Lung Cancer in Singapore

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Introduction

Singapore is a small island city-state in Southeast Asia (Fig. 1), with a multiracial population of 5.7 million people, comprising 76% Chinese, 15% Malays, and 9% Indians and other races.1 Lung cancer presents a significant health challenge to our aging population.

Our health care system is divided into the public and private sectors, with 10 public and nine private acute hospitals providing approximately 11,000 beds.1 Within the public health care system, hospitals are divided by location into three major clusters, each of which run multidisciplinary cancer centers that also provide services to the other hospitals.

Medical costs are paid by a variety of sources. In public institutions, the government subsidizes care costs depending on patients’ income levels. In addition, a national medical savings scheme known as Medisave, in which a portion of earnings is set aside for an individual’s future health care, and Medishield-Life, in which Singaporeans are enrolled onto a basic health insurance plan to partially cover medical costs. Other hospital-based programs are also available to support low-income patients. Patients can also tap on Medisave and private insurance for treatment in private hospitals. Overall, Singapore spends 4% to 6% of its gross domestic product on health care, which is low compared with most other developed countries, although the proportion is expected to rise with increased health care utilization.

Epidemiology

Lung cancer is the second most common cancer in men and the third most common cancer in women in Singapore. According to the Singapore Cancer Registry, there were 7780 new cases of lung cancer diagnosed between 2013 and 2017, and it is the leading cause of cancer death in men (Fig. 2A) and the second highest...
cause of cancer death in women (Fig. 2B). Since the 1980s, incidence and mortality rates of lung cancer have steadily declined, particularly in men, largely owing to measures that reduce smoking. However, most cases are still diagnosed at an advanced stage, with two-thirds of patients having stage IV disease at the time of diagnosis (Fig. 3). There is an increasing incidence of adenocarcinoma relative to squamous cell carcinoma, similar to most developed countries.

The smoking prevalence in Singaporeans is among the lowest in the world and has been stable between 12% and 14% over the past decade compared with 18.3% in 1992. It is estimated that smoking costs Singapore at least $600 million per year in direct health care costs and lost productivity. Singapore has implemented tobacco control policies since the 1970s and formed the National Tobacco Control Program in 1986 to develop and implement smoking control programs to reduce smoking rates. The government has also raised the minimum legal age for tobacco use to 20 years on January 1, 2020; it will be raised to 21 years on January 1, 2021. Recently, standardized packaging of tobacco products with enhanced graphic warnings has been instituted, and further expansion of smoke-free zones made as part of a multipronged approach to combat smoking. Electronic cigarettes are banned in Singapore under the Tobacco (Control of Advertisements and Sale) Act.

Screening

Currently, there is no national screening program for lung cancer in Singapore. Low-dose computed tomography (CT) scans are sometimes used, but there is a risk of having false positives given that tuberculosis is endemic. Patients with lung cancer often present to health services with a persistent cough, weight loss, or hemoptysis. Pulmonary nodules are also detected incidentally in asymptomatic individuals on screening chest radiographs during statutory, corporat or voluntary health screening or on CT scans for other indications.

We recently published a position article on CT lung cancer screening and proposed the development of a standard workflow model of image acquisition, nodule evaluation, management of positive screen results, monitoring of false-positive results and procedural complications, and collecting these in a lung cancer screening database to evaluate the efficacy of a screening program in our population. Aside from long-term smokers, such screening may
include never-smokers, women, East Asians, and those who are at an increased risk of EGFR-mutant lung cancers.

**Diagnosis**

**Radiology**

CT scan of the thorax is the imaging modality of choice for the initial evaluation of a patient with suspected lung cancer. In a region where tuberculosis is endemic, positron emission tomography scans have a more limited role in diagnostic evaluation because of false positives from granulomatous inflammation. False negatives in the workup of minimally invasive adenocarcinoma is also a concern. Positron emission tomography-CT is routinely used in the staging of lung cancer in Singapore.
**Tissue Sampling**

Histologic samples are often obtained either by means of CT-guided needle biopsy, which has a greater than 95% yield, or bronchoscopy with endobronchial ultrasound (EBUS), transbronchial lung biopsy, and transbronchial needle aspiration (TBNA). Accurate localization of lung lesions on bronchoscopy remains a challenge, limiting both the yield and therapeutic capabilities of bronchoscopy, thus, making CT-guided biopsy the preferred modality when feasible. In Singapore, EBUS-TBNA is typically performed in an ambulatory setting under moderate sedation. Therefore, most EBUS-TBNA scopes aim for a selective sampling of radiologically suspicious lymph nodes instead of systematic staging.

