Lung cancer in Singapore

Article contributed by
Dr Chin Tan Min¹, Professor Philip Eng²,
Dr See Kay Choong³, Dr Huang Yiqin⁴

¹Senior Consultant, Department of Haematology-Oncology, National University Cancer Institute, Singapore (NCIS); ²Senior Consultant Respiratory Physician, Philip Eng Respiratory and Medical Clinic, Mount Elizabeth Medical Centre, Singapore; ³Consultant, Division of Respiratory & Critical Care Medicine, National University Hospital, Singapore; ⁴Medical Oncologist, National University Cancer Institute Singapore, National University Hospital

PART 1: SYMPTOMS, SIGNS, RISK FACTORS

Lung cancer is the uncontrolled growth and spread of abnormal cells in the lungs and airways. These abnormal cells often takes months or years to develop, and if left alone, would invade surrounding tissue and distant organs. Among Singaporean males, lung cancer is ranked as the second most common cancer diagnosed in 2010-2014, with about 50 new cases per 100,000 residents per year. Among Singaporean females, lung cancer is ranked as the third most common, with about 25 new cases per 100,000 residents per year. In general, lung cancer can be divided into four stages, with the first two stages much more curable – usually by surgery – than the latter two stages. Unfortunately, four out of five cases were diagnosed only in the advanced stages of disease (Stage 3 or Stage 4). Given the large number of new cases, and generally advanced disease stage, lung cancer was unsurprisingly the deadliest cancer locally. To be precise, according to the Singapore Cancer Registry, 5,732 lung cancer patients died in 2010-2014.
Early detection of lung cancer may help to improve outcomes of this otherwise serious disease. To enable early detection, we need to know who is at higher risk of getting lung cancer. Take for example Mr. Wong, a seventy-year-old retired businessman, who has been smoking one pack of cigarettes daily for the past fifty years, but is otherwise healthy. Should he be worried about lung cancer? How about Mrs. Tan, a sixty-year-old homemaker, who has never smoked before? She has been coughing for more than six months, her phlegm has occasional streaks of blood, and she has gotten noticeably thinner. Should she be worried? To a certain extent, both should be, based on risk factors and symptoms.

Apart from tobacco smoke exposure, other less common risk factors exist. Asbestos, a mineral used in heat-resistant housing material, roofing and pipes, may be inhaled and trigger lung cancer many years later. Fortunately, asbestos has been banned in Singapore since 1989, though some older buildings and structures may still contain asbestos. Exposure to radon gas in poorly ventilated basements, or to polluted air containing arsenic, chromium, nickel, vanadium and smoke, and smoke from coal burning, can also predispose a person to lung cancer. Some risk factors may be less avoidable. For instance, radiotherapy for other cancers around the should (e.g. breast cancer, lymphoma) could result in lung cancer developing later, but is often necessary for control of the initial disease.

Yet, why does lung cancer occur in some people who have never smoked and who have no other known risk factors? This is because there are many subtypes of lung cancer. Some subtypes, like small-cell lung cancer and squamous cell lung cancer, are associated with tobacco smoke exposure. Other subtypes, like adenocarcinoma, are now increasingly known to occur in never smokers. It is unclear why never smokers can develop lung cancer. Perhaps it could be unrecognised second-hand smoke exposure, or unrecognised exposure to less common risk factors. Whatever the cause, one must be aware that the absence of smoking does not include the risk of getting lung cancer. This problem should not be trivialized; it has been estimated that about a fifth of male lung cancer patients and about half of female lung cancer patients have never smoked.

For never smokers like Mrs. Tan in our example, lung cancer detection would depend on symptoms, or when incidental abnormalities are found on chest X-rays done for other purposes (e.g. pre-employment screening, investigation of chest infection). Individuals with or without risk factors for lung cancer may have symptoms. Admittedly, symptoms would generally occur when lung cancer has become more advanced. The more common symptoms include cough, shortness of breath, blood in the phlegm (ranging from blood streaks to larger amounts of blood), chest pain, and weight loss. These symptoms occur when lung cancer invades the airways or fills the chest with cancerous fluid. When lung cancer enlarges to involve the vocal cord nerves, hoarseness of the voice may ensue. When lung cancer encases and constricts the large veins in the chest, a person’s face and neck may swell. When lung cancer spreads to lymph nodes in the neck, neck lumps may then be felt. When lung cancer spreads to the brain, weakness, numbness and confusion may result. Overall, many of these symptoms may also exist in other conditions (e.g. blood-streaked sputum may be due to tuberculosis). Some of these symptoms may also be a direct result of cigarette smoking (i.e. a smoker’s cough). The key is to be aware of new or worsening symptoms, which must trigger an expedited evaluation by a general practitioner or chest physician.

