually improve after treatment is over, although sometimes they may not go away completely. Radiation therapy to large areas of the brain can sometimes cause memory loss, headaches, trouble thinking, or reduced sexual desire. Usually these symptoms are minor compared with those caused by a brain tumor, but they can reduce your quality of life. Side effects of radiation therapy to the brain usually become most serious 1 or 2 years after treatment.

Chemotherapy for non-small cell lung cancer (Quoix *et al.*, 2011)

Chemotherapy (chemo) is treatment with anti-cancer drugs injected into a vein or taken by mouth. These drugs enter the bloodstream and go throughout the body, making this treatment useful for cancer anywhere in the body. Depending on the stage of non-small cell lung cancer (NSCLC), chemo may be used in different situations:

- Before surgery (sometimes along with radiation therapy) to try to shrink a tumor. This is known as neoadjuvant therapy.
- After surgery (sometimes along with radiation therapy) to try to kill any cancer cells

that may have been left behind. This is known as adjuvant therapy.

- As the main treatment (sometimes along with radiation therapy) for more advanced cancers or for some people who aren't healthy enough for surgery.

Doctors give chemo in cycles, with a period of treatment (usually 1 to 3 days) followed by a rest period to allow the body time to recover. Some chemo drugs, though, are given every day. Chemo cycles generally last about 3 to 4 weeks. Chemo is often not recommended for patients in poor health, but advanced age by itself is not a barrier to getting chemo.

The chemo drugs most often used for NSCLC are cisplatin,carboplatin,paclitaxel (Taxol®),albumin-bound paclitaxel (nab-paclitaxel, abraxane®),docetaxel (Taxotere®),gemcitabine (Gemzar®),vinorelbine (Navelbine®),Irinotecan (Camptosar®),etoposide (VP-16®),vinblastine,pemetrexed (Alimta®)

Most often, treatment for NSCLC uses a combination of 2 chemo drugs. Studies have shown that adding a third chemo drug doesn't add much benefit and is

likely to cause more side effects. Single-drug chemo is sometimes used for people who might not tolerate combination chemotherapy well, such as those in poor overall health or who are elderly. If a combination is used, it often includes cisplatin or carboplatin plus one other drug. Sometimes combinations that do not include these drugs, such as gemcitabine withvinorelbine or paclitaxel, may be used.

Possible side effects

Chemo drugs attack cells that are dividing quickly, which is why they work against cancer cells. But other cells in the body, such as those in the bone marrow (where new blood cells are made), the lining of the mouth and intestines, and the hair follicles, also divide quickly. These cells are also likely to be affected by chemo, which can lead to certain side effects. The side effects of chemo depend on the type and dose of drugs given and the length of time they are taken. Some common side effects include: hair loss, mouth sores, loss of appetite, nausea and vomiting, Diarrhea or constipation, Increased chance of infections (from having too few white blood cells),Easy bruising or bleeding (from having too few blood platelets),Fatigue (from having too few red blood cells)These side effects are usually short-term and go away after treatment is finished. There are often ways to lessen these side effects. For example, drugs can be given to help prevent or reduce nausea and vomiting. Some drugs can have specific side effects. For example, drugs such as cisplatin,vinorelbine, docetaxel, or paclitaxel can cause nerve damage (peripheral neuropathy).This can sometimes lead to symptoms (mainly in the hands and feet) such as pain, burning or tingling sensations, sensitivity to cold or heat, or weakness. In most people this goes away or gets better once treatment is stopped, but it may be long lasting in some
people.

Drugs that target tumor blood vessel growth (angiogenesis)

For tumors to grow, they must form new blood vessels to keep them nourished. This process is called angiogenesis. Some targeted drugs, called angiogenesis inhibitors, block this new blood vessel growth.bevacizumab (Avastin®) is an angiogenesis inhibitor used to treat advanced non-small cell lung cancer. It is a monoclonal antibody (a man-made version of a specific immune system protein) that targets vascular endothelial growth factor (VEGF), a protein that helps new blood vessels to form.This drug is often used with chemo for a time. Then if the cancer responds, the chemo may be stopped and the bevacizumab is given by itself until the cancer starts growing again. The possible side effects of this drug are different from (and may add to) those of chemotherapy drugs. Bevacizumab can cause serious bleeding, which limits its use to some extent. It is not used in patients who are coughing up blood.

