

CANCER FOCUS



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Lung cancer in Singapore

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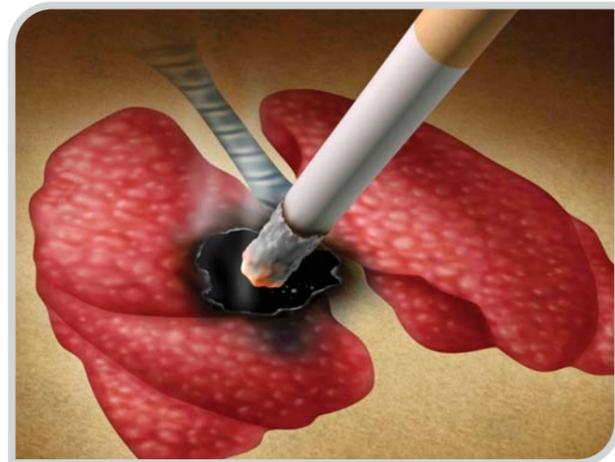
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PART 1: SYMPTOMS, SIGNS, RISK FACTORS

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.



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 therefore heartening that smoking is now prohibited in many public buildings and places locally.

In 2011, a very large study was done in the United States – the National Lung Screening Trial – enrolling more than 53,000 current or former smokers, aged 55 to 74, and who had smoked at least 30-pack years. The study investigators calculated the number of pack-years by multiplying the average number of packs of cigarettes smoked per day by the number of years a person has smoked. In these especially high-risk patients who did not have any symptoms of lung cancer (Mr. Wong would be one of them), screening with low-dose computed tomography scanning – when compared with normal chest X-ray – may improve detection of early cancer and reduce lung cancer-related death rates. This trial should trigger a discussion between such high-risk patients and their doctors about whether screening should be done, acknowledging practical difficulties like cost of scans and possibility of false positive findings (abnormal scan findings that eventually turn out non-cancerous).

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 pollutants containing arsenic, chromium, nickel, wood 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 chest (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 exclude the risk of getting lung cancer. This problem should not be trivialised: 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 bone, pain in those bones including the spine can occur. 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.

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.



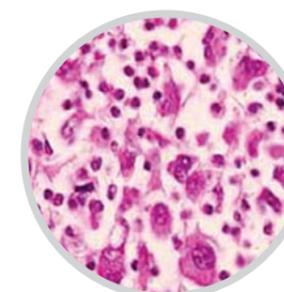
- *Needle Biopsy* – this involves a day surgery procedure where a needle is inserted through the chest to sample the abnormal area under ultrasound or CT guidance.
- *Surgical* – This involves a general anaesthesia procedure to open the chest to look at the suspected area. This



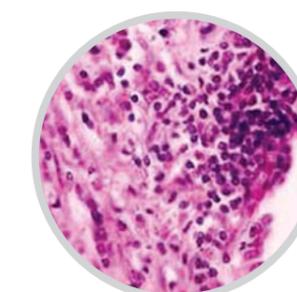
is usually the last resort when the abnormal area is very small or in area which is relatively inaccessible by other techniques.

- **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 anaesthesia 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



Non-small cell type



Small cell type

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.

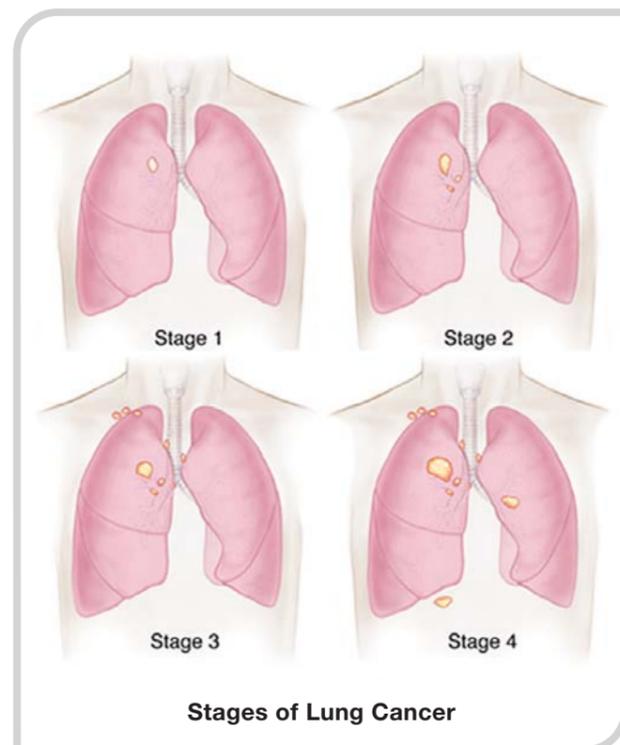
The other group of lung cancer patients have the small cell type on biopsy. Such patients have a distinct aggressive cancer behaviour characterised by rapid spread and poor prognosis. They are usually treated only by chemotherapy.

