

Lung Cancer in Malaysia



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Malaysia is a Southeast Asian country occupying parts of the Malay Peninsula and the island of Borneo. The population of Malaysia (just over 30 million) is multi-ethnic; approximately half the population is ethnically Malay, with large minorities of Chinese, Indians, and indigenous peoples. Approximately 70% of the population is urban (Fig. 1).¹ Life expectancy of Malaysians at birth is 74.9 years.²

Health care services in Malaysia are dichotomous between systems of public and private health care. Most patients (~65%) in Malaysia seek health care services in public facilities.³ However, the main drawback of public health care is a shortage of doctors and specialists in public hospitals.³ Public health care in Malaysia is heavily subsidized and offers services at a fraction of the cost of treatment in the private sector. Patients receiving treatment in private facilities, on the other hand, are usually covered by private health care insurance or make out-of-pocket payments.³ There is currently no universal-access national health care scheme in Malaysia.³ The total expenditure on health was 4.24% of the gross domestic product in 2017.⁴

The prevalence of smoking is high in Malaysia; nearly 50% of all adult males are smokers, and more than 90% of male lung cancer patients have a significant smoking history.⁵ However, nearly all young female lung cancer patients in Malaysia are never-smokers.⁶

Epidemiology

Lung cancer is one of the most common cancers in Malaysia, accounting for approximately 10% of all malignancies.^{7,8} The lifetime risk is approximately 1 in 55 for Malaysian males: risk is highest in Chinese males (1 in 43), followed by Malays (1 in 62) and Indians (1 in 103). For women, the risk is approximately 1 in 135.⁷ The age-standardized incidence rate of lung cancer increases rapidly from age 45 years and is highest in the 60- to 74-year-old age group.⁷ Nearly 90% of lung cancer patients in Malaysia are diagnosed with stage III or IV disease (Fig. 2).⁷

Lung cancer is the most common cause of cancer-related death in Malaysia.⁵ The 5-year observed survival rate is only 9.0% (95% confidence interval: 8.4–9.7), whereas the 5-year relative survival rate is 11.0% (95% confidence interval: 10.3–11.9).⁹ The survival rate of lung cancer patients in Malaysia at 1 and 5 years is one of the poorest compared to other cancer types, as shown in Figure 3A.⁹ Stage-specific 1- and 5-year survival rates are shown in Figure 3B.⁹

Screening

In a study of lung cancer survival in a single Malaysian hospital, all lung cancer patients presented with either stage III or IV disease, with a median survival of only 18 weeks from diagnosis.¹⁰ Screening of high-risk individuals to detect early-stage disease is anticipated to be of value due to the high smoking prevalence and tendency for late-stage presentation.¹¹