Drugs that target EGFR

Epidermal growth factor receptor (EGFR) (Sequist *et al.,* 2013) is a protein found on the surface of cells. It normally helps the cells to grow and divide. Some NSCLC cells have too much EGFR,which causes them to grow faster. Drugs that target EGFR used to treat non-small cell lung cancer (NSCLC) include:Erlotinib (Tarceva®),Afatinib (Gilotrif®) Erlotinib and afatinib block the signal from EGFR that tells cells to grow. They can be used alone (without chemo) as the first treatment for advanced NSCLCs that have certain mutations in the EGFR gene. Erlotinib is also used for advanced NSCLC without those mutations if chemo isn't working. Both erlotinib and afatinib are pills. Common side effects of these drugs include: Skin problems,diarrhea,mouth sores, loss of appetite Skin problems can include an acne-like rash on the face and chest, which in some cases can lead to skin infections.

Drugs that target the ALK gene

About 5% of NSCLCs have been found to have a rearrangement in a gene called ALK.This change is most often seen in non-smokers (or light smokers) who have the adenocarcinoma subtype of NSCLC. The ALK gene(Kwak *et al.,* 2010) rearrangement produces an abnormal ALK protein that causes the cells to grow and spread. Drugs that target ALK include:Crizotinib (Xalkori®),Ceritinib (Zykadia™)These drugs block the abnormal ALK protein and can shrink tumors in patients whose lung cancers have the ALK gene change. Although they can help after chemo has stopped working, they are often used instead of chemo in people whose cancers have the ALK gene rearrangement.Both of these drugs are pills. Common side effects include:Nausea and vomiting,diarrhea,Constipation,Fatigue,Changes in vision Some side effects can be severe, such as low white blood cell counts, lung inflammation, liver damage, and heart rhythm problems.

Palliative procedures for non-small cell lung cancer

Palliative, or supportive care, is aimed at relieving suffering and improving quality of life. People with lung cancer often benefit from procedures aimed at helping with problems caused by the cancer. For example, people with advanced lung cancer can have problems with shortness of breath. This can be caused by a number of

things, including fluid around the lung or an airway blockage. Although treating the cancer with chemotherapy may help with this over time, other treatments may be needed as well. Treating fluid buildup in the area around the lungs Sometimes fluid can build up in the chest outside of the lungs (called a pleural effusion).It can press on the lungs and cause trouble breathing.

Thoracentesis

This is done to drain the fluid. A doctor will numb an area in the chest, and then place a needle into the space between the lungs and the ribs and drain the fluid. This is often done using ultrasound to guide the needle into the area of fluid buildup.

Pleurodesis

A pleurodesis might be done to remove the fluid and keep it from coming back.One way to do this is to make a small cut in the skin of the chest wall, and place a hollow tube (called a chest tube) into the chest to remove the fluid. Then a substance is instilled into the chest cavity through the tube that causes the linings of the lung (visceral pleura) and chest wall (parietal pleura) to become irritated. This causes the linings to stick together, sealing the space and limiting further fluid buildup. The tube is often left in for a couple of days to drain any new fluid that might collect. A number of things can be placed through the tube to irritate the linings, such as talc, the antibiotic doxycycline, or a chemotherapy drug like bleomycin.Another way to do this is to blow talc into the space around the lungs (the pleural space) during an operation. This is done through a small incision using thoracoscopy.

Catheter placement

This is another way to control the buildup of fluid. One end of the catheter (a thin, flexible tube) is placed in the chest through a small cut in the skin, and the other end is left outside the body. This is done in a doctor's office or hospital. Once in place, the catheter can be attached to a special bottle or other device to allow the fluid to drain out on a regular basis.

Treating fluid buildup around the heart

Lung cancer can sometimes spread to the area around the heart. This can lead to fluid buildup (a pericardial effusion) that presses on the heart so that it doesn't work well.

Pericardiocentesis

In this procedure, the fluid is drained with a needle placed into the space around the heart. This is usually done using an echocardiogram (like an ultrasound of the heart), to guide the needle.

Pericardial window

This is done to keep the fluid from building up again. In an operation, a piece of the tissue around the heart (the pericardium) is removed to allow the fluid to drain into the chest or belly.

Treating airway blockage

If the cancer is growing into an airway in the lung, it can block the airway and cause problems like pneumonia or shortness of breath. Treatments can be used to relieve the blockage in the airway.