**Pathology**

Histopathology and cytopathology services for diagnosis of lung cancer are available in all major hospitals, with rapid on-site evaluation for fine-needle aspiration available in most centers. Lung tumor specimens are often sent for further immunohistochemistry and molecular testing, including EGFR, ROS1, ALK, and programmed death-ligand 1 (PD-L1) expression. These tests are available on-site in larger institutions or by means of established referral pathways. However, molecular pathology is not yet well-integrated with histopathology and cytopathology, sometimes resulting in tissue wastage and delays in reports. Improvements have been made over the years in obtaining adequate material for diagnosis and molecular testing, and there have been efforts to standardize sample acquisition, handling, and reporting. Next-generation sequencing of tumors is now increasingly performed.

**Management**

In the public cancer centers, there are weekly tumor board meetings involving a multidisciplinary team of respiratory physicians, radiologists, pathologists, cardiothoracic surgeons, radiation oncologists, and medical oncologists to discuss challenging cases and reach a consensus on management. In many cases, specialists advising at these tumor boards have a special interest or subspecialize in lung cancer.

**Surgery**

Thoracic surgery has developed into a distinct surgical subspecialty in Singapore over the past two decades, during which Singapore has embraced minimally-invasive thoracic surgery. Conventional video-assisted thoracoscopic surgery (VATS) is being performed in Singapore since the early 2000s, and robotic-assisted thoracoscopic surgery is performed since the late 2000s. Uniportal or single-incision VATS, which may offer incremental benefits over conventional multiport VATS, has also been pioneered in Singapore since 2009. Open thoracotomy is reserved for complex cases such as large, central tumors or salvage surgery postradical chemoradiation.

Patients with early-stage lung cancers (stage I–II) account for approximately 20% of lung cancers diagnosed in Singapore from 2008 to 2017 and are treated by surgical resection with lobectomy and mediastinal lymph node dissection (Fig. 3). In the past few years, lung-sparing surgeries have been increasingly performed. Sublobar resections, such as segmentectomy, are offered to patients with small tumors less than 2 cm or with borderline pulmonary function. Stage III lung cancer forms 13.7% of all lung cancers (Fig. 3). Surgical resection may be done as part of multimodality management, especially for patients with small volume, single-station N2 disease. Occasionally, salvage surgery is considered for local recurrence after radical chemoradiation.

The management of recurrent malignant pleural effusions using tunneled indwelling pleural catheters is available but limited by shortage of trained nursing support to assist and train caregivers for home therapy. Increased financial assistance in paying for the drainage bottles will also reduce the burden of care and increase the uptake of this option.

**Radiation**

Radiotherapy treatments in Singapore are delivered in both the private and public sectors. In general, there is consistency in radiotherapy practice for lung cancer across all centers. Radiation therapy can be used alone or integrated with systemic therapy as neoadjuvant, adjuvant, or definitive therapy, depending on the stage of cancer and other factors. Stereotactic ablative body radiotherapy (SABR) is offered for medically inoperable early stage NSCLC, and more conventionally fractionated treatments are offered for locally advanced disease either in the upfront or postoperative setting. Conventionally fractionated radiation doses are generally 60 Gy, depending on the center protocol. All centers have access to CT simulations with four-dimensional capabilities, with some using motion management accessories for breath-hold or respiratory-gated delivery. Symptomatic metastatic disease is often managed with palliative radiotherapy, but for limited metastatic disease, SABR is deployed for optimal local control and cytoreduction. All patients have access to complex delivery techniques such as SABR, image-guided intensity-modulated radiotherapy, volumetric-modulated arc radiotherapy, and tomotherapy.