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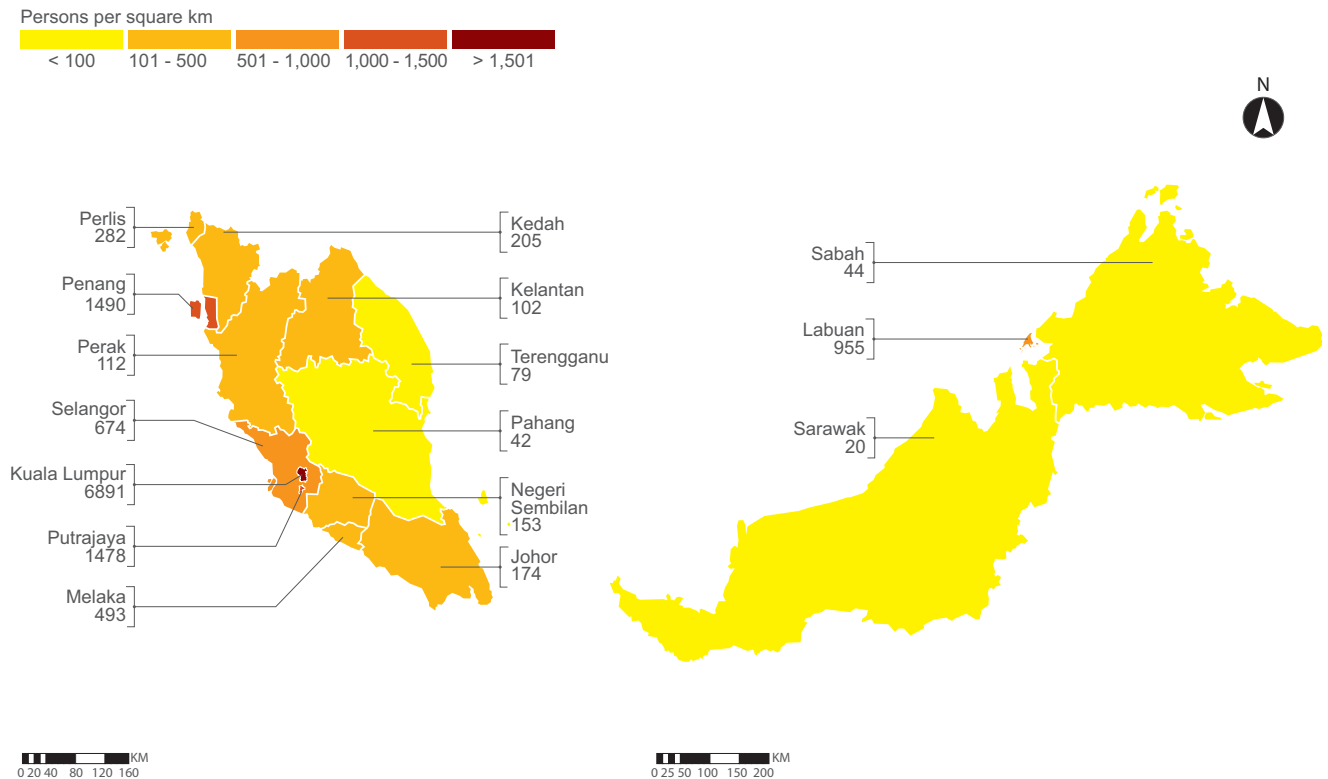


Figure 1. Population density by state, Malaysia, 2010. Approximately 70% of the population is urban. Adapted with permission from the Department of Statistics Malaysia, 2010.¹

Low-dose computed tomography (CT) is available predominantly in private institutions for lung cancer screening. A national multicenter pilot study (Pilot Study for Early Lung Cancer Screening [PEARLS]) evaluating the feasibility and outcome of a single low-dose CT as a

screening modality was previously introduced.¹² However, the study was terminated prematurely due to poor recruitment from the general public, possibly due to low awareness, refusal to be screened, and fear of cancer diagnosis.

