LITERATURE REVIEW

Lung Cancer: A Literature Review

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ABSTRACT

Lung cancer is a cancer whose onset starts in the lungs where there is an abnormal cell growth that is very fast and uncontrolled. The abnormal cell growth is triggered by deoxyribonucleic acid (DNA) damage, including deletions in the DNA section, inactivation of tumor suppressor genes, activation of proto-oncogenes to oncogenes, the absence of apoptosis, and the activity of the telomerase enzyme. Lung cancer is initiated by oncogeneous activity and inactivation of tumor suppressor genes. Oncogenes are genes that help cells grow and divide and are believed to cause a person to develop lung cancer. In general, lung cancer is divided into two types, namely non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). World Health Organization (WHO) classifies lung cancer based on histopathology into 4 major cell types, namely SCLC, NSCLC which includes adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma (LCC). The difference between the two is that SCLC has a higher aggressiveness than NSCLC. Cancer treatment is based on the type, size, location and stage of the cancer, as well as the patient's overall condition.

INTRODUCTION

Lung cancer is a cancer whose onset starts in the lungs where there is an abnormal cell growth that is very fast and uncontrolled. The abnormal cell growth is triggered by deoxyribonucleic acid (DNA) damage, including deletions in the DNA section, inactivation of tumor suppressor genes, activation of proto-oncogenes to oncogenes, the absence of apoptosis, and the activity of the telomerase enzyme.[1]

Cigarette smoking is the number one risk factor for lung cancer. Other risk factors for lung cancer are radiation and air pollution. In addition, nutrition and genetics also play a role in the onset of lung cancer.[1]

In general, lung cancer is divided into two types, namely non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC). SCLC has more aggressive behavior and has a worse prognosis. Even though, epidemiologically, NSCLC is more frequently found, about 85% of total lung cancer cases. World Health Organization (WHO) classifies lung cancer into 4 major cell types, namely SCLC, NSCLC which includes adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma (LCC). Histologically, tumors can occur either from single or mixed types.[1,2]

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The initial examination that can be performed to detect lung cancer is a chest X-ray (CXR). CXR is a radiographic projection of the lung which is often used for screening (early detection) of lung disease. Image of chest radiographs will give different results between healthy and unhealthy lungs. The presence of nodules in the CXR may result from malignancies, infections, and other lesion. However, these nodules are not necessarily an indication of lung cancer.[1,3] Further diagnosis using chest computed tomography (CT) is the gold standard for imaging of nodules in the lungs. Once the diagnosis of lung cancer has been made, staging is essential for determining appropriate management of the disease.

Lung cancer management is differentiated to the type of histology and stage. Management of lung cancer consists of surgery, chemotherapy, radiotherapy, and targeted therapy. Current therapeutic determinations are focused more on the molecular features of each cancer. This review covers pathogenesis and pathophysiology, risk factor, clinical manifestation, management, complication and prognosis of lung cancer.

Pathogenesis

The occurrence of lung cancer is based on the emergence of tumor suppressor genes in the genome (oncogenes). The presence of an initiator changes the tumor suppressor gene by removing (deletion) or inserting (insertion) parts of its base pair. The appearance of the erbB1 and/or erbB2 genes plays a role in anti-apoptosis (the mechanism for cells to die naturally, programmed cell death). Changes in the appearance of these genes cause target cells, namely lung cells, to turn into cancer cells with autonomic growth properties.[4,5]

Cigarettes play a very important role as an initiator as well as a promoter of lung cancer. Smoking is also known to be closely related to the occurrence of lung cancer. Therefore, cancer is a genetic disease which at first is limited to target cells and then becomes aggressive in surrounding tissues and even affects other organs.[6–8]

Causes and Risk Factor

The risk factors for lung cancer are very diverse. 1) Gender. Males have methylation levels in the Ras association domain family member 1 (RASSF1A) higher than females. The RASSF1A gene is one of the tumor suppressors encoding proteins resembling effector renin-angiotensin-system (RAS) protein. If there is methylation that induces the inactivation of expression of these genes, it will cause a loss of inhibition of Cyclin D1. Hence, cell cycle arrest does not occur. This causes cells divide uncontrollably and become cancerous.[9–11]

