

**Review on emerging concept of non-small cell lung carcinoma**

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**ABSTRACT**

Management of patients with lung cancer continues to create a considerable challenge to today's oncologist. However patient may cure in the early stage of the disease but most patients face an intensive and invasive treatment regimen comprising surgery, radiotherapy, or chemotherapy, or combinations thereof depending on disease stage/performance status. Most will require chemotherapy even if their initial surgery is potentially curative; for those with advanced disease, chemotherapy may be their only treatment option. Lung cancer is the leading cause of cancer-related mortality not only in the United States but also around the world.(1)

**Keywords:** Radiotherapy, Chemotherapy, Surgery.

**INTRODUCTION:**

**Lung Cancer**, a cancer that forms in tissues of the lung, usually in the cells lining. It has traditionally been classified into two major types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). About 85 percent of all lung cancers are identified as non-small cell, and approximately 75 percent of these are metastatic, or advanced. When we breathe in, air enters through our mouth and nose and goes into our lungs through the trachea. The trachea further divides into tubes called the bronchi, which divide into smaller branches called the bronchioles. At the end of the bronchioles are tiny air sacs known as alveoli. Alveoli absorb oxygen from the air we breathe in and pass carbon dioxide from the body into the alveoli to be breathed out when we exhale.

The lining around the lungs, called the pleura, helps to protect the lungs and allows them to move during breathing. Below the lungs, a muscle called the diaphragm separates the chest from the belly (abdomen). When we breathe, the diaphragm moves up and down, forcing air in and out of the lungs.(2.1)

**Start and spread of lung cancer:**

Lung cancer can start in the lining of the bronchi or in other parts of the lung. Lung cancers are thought to start as areas of pre-cancerous changes in the lung. These changes are not a mass or tumor. They can't be seen on an x-ray and they don't cause symptoms. Over time, these pre-cancerous changes in cells may go on to become true cancer. The cancer makes chemicals that cause new blood vessels to form nearby. These new

blood vessels feed the cancer cells and allow a tumor to form. In time, the tumor becomes large enough to show up on an x-ray. At some point, cancer cells can break away and spread to other parts of the body in a process called metastasis. Lung cancer is often a life-threatening disease because it can spread in this way before it is found.(2.2)

**Types of lung cancer:**

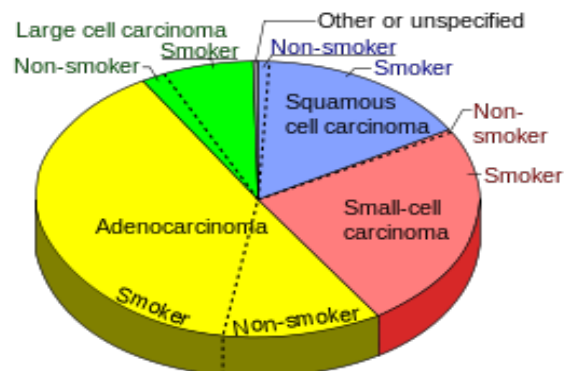
There are 2 main types of lung cancer and they are treated differently.

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

The category of lung cancer is mixed small cell lung cancer or large cell cancer. In this type of cancer both sclc and nsdc features has been identified but it is generally not common.

**Non-small cell lung cancer (NSCLC):**

There are 3 main sub-types of NSCLC. The cells in these sub-types differ in size, shape, and chemical make-up.

**TYPES OF NSCLC:**

**(a) Squamous cell lung carcinoma:**

Squamous cell carcinoma (SCC) of the lung is more common in men than in women. The major risk factor of this type of cancer is tobacco smoking. According to the Nurses' Health Study, the relative risk of SCC is approximately 5.5, both among those with a previous duration of smoking of 1 to 20 years, and those with 20 to 30 years, compared to never-smokers. The relative risk increases to approximately 16 with a previous smoking duration of 30 to 40 years, and approximately 22 with more than 40 years.

**(b) Large-cell lung carcinoma:**

Large cell lung carcinoma (LCLC) is a heterogeneous group of undifferentiated malignant neoplasms originating from transformed epithelial cells in the lung. LCLC's have typically comprised between around 10% of all NSCLC in the past, although newer diagnostic techniques seem to be reducing the incidence of diagnosis of "classic" LCLC in favor of more poorly differentiated squamous cell carcinomas and adenocarcinomas. LCLC is, in effect, a "diagnosis of exclusion", in that the tumor cells lack light microscopic characteristics that would classify the neoplasm as a small-cell carcinoma, squamous-cell carcinoma, carcinoma, or other more specific histologic type of lung cancer. LCLC is differentiated from small cell lung carcinoma (SCLC) primarily by the larger size of the anaplastic cells, a higher cytoplasmic-to-nuclear size ratio, and a lack of "salt-and-pepper" chromatin.

**(c) Lung adenocarcinoma:**

This type of lung carcinoma mostly occur in life long non smoker. Adenocarcinomas account for approximately 40% of lung cancers. Historically, adenocarcinoma was more often seen peripherally in the lungs than small cell lung cancer and squamous cell lung cancer, both of which tended to be more often centrally located.(2.3)

**MAJOR RISK FACTORS:**

**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. About 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.

**Radon:**

It is a naturally occurring radioactive gas that results from the breakdown of uranium in soil and rocks. It cannot be seen, tasted, or smelled.