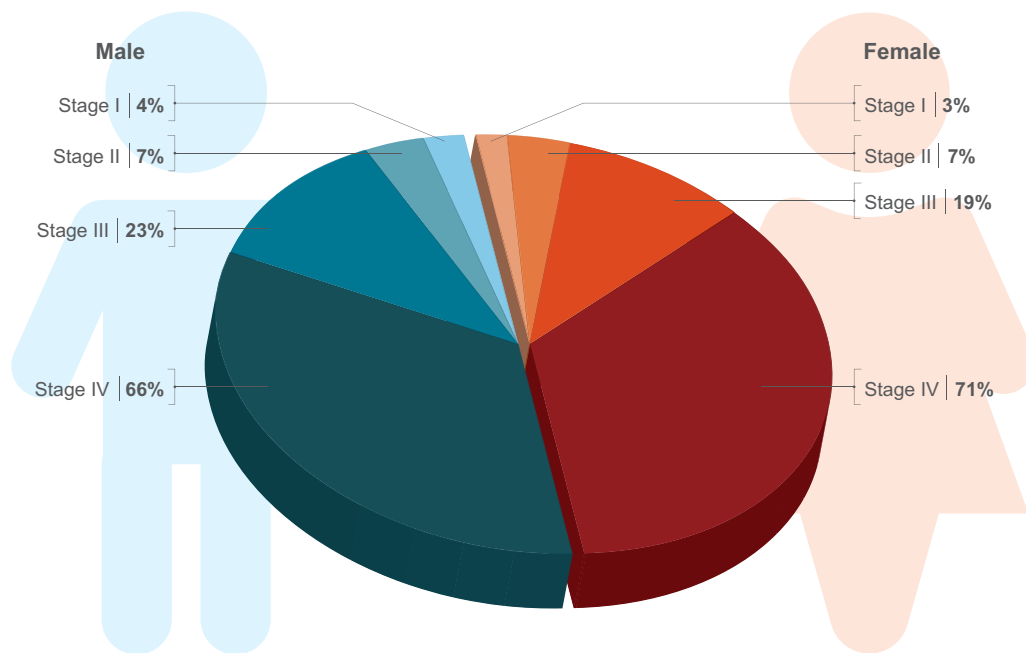


Figure 2. Stage of lung cancer at diagnosis in male and female patients. Adapted with permission from Malaysian National Cancer Registry report, 2007-2011.⁷