2) Age. The risk of getting cancer will increase with age. A previous study showed a trend toward a suitable smoking pattern age also affects the occurrence of lung cancer.[12] Population aged 45-49 years old showed the highest methylenetetrahydrofolate reductase (MTHFR) gene inactivation than other age groups that are closely related to smoking habits. The 50-64 years old group has the highest gene inactivation in Cadherin-1 (CDH1) and Glutathione S-transferase P-1 genes (GSTP1), while the age group >70 years old has a tendency to inactivate GSTP1 and RASSF1A genes the highest compared to other age groups. This causes the age group over 45 years old to have a higher risk to lung cancer.[12]

3) Family history. This is related to the susceptibility to chromosome 6q23–25. The risk of lung cancer in individuals with a family history of lung cancer first-degree relatives increased by 50% in comparison with those with no family history of developing lung cancer.[12]

4) Smoking. Cigarettes contain various carcinogens that can trigger lung cancer. Carcinogens that are closely related to lung cancer are 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N-Nitrosonornicotine (NNN), and polycyclic aromatic hydrocarbon (PAH).[7]

Clinical Manifestation

In the early stages, most lung cancers do not show clinical symptoms. If symptoms are present, it means that the patient may be in an advanced stage. If the tumor is localized, the symptoms that can arise are coughing, hemoptysis, and wheezing due to airway obstruction. Sometimes there are cavities such as lung abscesses and atelectasis.[13,14]

On reaching local invasion, the clinical manifestations that appear vary as chest pain, dyspnea due to pleural effusion, invasion of the pericardium, superior vena cava syndrome, Horner's syndrome (facial anhidrosis, ptosis, miosis), hoarseness, due to compression of the recurrent laryngeal nerve and Pancoast's syndrome, due to invasion of the brachial plexus and cervical sympathetic nerves. When it has metastases, manifestations will appear at the location of the metastases such as headache in brain metastases, and bone pain when metastasized in the bones. In addition, cervical and supraclavicular lymphadenopathy will usually appear.[4,13,15]

Classification

The classification of lung cancer aims to determine the appropriate treatment. The term secondary lung cancer refers to metastasis of other malignancy to

the lung and will not be discussed further in this review.[10,11]

Primary lung cancer is divided into two types, namely NSCLC and SCLC. The difference between the two is that SCLC has a higher aggressiveness than NSCLC. About 85% of lung cancer cases is NSCLC. Histologically, tumors can occur in either single or mixed types.[8,9,16]

SCC is the most common type of diagnosed NSCLC. The morphology of SCC resembles an extrapulmonary tumor that appears as an inflated tumor nest without an intracellular bridge. Keratin often appears in the morphology of SCC tissue. The occurrence of SCC is thought to be influenced by smoking. As the number of smokers decreases, SCC is replaced by adenocarcinoma as the most frequently diagnosed type of NSCLC. Adenocarcinoma most commonly affects women under 60 years old. It has glandular, papillary structure, branchioalveolar pattern, cell mucin, or poorly differentiated solid pattern. It has a signet ring, clear cell and mucinous type, and fetal adenocarcinoma.[13,17]

SCLC is a neuroendocrine tumor that tends to present as a central mass with endobracial growth and is strongly associated with smoking. SCLC has cells with a small cytoplasm, a small hyperchromatic nucleus with a chromatin pattern such as "salt and pepper" and a prominent nucleolus. SCLC often produces specific hormones such as adrenocorticotropic hormone (ACTH), arginine vasopressin (AVP), atrial natriuretic factor (ANF), and gastrin-releasing peptide (GRP) which are associated with distinctive paraneoplastic syndrome.[7]