Tobacco smoking remains the most important risk factor for lung cancer, and stopping tobacco smoke exposure is still the most important method to prevent the disease. Apart from cigarettes, other tobacco products like “ang-hoon” (dried tobacco leaves wrapped in paper) and shisha (waterpipe) also contain cancer-causing agents and are equally harmful. Second-hand smoke from any of these sources may also lead to lung cancer, and one should avoid such toxic smoke as much as possible. It is also important to avoid second-hand smoke from others. These sources may also lead to lung cancer, and one should avoid such toxic smoke as much as possible. It is also important to avoid second-hand smoke from others.

PART 2: INVESTIGATING SUSPECTED LUNG CANCER

If the doctor has any suspicion that one has lung cancer, the usual first step is to order a chest X-ray. If the chest X-ray is abnormal, the next step is to do a CT Scan (which is a more detailed imaging examination, often requiring the use of contrast injections). The CT Scan is able to better clarify the size and position of the abnormality and is usually used to plan the biopsy (which means sampling of the abnormal tissues with the intent of confirming the presence of abnormal cancer cells). Chest X-ray can be normal in patients with lung cancer but this is relatively uncommon. Common subsequent tests include:

- Sputum Cytology: If the patient has a productive cough, looking for cancer cells in the sputum is sometimes the easiest way to confirm cancer.
- Biopsy
  - Bronchoscopy – This involves a day surgery procedure where a scope is inserted into the airway to obtain biopsy samples.

- Needle Biopsy – This involves a day surgery procedure where a needle is inserted through the chest to sample the abnormal area under ultrasound or CT guidance.
- Surgical – This involves a general anaesthesia procedure to open the chest to look at the suspected area. This is usually the last resort when the abnormal area is very small or in a area which is relatively inaccessible by other techniques.

- Others: Sometimes the cancer has spread out of the lung and other techniques can be deployed.
  - Pleural Tap – Lung cancer often spreads to the membrane surrounding the lung, causing excess fluid to build up around the lungs (a condition called pleural effusion). A needle can be inserted through the chest under local anesthesia to extract the fluid for analysis.
  - Lymph Node Biopsy – Lung cancer often spread to the neck lymph nodes and this can be accessible for biopsy by needle or excision under anaesthesia.

PART 3: CELLS TYPE FOR LUNG CANCER

Majority of lung cancer patients have the non-small cell type on biopsy. This is a group of many cell types like adenocarcinoma, large cell and squamous cell carcinoma. Adenocarcinoma is the commonest single cell type for lung cancer.

The other group of lung cancer patients have the small cell type on biopsy. Such patients have a distinct aggressive cancer behaviour characterised by rapid spread and poor prognosis. They are usually treated only by chemotherapy.

Non-small cell type

Small cell type
**PART 4: STAGING OF LUNG CANCER**

Once the lung cancer is confirmed, the doctor will order tests to determine the stage of lung cancer. This usually involves CT-PET Scans, MR of the brain or bone scans as lung cancer often spreads to other areas like the brain, bones and liver in addition to those mentioned above.

Non-small cell lung cancer is staged 1 to 4. Stages 1 and 2 are limited to the chest. Stage 3 is locally advanced lung cancer, whereas Stage 4 is characterised by cancer that has spread to distant sites like liver, bones or brain.

Small cell lung cancer is usually staged as limited or extensive. Limited stage small cell lung cancer means the cancer is restricted to one lung whereas extensive stage lung cancer has spread beyond the single lung.

**Stages of Lung Cancer**

- **Stage I**: Cancer has not spread outside the lungs.
- **Stage II**: Cancer has spread to the lymph nodes in the area closest to the lungs, but has not spread to the other lymph nodes or to distant organs.
- **Stage III**: Cancer has spread to lymph nodes in other areas of the chest or to other organs or tissues.
- **Stage IV**: Cancer has metastasized (spread) to other parts of the body, such as the lungs, bones, brain, liver or other distant organs.