**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.

**OTHER FACTORS:**

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

**Gene changes may lead to lung cancer:**

Scientists have begun to understand how the known risk factors for lung cancer may produce certain changes in the DNA of cells in the lungs, causing them to grow abnormally and form cancers. DNA is the chemical in each of our cells that makes up our genes – the instructions for how our cells function. We usually look like our parents because they are the source of our DNA. However, DNA affects more than how we look. It also can influence our risk for developing certain diseases, such as some kinds of cancer. Some genes contain instructions for controlling when cells grow and divide. Genes that promote cell division 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.(3.1)

**Inherited gene changes:**

Some people inherit DNA mutations (changes) from their parents that greatly increase their risk for developing certain cancers. However, inherited mutations 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 prepares to divide 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. Researchers are

developing tests that may help identify such people, but these tests are not yet reliable enough for routine use. For now, doctors recommend that all people avoid tobacco smoke and other exposures that might increase their cancer risk.

**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 external cause. Acquired changes in certain genes, such as the p53 or p16 tumor suppressor genes and the K-RAS 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 likely to grow and spread more rapidly than others. Not all lung cancers share the same gene changes, so there are undoubtedly changes in other genes that have not yet been found.(3.2)

**Common signs and symptoms of lung cancer:**

**The most common symptoms of lung cancer are:**

- A cough that does not go away or gets worse
- Chest pain, often made worse by 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 the hips)
- Weakness or numbness of the arms or legs
- Headache, dizziness, balance problems, or seizures
- Jaundice (yellow coloring of the skin and eyes)
- Lumps near the surface of the body, caused by cancer spreading to the skin or to lymph nodes in the neck or above the collarbone.

Some lung cancers can cause a group of very specific symptoms. These are often described as syndromes.(2.4)

**Horner syndrome:**

Cancers of the top part of the lungs (sometimes called Pancoast tumors) may damage a nerve that passes from the upper chest into your neck. This can cause severe shoulder pain. Sometimes these tumors also cause 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 press on the SVC, which can cause swelling in the face, neck, arms, and upper chest. It can also cause headaches, dizziness, and a change in consciousness if it affects the brain. While SVC syndrome can develop slowly over time, in some cases it can become life-threatening, and needs to be treated right away.

**Paraneoplastic syndromes:**

Some lung cancers may 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 other organs, patients and their doctors at first may suspect that something other than lung cancer is causing them.

The most common paraneoplastic syndromes caused by non-small cell lung cancer are:

- High blood calcium levels, which can cause frequent urination, constipation, nausea, weakness, dizziness, confusion, and other nervous system problems.
- Too much growth of certain bones, like those in the finger tips.

**Tests to find lung cancer:**

- (a) Bronchoscopy.
- (b) Endobronchial ultrasound.
- (c) Endoscopic esophageal ultrasound.
- (d) Mediastinoscopy and mediastinotomy.
- (e) Thoracentesis.
- (f) Thoracoscopy.(2.5)

Table 1: (4.1) the standard treatment options for each stage of NSCLC are presented in

Stage (TNM Staging Criteria)		Standard Treatment Options
Occult NSCLC		Surgery
Stage 0 NSCLC		Surgery
		Endobronchial therapies
Stages IA and IB NSCLC		Surgery
		Radiation therapy
Stages IIA and IIB NSCLC		Surgery
		Neoadjuvant chemotherapy
		Adjuvant chemotherapy
		Radiation therapy
Stage IIIA NSCLC	Resected or resectable disease	Surgery
		Neoadjuvant therapy
		Adjuvant therapy
	Unresectable disease	Radiation therapy
		Chemoradiation therapy
	Superior sulcus tumors	Radiation therapy alone
		Radiation therapy and surgery
		Concurrent chemotherapy with radiation therapy and surgery
		Surgery alone (for selected patients)
	Tumors that invade the chest wall	Surgery
		Surgery and radiation therapy
		Radiation therapy alone
Chemotherapy combined with radiation therapy and/or surgery		
Stage IIIB NSCLC		Sequential or concurrent chemotherapy and radiation therapy
		Chemotherapy followed by surgery (for selected patients)
		Radiation therapy alone
Stage IV NSCLC		Cytotoxic combination chemotherapy (first line)
		Combination chemotherapy with bevacizumab or cetuximab
		EGFR tyrosine kinase inhibitors (first line)
		EML4-ALK inhibitors in patients with EML-ALK translocations
		Maintenance therapy following first-line chemotherapy
		Endobronchial laser therapy and/or brachytherapy (for obstructing lesions)
		External-beam radiation therapy (primarily for palliation of local symptomatic tumor growth)
Recurrent NSCLC		Radiation therapy (for palliation)
		Chemotherapy or kinase inhibitors alone
		EGFR inhibitors in patients with/without EGFR mutations
		EML4-ALK inhibitors in patients with EML-ALK translocations
		Surgical resection of isolated cerebral metastasis (for highly selected patients)
		Laser therapy or interstitial radiation therapy (for endobronchial lesions)
		Stereotactic radiation surgery (for highly selected patients)

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