LCC tends to appear peripherally and appears as a poorly differentiated carcinoma of the lung composition without evidence of squamous, grandular differentiation, or SCLC on light microscopy. These tumors consist of a large malignant layer of cells associated with necrosis. Variants of LCC include basaloid carcinoma which presents as an endobracial lesion resembling a high-stage neuroendocrine tumor and an associated lymphoepithelioma-like carcinoma with Ebstein-Barr virus (EBV) infection.[7]

Staging

Current staging system of lung cancer used is based on 8th edition of lung cancer staging by the Union Internationale Contre le Cancer (UICC) and American Joint Committee on Cancer (AJCC). This staging system is based on three components, namely tumor, node, and metastasis (TNM). Descriptors and grouping can be seen in Table 1 and 2.[18]

Table 1. Definitions for T, N, and M descriptors[19]

Table 1 Changes to T-descriptors based on tumour size; comparing the 8th edition with the 7th. Changes are in italic

Tumour size	7th edition	8th edition
Cannot be assessed, not visualized on imaging	Tx	Tx
No evidence of primary tumour	T0	T0
Carcinoma *in situ*	Tis	Tis
≤1 cm	T1a	T1a
>1–≤2 cm	T1a	*T1b*↑
>2–≤3 cm	T1b	*T1c*↑
>3–≤4 cm	T2a	T2a
>4–≤5 cm	T2a	*T2b*↑
>5–≤7 cm	T2b	*T3*↑
>7 cm	T3	*T4*↑

Table 3 N-descriptors for the 8th edition, unchanged from the 7th. Permission from *Journal of Thoracic Oncology*

N-stage	Nodal descriptor
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or hilar lymph node and intrapulmonary node, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral, or contralateral scalene, or supraclavicular lymph node(s)

Table 4 M-descriptors for the 8th edition, with the introduction of M1c denoting extrathoracic metastases. Permission from *Journal of Thoracic Oncology*

M-stage	Descriptor
M0	No distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; pleural nodules or malignant pleural or pericardial effusion
M1b	Single extrathoracic metastasis or involvement of a single distant (non-regional) node
M1c	Multiple extrathoracic metastases in one or several organs

Table 2. Grouping of lung cancer staging

T/M	Label	N0	N1	N2	N3
T1	T1a *≤1*	IA1	IIB	IIIA	IIIB
	T1b *>1-2*	IA2	IIB	IIIA	IIIB
	T1c *>2-3*	IA3	IIB	IIIA	IIIB
T2	T2a *Cent, Visc Pl*	IB	IIB	IIIA	IIIB
	T2a *>3-4*	IB	IIB	IIIA	IIIB
	T2b *>4-5*	IIA	IIB	IIIA	IIIB
T3	T3 *>5-7*	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 *>7*	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a *Contr Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

Treatment

Cancer treatment is based on the type, size, location, and stage of the cancer, as well as the patient's overall condition. In general, lung cancer treatment is divided into surgery, chemotherapy, radiotherapy, and others.[9] Current guidelines used for the management of lung cancer is National Comprehensive Cancer Network 2021. Here are the modalities for the treatment for lung cancer.

- Surgery
  Surgery is performed if the cancer is still on one side of the lung and has not spread to the other side of the lung or other organs (stages I and II). The thoracotomy procedure aims to remove the tumor and some of the healthy tissue around it. This action is performed to inhibit the spread of cancer cells. Large enough, the thoracic surgeon will perform a lobectomy to remove part of the lung. If the cancer has spread to the entire right or left lung, the doctor will remove one lung as a whole. Lung cancer sufferers can still breathe normally, even with only one lung.[8,9,20]
- Chemotherapy
  In advanced cancer, chemotherapy is performed for several weeks or months to kill cancer cells, and inhibit the growth and spread of cancer cells that remain after surgery. Chemotherapy can also be performed before surgery with the aim of making the

cancer shrink, making it easier to remove. Another function of chemotherapy is to relieve cancer symptoms experienced by sufferers.[7,8]