Notably, over the next few years, three proton beam therapy systems will be installed in Singapore, increasing the range of therapeutic options available to patients, especially for higher-risk groups and thoracic reirradiations.
Systemic Therapy

Adjuvant chemotherapy is the current standard of care for patients with resected pathologic stage II to III disease. The positive results of the ADAURA trial with adjuvant osimertinib in EGFR-mutant lung cancers may lead to a change in practice in this group of surgically resected patients. In patients with inoperable stage III NSCLC, patients receive radical chemoradiotherapy followed by durvalumab.

In SCLC, surgery or locally ablative radiotherapy may be considered in highly selected patients with very early-stage disease. In general, patients with limited-stage SCLC are treated with concurrent chemoradiotherapy followed by prophylactic cranial irradiation, whereas extensive SCLC in the first line is treated with platinum-doublet chemotherapy in combination with either atezolizumab or durvalumab. Relapsed or refractory disease is managed with agents such as irinotecan, topotecan, CAV (cyclophosphamide, Adriamycin [doxorubicin], and vincristine), immune checkpoint inhibitors, and other treatment modalities such as palliative radiotherapy, when indicated.

At the time of diagnosis of advanced disease, all patients with NSCLC should undergo PD-L1 testing, and adenocarcinomas are tested for genetic alterations in EGFR, ALK, and ROS1. BRAF and other targetable mutations may also be tested. In patients with targetable mutations, the EGFR tyrosine kinase inhibitors afatinib, dacomitinib, erlotinib, gefitinib, and osimertinib are approved in EGFR-mutant NSCLC. Alectinib, ceritinib, and crizotinib are approved for first-line therapy in patients with ALK-positive NSCLC, and crizotinib is approved in the first line for ROS1-positive patients. Trametinib and dabrafenib are approved as the first line treatment in patients with BRAF V600E-positive NSCLC (Fig. 4).

In patients without driver mutations, options include platinum-doublet chemotherapy alone, platinum-doublet chemotherapy combined with pembrolizumab, platinum-doublet chemotherapy combined with ipilimumab and nivolumab, or, in patients with nonsquamous lung cancer, platinum-doublet chemotherapy with atezolizumab and bevacizumab. In those with PD-L1 greater than or equal to 50%, single-agent pembrolizumab is also approved in both squamous and nonsquamous lung cancers (Fig. 4).

Challenges for Singapore

Singapore’s small geographic size brings benefits and specific challenges. Health care professionals rely on guidelines developed by larger countries with a different spectrum of lung cancer. The organization of the national health care system into clusters creates challenges in the centralization of services or interinstitution training, collaboration, and standardization.

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**Figure 4.** Outline of approved systemic therapy for advanced NSCLC. +, positive; 1L, first line; 2L, second line; 3L, third line; Atezo, atezolizumab; Bev, bevacizumab; BSC, best supportive care; Carbo, carboplatin; I/O, immunotherapy; Ipi, ipilimumab; Nivo, nivolumab; PD-L1, programmed death-ligand 1, Pembro, pembrolizumab.
With our aging population (the proportion of those aged at least 65 years old is expected to increase from 9.9% in 2009 to 23.7% in 2030), the health care system will need to adapt to cope with higher patient loads and increased costs. This is compounded by the pace at which newer, costlier treatment is emerging as the standard of care. Even with current subsidies, patients rely on patient access programs to offset drug costs, which are at the discretion of pharmaceutical companies. There has also been a push to increase the health care capacity of the country, with five new acute hospitals built in the past 10 years, and an effort to strengthen our primary and community care systems.

In addition, there remains a discrepancy in the uptake of health care services among different ethnic groups. Health education efforts continue to try and address this, educating the population on the symptoms of lung cancer and also the promotion of smoking cessation programs. Screening tools better suited to the various risk groups in Singapore, such as EGFR mutation screening in never-smoking older people, should be developed.

Personalized medicine brings with it an increased need for comprehensive molecular testing and the use of artificial intelligence in machine learning. These have both led to a massive increase in bioinformatic data. Singapore’s health care workers will need to embrace these changes and continue to learn on the job to deal with this shifting landscape. The health care system will also have to enable such changes through investments in appropriate technology and infrastructure.

References