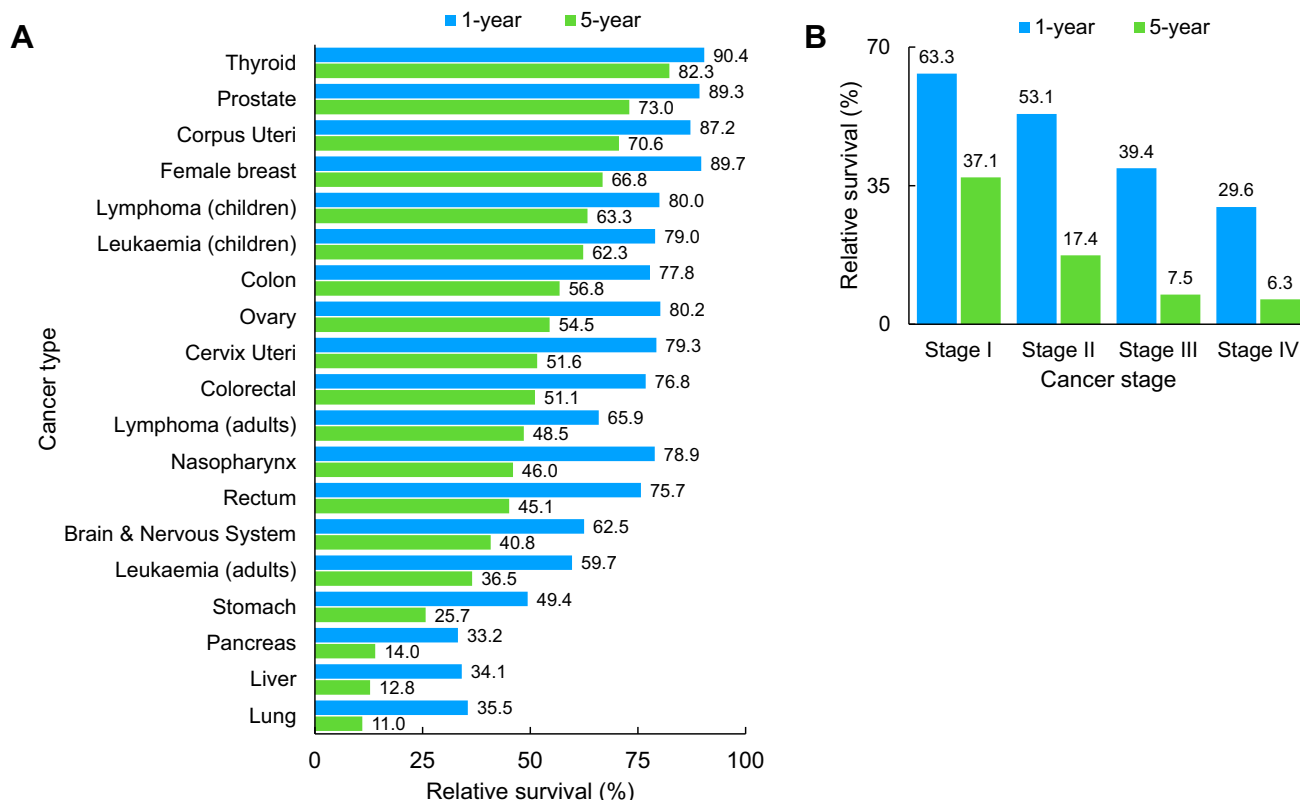


Figure 3. Relative survival of cancer patients in Malaysia. *A*, Relative survival at 1-year and 5-year by cancer type in Malaysia. *B*, Stage-specific 1- and 5-year relative survival of lung cancer patients in Malaysia. Adapted with permission from Malaysian Study on Cancer Survival (MyScan), 2018.⁹

In an effort to improve awareness, a national-level non-governmental organization, Lung Cancer Network Malaysia was established in 2018. The Lung Cancer Network Malaysia aims to increase awareness, promote appropriate screening, and counter misconceptions so that more patients will be diagnosed at earlier stages amenable to curative treatment.¹³

Diagnosis

CT is the most common imaging procedure for staging as it is relatively cheaper than a positron-emission tomography scan, which is mostly offered in private practice for patients with stage II disease or higher.¹⁴ Nineteen centers offer positron-emission tomography/CT scanning; approximately 75% of these are in private health care facilities. Chest radiography and ultrasonography are uncommonly used for staging.

Core biopsy is the preferred sampling modality for primary diagnosis of lung cancer. Endobronchial biopsy and fluoroscopy-guided transbronchial lung biopsy are commonly performed in all hospitals, although electromagnetic navigational bronchoscopy is only available at two government hospitals. Medical pleuroscopy and CT-guided percutaneous core biopsy are generally available

in local hospitals. Physicians occasionally perform only lymph node fine-needle aspiration cytology and pleural fluid cytology, especially in patients who are too ill for invasive procedures. Endoscopic ultrasound-guided fine-needle aspiration and endobronchial ultrasound-guided transbronchial needle aspiration are offered in some hospitals. As of 2019, there are 127 chest physicians registered in Malaysia (~4 per million population).

EGFR mutation prevails in nearly 40% of all NSCLC cases in Malaysia, whereas 13% of adenocarcinoma patients with wild-type *EGFR* harbor anaplastic lymphoma kinase (*ALK*) mutations.^{15,16} Testing for these molecular aberrations are performed via single-gene or panel testing. Additional mutational testing (e.g., *ROS1* and *BRAF*) is performed as part of an expanded panel for patients without common driver mutations. In most centers, programmed cell death ligand 1 (PD-L1) immunohistochemistry is performed if immunotherapy is contemplated. Some centers, especially private hospitals, perform PD-L1 immunohistochemistry as reflex testing. Except for *EGFR*, *ALK*, and PD-L1 testing, all other tests are not reimbursed. Liquid biopsy assays using reverse-transcriptase polymerase chain reaction or droplet digital PCR have been available locally since 2018. These tests are primarily used to detect early

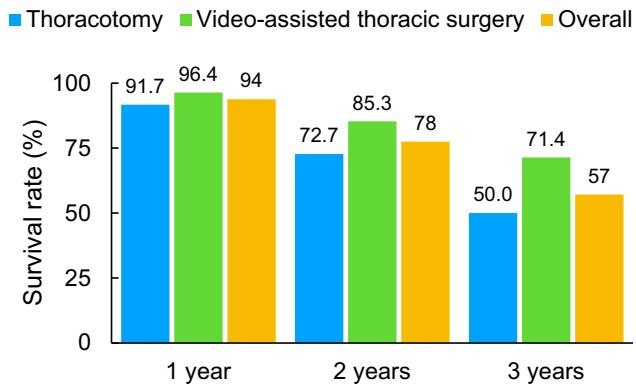


Figure 4. Survival rate at 1, 2, and 3 years for primary lung cancer resected by thoracotomy and video-assisted thoracic surgery.

emergence of *T790M* and *C797S* mutations. A limited 21-gene next-generation sequencing panel to detect common driver mutations and a pan-cancer liquid biopsy assay are also available. The main molecular testing laboratories are either International Organization for Standardization-certified (ISO 15189), and/or College of American Pathologists-accredited, and also subscribe to external quality assurance programs such as the UK National External Quality Assessment Service or the European Molecular Genetics Quality Network.

