ORIGINAL RESEARCH PAPER

Medicine

LUNG CANCER

KEY WORDS:

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(1) INTRODUCTION

The number of newly diagnosed patients of Lung cancer was 1.8 million, and 1.6 million were dead in 2012 in all of the world.[1)]

Cigarette smoking is the most common risk factor for lung cancer. Other risks include passive inhalation, residential Radon, pollution and air quality, occupational exposures such as Asbestos, infection and genetic susceptibility.[2)]

Incidence trends and geographical patterns are different for men and women and primarily reflect historical, cultural and regional differences in tobacco smoking.[1)]

However, the rates of lung cancer increased in female worldwide.[3)] Lung cancer in never smokers occurs predominantly in women and younger patients increased in recent years.[4)]

Lung cancer is classified into SCLC (small cell lung cancer) and non-SCLC. This classification is due to that chemotherapy and radiotherapy is very effective for SCLC. Non-SCLC includes Squamous cell carcinoma, adenocarcinoma, and Large cell carcinoma.

(2) Symptom of lung cancer

There are no symptoms in early stage. Some symptoms occur, as lung cancer progress.

- Cough with sputum (including blood)
- Shortness of breath.
- Repeated chest infection..
- Hoarse voice.
- Wheezing.
- Chest pain.
- Weight loss.
- Extreme Fatigue.

(3) Diagnosis

- If symptom and sign are thought to be due to lung cancer, tests of Chest X-ray, Computed tomography (CT) or PET-scan (Positron emission tomography), cytology of sputum will be recommended at first. There is suspicious of lung cancer, therefore, Bronchoscopy including biopsy or EBUS (Endobronchial ultrasound scan) with biopsy will be done.

If there is cancer in subpleural, CT guided needle biopsy is needed. Neck lymph node biopsy is also needed case by case.

Further tests include mediastinoscopy, thoracoscopy, and MRI (magnetic resonance imaging) for the examination of presence of brain metastasis, bone scan for the bone metastasis of unexplained skeletal pain. US (ultrasound) for liver metastasis etc.

Low dose CT test is recommended for high risk person who have 1 (or 2) pack per day for 20 (or 10) years or more smoking history, and smoke now, and quit within the past 15 years, between 50-80 years old. The results are taken by doctor for a few days or a week.

(4) Staging of lung cancer
TNM classification 8th edition[5)]

T for the extent of the primary tumor, N for lymph node involvement, and M for metastatic disease.

T-classification
Tx : tumor in sputum/ bronchial washings but not be assessed in imaging or bronchoscopy
T_0 : No evidence of tumor
Tis : Carcinoma in situ (Fig.1)

T_1 <3cm surrounded by lung/visceral pleura, not involving main bronchus
$T_1a_{(mi)}$ Minimally invasive carcinoma
T_1a <1cm
T_1b >1cm to <2cm
T_1c >2cm to <3cm (Fig.2)

T2 involvement of main bronchus without carina, regardless of distance from carina or invasion visceral pleura or atelectasis or post obstructive pneumonitis extending to hilum

T_2a >3cm to <4cm
T_2b >4cm to <5cm (Fig.3a)
T3 >5cm to <7cm in greatest dimension
or tumor of any size that involves chest wall, pericardium, phrenic nerve or satellite nodules in the same lobe

T4 >7cm in greatest dimension or

Any tumor with invasion of mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine or separate tumor in different lobe of ipsilateral lung (Fig.4)

N1 Ipsilateral peribronchial and/or hilar nodes and intrapulmonary nodes (Fig.3b)
2 Ipsilateral mediastinal and/or subcarinal nodes
3 Contralateral mediastinal or hilar; ipsilateral/ contralateral scalene/supraclavicular

M_1 Distant metastasis
M_1a Tumor in contralateral lung or pleural/pericardial nodule/malignant effusion
M_1b Single extrathoracic metastasis, including single non-regional lymphnode (Fig.3b)
M_1c Multiple extrathoracic metastases in one or more organs

Non-small cell lung cancer stage
Subsets of T, N and M categories are grouped into certain stages, because these patients share similar prognosis[6)].

	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB

(5) Treatment

- **Surgery:** Surgeon remove cancer with a margin of healthy tissue and metastatic lymphnodes. The type of surgery includes Wedge resection, Segmental resection, Lobectomy, and Pneumonectomy. Surgeon also remove cancer after shrinkage cancer cells by radiation and/or chemotherapy. Residual cancer tissue may be applied to radiation therapy and/or chemotherapy after surgery.
- **Radiation:** Radiation therapy uses high-powered energy beams such as X-rays and protons to kill cancer cells. If the case is no indication of surgery, radiation and/or chemotherapy is used[7].
- **Stereotactic radiotherapy:**
- It is also known as radiosurgery, and is a intense radiation treatment that aims many beams of radiation from many angles at the cancer. It may be an option of small lung cancer who can't undergo surgery. It may also be used to treat lung cancer that spread to other parts of the body, including the brain.
- Chemotherapy: One or more chemotherapy drugs may be given to kill cancer cells through a vein or oral several weeks or months. Chemotherapy is often used before surgery to shrink the size of cancer to remove smoothly, and after surgery to residual cancer cells. It is often used with radiotherapy. In the case of small cell lung cancer, chemotherapy is often the first indication of therapy.