Photodynamic therapy (PDT)

Photodynamic therapy is sometimes used to treat very early stage lung cancers that are still confined to the outer layers of the lung airways when other treatments aren't appropriate. It can also be used to help open up airways blocked by tumors to help people breathe better.For this technique, a light-activated drug called porfimer sodium (Photofrin®) is injected into a vein. This drug is more likely to collect in cancer cells than in normal cells. After a couple of days (to give the drug time to build up in the cancer cells), a bronchoscope is passed down the throat and into the lung. This may be done with either local anesthesia (where the throat is numbed) and sedation or with general anesthesia. A special laser light on the end of the bronchoscope is aimed at the tumor,which activates the drug and causes the cells to die. The dead cells are then removed a few days later during a bronchoscopy. This process can be repeated if needed.PDT may cause swelling in the airway for a few days, which may lead to some shortness of breath, as well as coughing up blood or thick mucus. Some of this drug also collects in normal cells in the body, such as skin and eye cells. This can make you very sensitive to sunlight or strong indoor lights. Too much exposure can cause serious skin reactions (like a severe sunburn), so doctors recommend staying out of any strong light for 4 to 6 weeks after the injection.

Laser therapy

Lasers can sometimes be used to treat very small tumors in the linings of airways. They can also be used to help open up airways blocked by larger tumors to help people breathe better.

Stent placement

Lung tumors that have grown into an airway can sometimes cause trouble breathing or other problems. To

help keep the airway open (often after other treatments such as PDT or laser therapy), a hard silicone or metal tube called a stent may be placed in the airway using a bronchoscope.

New treatment in non-small cell lung cancer research
Fluorescence bronchoscopy

Also known as auto fluorescence bronchoscopy, this technique may help doctors find some lung cancers earlier, when they may be easier to treat. For this test, the doctor inserts a bronchoscope through the mouth or nose and into the lungs. The end of the bronchoscope has a special fluorescent light on it, instead of a normal (white) light. The fluorescent light causes abnormal areas in the airways to show up in a different color than healthy parts of the airway. Some of these areas might not be visible under white light, so the color difference may help doctors find these areas sooner. Some cancer centers now use this technique to look for early lung cancers, especially if there are no obvious tumors seen with normal bronchoscopy.

Virtual bronchoscopy

This imaging test uses CT scans to create detailed 3-dimensional pictures of the airways in the lungs. The images can be viewed as if the doctor were actually using a bronchoscope. Virtual bronchoscopy has some possible advantages over standard bronchoscopy. First, it is non-invasive and doesn't require anesthesia. It also helps doctors view some airways that might not be seen with standard bronchoscopy, such as those being blocked by a tumor. But it has some drawbacks as well. For example, it doesn't show color changes in the airways that might indicate a problem. It also doesn't let a doctor take samples of suspicious areas like bronchoscopy does. Still, it can be a useful tool in some situations, such as in people who might be too sick to get a standard bronchoscopy.

Electromagnetic navigation bronchoscopy

Lung tumors near the center of the chest can be biopsied during bronchoscopy, but bronchoscopes have trouble reaching the outer parts of the lungs, so tumors in that part of the lung often need to have a needle biopsy. This test can be a way to use a bronchoscope to biopsy a tumor in the outer part of the lung. First, CT scans are used to create a virtual bronchoscopy. The abnormal area is identified, and a computer helps guide a bronchoscope to the area so that it can be biopsied. The bronchoscope used has some special attachments that allow it to reach further than a regular bronchoscope.

Real-time tumor imaging

Researchers are looking to use new imaging techniques, such as four-dimensional computed tomography (4DCT), to help improve treatment. In this technique, the CT machine scans the chest continuously for about 30 seconds. It shows where the tumor is in relation to other structures as a person breathes, as opposed to just giving a 'snapshot' of a point in time, like a standard CT does. 4DCT can be used to determine exactly where the tumor is during each part of the breathing cycle, which can help doctors deliver radiation to a tumor more precisely. This technique might also be used to help show if a tumor is attached to or invading important structures in the chest, which could help doctors determine if a patient might be eligible for surgery.