In 2019, a consensus statement on molecular testing for advanced NSCLC patients localized to the Malaysian setting was published for the benefit of Malaysian health care practitioners involved in the management of advanced NSCLC patients.¹⁷

Surgical Approaches

The majority of Malaysian lung cancer patients are diagnosed with locally advanced or metastatic disease, which precludes curative resection.^{7,11,14} This contributed to a low resection rate of 4.8% as reported at a major tertiary public hospital.¹⁸ The low rates may also be attributed to a lack of dedicated thoracic surgeons (due to heavy cardiac surgical workload), patients' refusal of surgery, or prohibitive medical comorbidities.¹¹ Survival rates for resected lung cancer at 1, 2, and 3 years by thoracotomy and video-assisted thoracic surgery are shown in Figure 4 (unpublished registry data).

In Malaysia, the Medical Professions Act mandates all specialist doctors be certified on the National Specialist Register before commencing independent consultant practice. Currently, 81 cardiothoracic surgeons and six general/thoracic surgeons hold National Specialist Register accreditation, although several have since ceased practice or retired.

Most Malaysian cardiothoracic surgeons were trained either in the United Kingdom or Australia. In anticipation of impending retirement of the first-generation

surgeons, the Malaysian Board of Cardiothoracic Surgery in collaboration with the Royal College of Surgeons of Edinburgh commenced a 6-year structured postgraduate training program in 2016 to locally produce the next generation of thoracic surgeons.

Radiation Approaches

There are 36 oncology centers providing radiotherapy in Malaysia, equipped with 56 conventional mega-voltage linear accelerators, three Gamma Knife (Elekta, Sweden), and one CyberKnife (Accuray Inc., Sunnyvale, California) systems. Approximately two-thirds of these machines are housed in private oncology centers, whereas the remaining one-third are in government centers or academic institutions. Services are fully funded in the academic institutions but may incur some out-of-pocket expenditure, albeit at a subsidized rate, in the government centers.

The wait time for radical lung radiotherapy is between 6 and 8 weeks in the government sector, and between 1 and 2 weeks in the private sector. For stage III NSCLC, a conventional 30 to 33 fractions is typically used. Intensity-modulated radiotherapy or volumetric modulated arc therapy for lung cancer is rarely used in the government setting but more commonly used in the private setting. Lung stereotactic body radiotherapy using four-dimensional (4D) image-guided motion management is available in approximately 20% of centers nationwide. All stereotactic body radiotherapy centers can perform 4D computed tomography (4DCT) planning and internal target volume delineation. A few centers have gating capabilities, whereas one center uses tumor tracking. Proton therapy and endoluminal brachytherapy are not available in Malaysia, and patients are rarely referred for such services. Despite the availability of clinical trials for systemic therapy conducted in the country, there are currently no such trials for radiation oncology.

There are ~4 oncologists per million population. The Malaysian radiation oncology practice and guidelines are historically influenced by the United Kingdom clinical oncology practice; many pioneer oncologists in the country were trained in the United Kingdom. A national 4-year clinical oncology training program modeled on the Royal College of Radiologists (UK)'s fellowship in clinical oncology curriculum has been running since 2002. Clinical oncologists, who constitute more than 90% of oncologists in Malaysia, deliver both radiation and systemic therapies.

Systemic Therapy

Gefitinib is provided for free as first-line treatment to a limited number of patients in designated public

hospitals. Patients must purchase EGFR tyrosine kinase inhibitors (TKIs) out-of-pocket when this allocation is exceeded. Osimertinib is seldom prescribed as first-line treatment as it is unavailable for free in public hospitals and is very costly for patients without private insurance. ALK TKIs are also not available for free in public hospitals; most patients who cannot afford ALK TKIs opt for chemotherapy. Non-governmental organizations such as the National Cancer Council and zakat (annual alms tax for the Muslim community) do provide limited financial assistance to fund medications. Crizotinib is approved for *ROS1*-positive NSCLC, whereas BRAF TKIs are not registered in the country. Drugs approved in Malaysia for advanced/metastatic NSCLC as well as their reimbursement status are listed in Table 1.