**Non-Small Cell Lung Cancer (NSCLC)**

Adjuvant chemotherapy is offered to those with resected stage II and III lung cancer. It has been shown to reduce the risk of relapse and improve survival. Treatment usually involves four cycles of platinum-based chemotherapy.

The role of adjuvant chemotherapy for stage IIB lung cancer remains controversial. Oncologists often discuss the pros and cons of chemotherapy in this group of patients.

Adjuvant radiotherapy is reserved for those with positive margins or lymph nodes in the mediastinum (stage III disease discussed in further detail in the next section) to reduce the risk of local relapse.

### Locally advanced (Stage III)

Stage III lung cancer is a heterogeneous group. Management involves a multi-disciplinary approach with chemotherapy, radiotherapy and in selected cases, surgery.

- **Upfront surgery** may be considered for T3N0 (Stage IIIA) disease.
- **Involvement of mediastinal lymph nodes** portends a poorer prognosis, and treatment usually excludes surgery.
- **In selected cases with single nodal disease**, surgery may be considered after a course of neo-adjuvant treatment.
- **In all other patients with multiple mediastinal lymph node disease**, involvement of contralateral mediastinal, contralateral hilar or supraclavicular lymph nodes, treatment involves chemo-radiation. The addition of chemotherapy to radiotherapy, either sequentially or concurrently, has been shown to improve survival.

### Metastatic (Stage IV)

There have been major advances in the treatment of stage IV lung cancer in the last decade.

- **Targeted therapy**
  - Treatment upfront depends on the histology: Squamous cell carcinomas are treated with palliative chemotherapy, while adenocarcinomas can be treated with targeted therapy if sensitizing mutations are found.
  - Mutations seen in adenocarcinoma include EGFR (Epidermal Growth Factor Receptor), ALK (Anaplastic Lymphoma Kinase) and ROS1 (One of the molecular markers for Lung Cancer). The presence of these mutations confers a better prognosis. They are more prevalent among non-smokers, compared to smokers. In non-smokers, the prevalence of EGFR, ALK and ROS1 mutation is 60%, 4% and 2% respectively. Gefitinib, Erlotinib and Afatinib are tyrosine kinase inhibitors targeting EGFR. They have demonstrated superiority to chemotherapy in terms of response rates and progression free survival. They are used in the 1st line setting for patients with EGFR mutation.
  - Common side effects of these drugs include rash, diarrhea and liver toxicity.

### ALK mutation or translocation is seen in less than 5% of patients. Crizotinib, a tyrosine kinase inhibitor targeting ALK, is the treatment of choice in the 1st line setting. Compared to palliative chemotherapy, crizotinib yields a higher response rate and progression free survival in ALK positive patients. Common side effects of Crizotinib worth highlighting include visual disorders, arrhythmia, gastrointestinal side effects and liver toxicities.

**Conclusion for NSCLC treatment and prognosis**

In this era of targeted therapy for EGFR/ALK/ROS1 mutants, prognosis for this group of patients has reached a median of 1-2 years.

The prognosis for non-targetable lung cancer, however, remains poor, with 1 year overall survival ranging between 30 to 40%. Immunotherapy however has resulted in durable responses in a subset of patients who can potentially do well in the longer term with improved overall survival.

Nonetheless, lung cancer remains to be one of the top cancer killers in Singaporean males and females. There remains a strong need to develop better drugs for our patients. Ongoing research and clinical trials are prudent to developing newer strategies and therapies against this disease.

**Small Cell Lung Cancer (SCLC)**

About 10-15% of all lung cancers belong to the small cell lung cancer type. This usually occurs in smokers. As alluded to earlier, staging is usually classified into limited versus extensive stage.

Limited stage lung cancers are usually treated with chemoradiation with curative intent in an otherwise fit patient. Extensive stage lung cancers are treated with chemotherapy mainly with a palliative intent to control disease and symptoms arising from the cancer.

Small cell lung cancer is a chemo and radio-sensitive cancer. Relapses however are common. Long-term survivors are possible, although this group remains small, and surveillance for second cancers in the zero-digestive tract are necessary.