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, MRI of the brain or bone scans as lung cancer often spread 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.



PART 5: TREATMENT AND PROGNOSIS

Non-Small Cell Lung Cancer (NSCLC)

■ Early stage (Stage I, II)

Management of Stage I and II Lung Cancer involve surgery and adjuvant chemotherapy.

For patients who are fit and have adequate lung reserves, resection offers the best chance of cure. The 5 year overall survival of resected stage I & II lung cancer is 70% and 50% respectively. Depending on the extent and size of tumour, surgical options that can be offered include lobectomy (removal of one lobe of the lung) or pneumonectomy (removal of entire lung).

In patients who are unable to tolerate definitive surgery (such as the elderly or those with poor lung reserves), radical radiotherapy is a reasonable alternative.

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 1B 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 T3N1 (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.

However, despite chemotherapy and definitive doses of radiotherapy, prognosis in this group of patients remain poor, with 5 year overall survival ranging between 5 to 15%.

■ 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. Newer generation agents that target ALK translocation such as Ceritinib, Alectinib, Brigatinib and Lorlatinib have also shown promising activities. They are potentially more potent than Crizotinib, and are indicated for patients who are resistant or intolerant to Crizotinib.

ROS1 rearrangement is seen in 2% of lung cancer. Crizotinib, an ALK inhibitor, also has activity against ROS1 rearrangement, yielding a response rate as high as 70%.

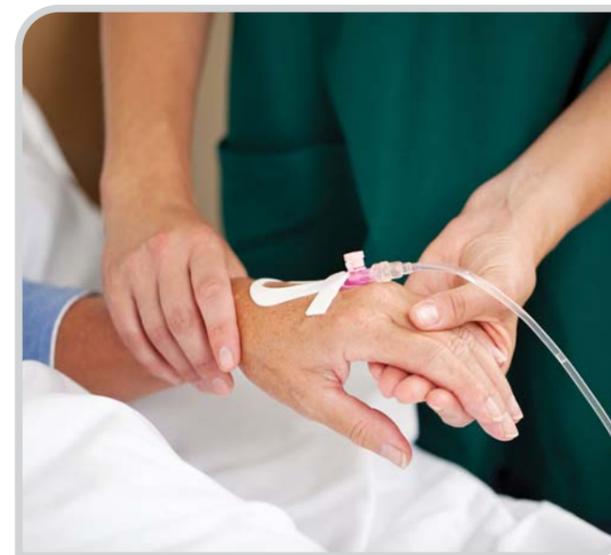
• Chemotherapy

Although the advent of targeted therapy has changed the paradigm of lung cancer treatment, a significant proportion of patients do not carry these mutations.

In this group of patients, palliative chemotherapy is the treatment of choice. Chemotherapy improves survival and quality of life in stage IV lung cancer. Treatment usually constitutes a platinum doublet. Common adverse effects to expect are nausea, diarrhea, a lower immunity, rash and fatigue.

• Anti-angiogenesis treatment

In addition to chemotherapy which traditionally forms the backbone of treatment in patients with no targetable mutation, addition of an anti-VEGF (Vascular Endothelial Growth Factor) agent (eg Bevacizumab) can also enhance the efficacy of treatment of stage IV lung cancer patients. As this group of medication targets the blood vessels, patients have to be counselled about the possible side effects of hypertension, strokes, heart attacks, and bleeding.



• Immunotherapy

In the recent 1-2 years, the role of immunotherapy has been established in advanced lung cancer. Immunotherapy is the use of a medication to stimulate a person's own immune system to recognize and destroy cancer cells more effectively. Nivolumab and Pembrolizumab are antibodies that target PD-1, a protein expressed on tumor cells. By blocking PD-1, these drugs boost the immune response against cancer cells, thus shrinking and slowing their growth.

For patients who have progressed on one line of chemotherapy, immunotherapy has been shown to be superior to 2nd line chemotherapy in both adenocarcinomas and squamous cell carcinomas. Unlike non-smokers, smokers respond better to immunotherapy. Common side effects of immunotherapy include fatigue, decreased appetite, nausea and gastrointestinal side effects. However, rare immune related adverse effects may occur and these can be potentially life threatening. This happens when the immune system affects other parts of the body, such as the lungs, intestines, liver and other organs. On the whole, the side effects from immunotherapy are less frequent than chemotherapy. On-going studies are evaluating its role in the 1st line setting for stage IV lung cancer.

■ 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 2-3 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 response 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 chemo-radiation 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 aero-digestive tract are necessary.