Maintenance chemotherapy:

For people with advanced lung cancers who can tolerate chemotherapy, combinations of 2 chemo drugs (sometimes along with a targeted drug) are typically given for about 4 to 6 cycles. Some recent studies have found that with cancers that have not progressed, continuing treatment beyond the 4 to 6 cycles with a single chemo drug such as pemetrexed or a targeted drug such as erlotinib may help some people live longer. This is known as maintenance therapy. A possible downside to this continued treatment is that people may not get a break from having side effects from chemotherapy.

Targeted therapies
Immune treatments

Researchers are hoping to develop drugs that can help the body's immune system fight
the cancer.

Drugs that block PD-1 and PD-L1:

Cancer cells may use natural pathways in the body to help avoid detection and destruction by the immune system. For example, they often have a protein called PD-L1 on their surface that helps them evade the immune system. New drugs that block the PD-L1 protein, or the corresponding PD-1 protein on immune cells called T cells, can help the immune system recognize the cancer cells and attack them. In early studies, an anti-PD-1 drug known as nivolumab (BMS-936558) shrank tumors in about 1 out of 5 people with NSCLC, while a drug targeting PD-L1 (known as BMS-936559) shrank tumors in about 1 out of 10 people. Many of the tumor responses have been long-lasting so far. Other agents such as pembrolizumab, MPDL3280A,andMEDI4736 can also to shrink tumors in patients with lung cancer. Larger studies of these new drugs are now being done.

Vaccines:

Several types of vaccines for boosting the body's immune response against lung cancer cells are being tested in clinical trials. Unlike vaccines against infections like measles or mumps, these vaccines are designed to help treat, not prevent, lung cancer.These types of treatments seem to have very limited side effects, so they might be useful in people who can't tolerate other treatments.Some vaccines are made up of lung cancer cells that have been grown in the lab, or even of cell components, such as parts of proteins commonly found on cancer cells. For example, the MUC1 protein is found on some lung cancer cells. A vaccine called TG4010 causes the immune system to react against that protein. A recent study compared combining the vaccine with chemotherapy to treatment with the same chemotherapy alone in patients with advanced lung cancer. The cancers in the group that got the vaccine were more likely to shrink or stop growing than the cancers in the group that just got chemo. More studies are planned to see if the vaccine will actually help patients live longer.L-BLP25 (tecemotide) is another vaccine that targets the MUC1 protein. It is made up of the protein (MUC1) encased in a fat droplet (liposome) to try to make it more effective.A small study of patients with advanced NSCLC suggested it might improve survival time, although recent results from a larger study did not find it helped people live longer.This vaccine is now being studied for patients with stage III disease after treatment with chemotherapy and radiation, in efforts to improve the cure rate.

Occult cancer(Park *et al.*, 2010)

For these cancers, malignant cells are seen on sputum cytology but no obvious tumor can be found with bronchoscopy or imaging tests. They are usually early stage cancers. Bronchoscopy and possibly other tests are usually repeated every few months to look for a tumor. If a tumor is found, treatment will depend on the stage.

Stage 0

Because stage 0 non-small cell lung cancer is limited to the lining layer of airways and has not invaded deeper into the lung tissue or other areas, it is usually curable by surgery alone. No chemotherapy or radiation therapy is needed.

Stage I

The tumor may be removed either by taking out one lung lobe (lobectomy) or by taking out a smaller piece of a lung (sleeve resection, segmentectomy, or wedge resection). At least some lymph nodes within the lung and outside the lung in the mediastinum will be removed to check them for cancer cells. Segmentectomy or wedge resection is recommended only for treating the smallest stage I cancers (those less than 2 cm across) and for patients with other medical conditions that make removing the entire lobe dangerous. For people with stage I NSCLC that has a higher risk of coming back (based on size, location, or other factors), adjuvant chemotherapy after surgery may lower the risk that cancer will return. Recent studies suggest that patients whose tumors are greater than 4 cm in size might benefit from adjuvant chemotherapy. After surgery, the tissue that is removed is checked to see if there are cancer cells at the edges of the surgery specimen. This, called positive margins, means that some cancer may have been left behind, and so a second surgery might be done to try to ensure that all the cancer has been removed.

Stage II

People who have stage II non-small cell lung cancer (NSCLC) and are healthy enough for surgery usually have the cancer removed by lobectomy or sleeve resection. Sometimes removing the whole lung (pneumonectomy) is needed. Any lymph nodes likely to have cancer in them are also removed. The extent of lymph node involvement and whether or not cancer cells are found at the edges of the removed tissues are important factors when planning the next step of treatment. In some cases, chemotherapy (often along with radiation) may be recommend before surgery to try to shrink the tumor to make the operation easier.