- Radiotherapy
  Radiotherapy is a treatment method performed after surgery to kill any remaining cancer cells. When surgery is no longer possible for advanced cancer, radiation therapy aims to relieve symptoms and prevent the spread of cancer.[7–9]
- Target therapy
  Target therapy is a tablet drug that directly attacks the growth proteins of cancer cells. This drug is given at an advanced stage, when surgery and radiotherapy cannot be performed to treat cancer. Examples of targeted therapy drugs for lung cancer are protein kinase inhibitors, such as erlotinib and gefitinib.[18]
- Immunotherapy
  Immunotherapy is basically classes of drugs that uses the body's immune system to kill cancer cells. This modality usually direct to advanced stage of NSCLC or SCLC. Numerous trials are underway to explore the role and mechanism of immunotherapy in the treatment of lung cancer. A recent study of novel agents, especially the checkpoint inhibitors, have shown promising preliminary results in achieving beneficial and durable treatment.[21]
- Cryotherapy
  Cryotherapy is a type of treatment that uses gas with very cold temperatures to shrink tumors or kill cancer cells. Cryotherapy is performed if the cancer has blocked the respiratory tract, making it difficult for the patient to breathe.[12,18]

Common Comorbidities in Lung Cancer and Prognosis

Anemia and pleural effusion are common comorbidities which usually present in lung cancer. Anemia may be caused due to complication of lung cancer (e.g., hemoptysis) or other condition. It has the prevalence of 60%. It is associated with a poor prognosis in cancer patients. It interferes with the response to radiation treatment, because it reduces the blood's ability to carry oxygen, leaving tissues deprived of oxygen. It causes tumor hypoxia. Hence, solid tumors are resistant to ionization radiation and some forms of chemotherapy.[19]

Pleural effusion due to lung cancer can occur in all types of histology, but the cause is often adenocarcinoma. Accumulation of effusions in the pleural cavity occurs due to increased vascular permeability due to inflammatory reactions induced by cancer cell infiltration of the parietal and/or visceral pleura, direct invasion of the tumors adjacent to the pleura, and obstruction of the lymph nodes. The presence of malignant pleural effusion in lung cancer describes a terminal condition (end stage) of malignancy with a poor prognosis.[3,5]

The prognosis of lung cancer is poor. The life expectancy of up to 5 years in patients with SCLC is about 20%, while the extensive stage is very poor <1%. Life expectancy of up to 5 years of NSCLC patients varies by stage, 60-70% of patients with stage I, and <1% in patients with stage IV. NSCLC patients who have metastasized, if not treated, has life expectancy of 6 months. Currently, the life expectancy of patients with NSCLC at an early or advanced stage is increasing, compared to the life expectancy of patients at an early stage when given a platinum-based regimen after resection. Targeted therapy also increases the life expectancy of patients with stage IV. However, in metastatic disease, the results are still disappointing.[15,17,21]

SUMMARY

Lung cancer is a rapidly growing, uncontrolled cancer that originates in the lungs and is triggered by DNA damage, including deletions, inactivation of tumor suppressor genes, and activation of proto-oncogenes. Cigarette smoking is the leading risk factor for lung cancer, along with radiation, air pollution, nutrition, and genetics. Lung cancer is divided into two types, NSCLC and SCLC. WHO classifies lung cancer into four major cell types, SCLC, NSCLC, SCC, and LCC.

Detection of lung cancer involves CXR, which can reveal nodules from malignancies, infections, and other lesions. Further diagnosis using chest CT is the gold standard for imaging nodules in the lungs. Management consists of surgery, chemotherapy, radiotherapy, and targeted therapy. Pathogenesis is based on the emergence of tumor suppressor genes, which cause cancer cells to turn into cancerous cells. Risk factors for lung cancer include gender, age, and smoking habits.

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Conflict of Interest
The authors declared there is no conflict of interest.

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Authors' Contributions

Writing the manuscript, co-coordinating study design, collecting data: YES. Data analysis: YES, PP, IGAMAPP, ANOS, SPWBN. Data interpretation: YES, PP. Revising: PP. Reviewing: WIE, JJD, HS, DJSW. All authors contributed and approved the final version of the manuscript.

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