Recently, relationship lung cancer and oncogene was actively reported on NSCLC.

- Somatic mutations that activates EGFR/RAS pathways signaling are a hallmark of lung adenocarcinoma[8]. Oncogenes in the EGFR/RAS pathway display 'oncogene addiction', a tumor-specific reliance on sustained cell signaling for cell survival, and consequently these mutated oncogenes represent powerful drug targets for lung cancer therapy[9].

Several of the mutated genes in this pathway are clinically targeted to improve outcomes for lung cancer patients. For example, somatic mutations in EGFR underlie sensitivity to EGFR inhibitors erlotinib and osmertinib[10)11)], and chromosomal rearrangements involving ALK underlie sensitivity to crizotinib12) and other inhibitors.

Anaplastic lymphoma kinase (ALK) is a tyrosine kinase that can be aberrantly expressed in several tumor types. In non-small lung cancer (NSCLC), chromosomal rearrangements involving the ALK foci on chromosome 2 are found in approximately 5 percent of NSCLC tumors[12].

The most common ALK rearrangement in NSCLC juxtaposes the 5' end of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the 3' end of the ALK gene, resulting in the novel fusion oncogene EML4-ALK[13].

Tumors that contain ALK fusion oncogenes or its variants are associated with specific clinical features, including never-or light smoking history, younger age, and adenocarcinoma with signet ring or acinar histology. Testing for this fusion gene in NSCLC is important, as "ALK-positive" tumors (tumors harboring a rearranged ALK gene/fusion protein) are highly sensitive to therapy with ALK-targeted inhibitors[14].Other gene rearrangement such as ROS-1, RET, NTRK, and BRAF are reported in NSCLC[15]).

- immunotherapy: Human body has a immune system that activate T cells to attack and remove foreign body such as virus or bacteria. While, we has an immune system that judge immune checkpoint to do not over work. Cancer cell utilize this system, and escape from the attack of immune system.

PD-1(Programmed cell Death-1) is one of the host immune checkpoint receptor. When PD-L1 (Programmed cell Death 1-Ligand 1) that presents surface of the cancer cell binds to this host receptor, immune system is suppressed by cancer cell.

Immune checkpoint inhibitor, anti-PD-1 antibody binds to this receptor and block the interaction of PD-1 and PD-L1 protein. After that, T-cell attack cancer cell effectively.[16]

Cytotoxic T lymphocyte antigen 4 (CTLA-4) is an immune checkpoint receptor that negatively regulates the immune response. Inhibition of CTLA-4 can directory activate T cells, release T cell suppression by regulatory T cells (T reg), and have long-term antitumor effects.[17]

After the diagnosis of lung cancer, genetic tests are performed to determine the presence or absence of six gene mutations related to the cancer cell organs side. The six genes are EGFR, ALK, ROS1, BRAF, NTRK, and MET. If mutations are found in these genes, molecularly targeted drugs targeting each genes are used. If mutations are not found in these genes, PD-1 tests are performed to determine whether immunotherapeutics work.

- Side effect of Lung cancer Treatment
- Breathing problems
- Fatigue
- Infection, bleeding and anemia (chemotherapy can lower blood counts)
- Stomach problems (nausea, vomiting, diarrhea or constipation)
- Changes in appearance, including hair loss.
- Pain and discomfort
- Changes in sexual functioning and effects on fertility

Potentially serious side effects of chemotherapy may include lowered blood cell counts, which increase the risk of infection.

- Palliative (Supportive) care

Palliative care is a specialized medical care focused on relieving the symptoms and stress of a serious illness. It is not treatment for the lung cancer itself. It is appropriate at any age and at any stage. You can get it along with curative treatment. The goal is to improve quality of life for both the patient and the family. Palliative care is provided by a specially-trained team of doctors, nurses, and other specialists. They work together with a patient's medical team to provide an extra layer of support.[18]

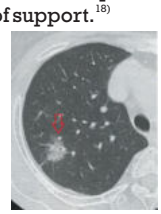


Fig.1

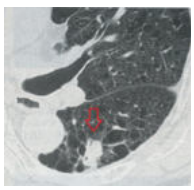


Fig.2

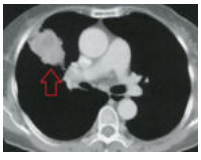
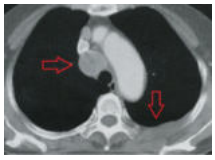


Fig.3 (a)



(b)

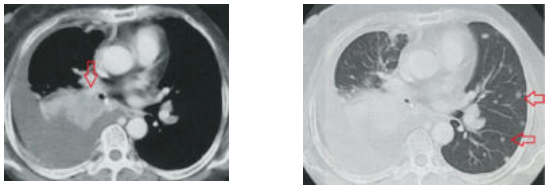


Fig.4

Fig.1-4: Japanese Journal of Lung Cancer Vol.43. No3. June.2003

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