Stage IIIA

Treatment for stage IIIA non-small cell lung cancer (NSCLC) may include radiation therapy, chemotherapy (chemo), surgery, or some combination of these. For this reason, planning treatment for stage IIIA NSCLC will often require input from a medical oncologist, radiation oncologist, and a thoracic surgeon. Treatment options will depend on the size of the tumor, where it is located in patient's lung, which lymph nodes it has spread to, patient's overall health.

For patients who can tolerate it, treatment usually starts with chemo, sometimes combined with radiation therapy. Surgery may be an option after this if the doctor thinks any remaining cancer can be removed and the patient is healthy enough.

Stage IIIB

Stage IIIB non-small cell lung cancer (NSCLC) has spread to lymph nodes that are near the other lung or in the neck, and may also have grown into important structures in the chest. These cancers cannot be completely removed by surgery. As with other stages of lung cancer, treatment depends on the patient's overall health and how well they are expected to tolerate

treatments. If you are in fairly good health you may be helped by chemotherapy (chemo) combined with radiation therapy.

Stage IV

Photodynamic therapy (PDT) or laser therapy, may also be used to help relieve symptoms. Cancer that is limited in the lungs and has only spread to one other site (such as the brain) is not common, but it can sometimes be treated (and even potentially cured) with surgery and/or radiation therapy to treat the area of cancer spread, followed by treatment of the cancer in the lung. Treatment for the lung tumor is then based on its T and N stages, and may include surgery, chemo, radiation, or some of these in combination. For people who are not at high risk for bleeding (that is, they do not have squamous cell NSCLC and have not coughed up blood), the targeted drug bevacizumab (Avastin) might be given with chemo. Some people with squamous cell cancer might still be given bevacizumab, as long as the tumor is not near large blood vessels in the center of the chest. If bevacizumab is used, it is often continued even after chemo is finished. For tumors that have the ALK gene change, crizotinib (Xalkori) is often the first treatment. Ceritinib (Zykadia) can be used if crizotinib stops working or is not tolerated well.For people whose cancers have certain changes in the EGFR gene, either of the anti-EGFR drugs erlotinib (Tarceva) or afatinib (Gilotrif) may be used without chemotherapy as the first treatment(Lee *et al.*, 2007).

Figure 1. Anatomy of lungs

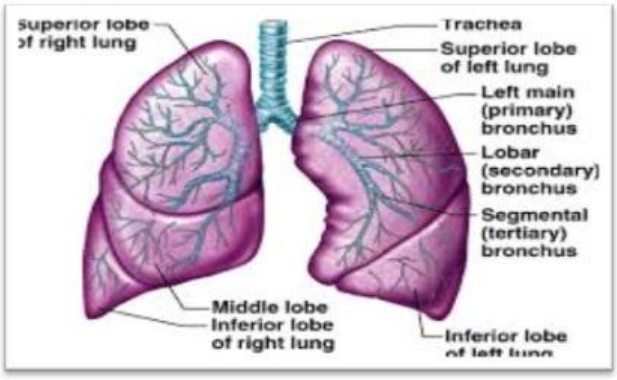

Table 1. International System for Staging Lung Cancer 1997

Stage			
Occult(hidden)	Tx	N0	M0
Stage 0	Carcinoma in situ		
Stage IA	T1	N0	M0
IB	T2	N0	M0
Stage IIA	T1	NI	M0
IIB	T2	N1	M0
	T3	N0	M0
	T3	N1	M0
Stage IIIA	T1-3	N2	M0
	T4	N0-1	M0
IIIB	Tany	N3	M0
	T4	N2	M0
Stage IV	Tany	Nany	M1

CONCLUSION

The life expectancy of non small cell lung cancer patients is increased due to effective treatment options available today. Nonetheless, persistent chronic pain of oncologic origin has depreciated the quality of life in advanced stage lungs cancer survivors after treatment. A range of diagnosis and adjuvant medications are accessible to the patients. These medicines provide satisfactory effect but are allied to a number of side effects. Hence, more effective ways for managing lungs cancer treatments are needed. However, further studies are needed for the novel therapies and agents to assure fast and adequate relief with minimum side effects.

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