Patients without driver mutations are commonly treated with platinum doublet chemotherapy in public hospitals. Cisplatin-based chemotherapy is used in patients with good Eastern Cooperative Oncology Group performance status. In public hospitals, pemetrexed is listed as a second-line drug and cannot be used for maintenance therapy.¹⁹ The combination of pembrolizumab and chemotherapy is approved for first-line treatment in advanced NSCLC regardless of PD-L1 expression, and pembrolizumab alone is approved for first-line in patients with PD-L1 expression of at least 1%. Durvalumab is registered for use in patients with stage III lung cancer after chemoradiotherapy. Atezolizumab, nivolumab, and pembrolizumab are approved as second-line treatment in patients who fail chemotherapy. However, none of these immune checkpoint inhibitors are available for free at public hospitals. Currently, clinical trials investigating immune checkpoint inhibitors combined with other therapeutic agents are open, and this would be an option for a limited number of patients.

For small cell lung cancer, patients are commonly treated with first-line cisplatin or carboplatin and etoposide, whereas second-line treatment options include topotecan, irinotecan, and gemcitabine.

Specific Challenges

Lung cancer awareness remains limited, which contributes to the late-stage presentation in a majority of cases. The stigma of lung cancer as a 'self-inflicted' cancer, fear surrounding treatments such as chemotherapy and radiotherapy, and a cultural bias towards alternative traditional and complementary therapies are additional obstacles.¹⁴

Because of the relatively high prevalence of tuberculosis in certain regions in Malaysia, lung cancer screening may be complicated by false-positive results, which may lead to unnecessary and expensive investigations with their attendant risks. Other challenges faced in implementing a lung cancer screening program in Malaysia include lack of resources, uncertainty regarding its cost-effectiveness, and poor participation by high-risk individuals because of lack of awareness.

Some patients choose to opt for alternative treatments such as traditional and complementary medicine despite the lack of evidence of its efficacy.^{20,21} In addition, as many as 20% of lung cancer patients default follow-up appointments due to deterioration of health status and logistic difficulty.²¹

Clinical trials on lung cancer treatment are limited in Malaysia. This, in combination with the high costs of molecular testing, systemic therapy and radiotherapy, limits the available treatment options for many Malaysian patients. Targeted therapy and immunotherapy are mostly difficult to afford out-of-pocket without private health care insurance.

Although a multidisciplinary team approach admittedly is ideal for optimal lung cancer care, implementing

Table 1. Drugs Approved in Malaysia for Advanced/Metastatic NSCLC and Their Reimbursement Status

Drug	Approved in First-Line	Approved in Second-Line	Available for Free (Public Hospitals)	Reimbursement (Private Insurance)
Gefitinib	Yes	Yes	Yes (first-line and second-line)	Yes
Erlotinib	Yes	Yes	Yes (second-line)	Yes
Afatinib	Yes	Yes	No	Yes
Osimertinib	Yes	Yes	No	Yes
Crizotinib	Yes	Yes	No	Yes
Ceritinib	Yes	Yes	No	Yes
Alectinib	Yes	Yes	No	Yes
Pembrolizumab	Yes	Yes	No	Yes
Nivolumab	No	Yes	No	Yes
Atezolizumab	No	Yes	No	Yes
Durvalumab	Yes (stage III, post-CCRT)	No	No	Yes

CCRT, concurrent chemoradiation therapy.

this is challenging in most centers in the country because of insufficient staffing of chest physicians, interventional radiologists, pathologists, thoracic surgeons, clinical oncologists, radiation oncologists, and palliative care physicians. Multidisciplinary team meetings are limited to academic institutions as well as larger public and private facilities with a more complete team of relevant specialists.

There is a need for a comprehensive national database for up-to-date information on the management of lung cancer in the country. Currently, national databases such as the National Cancer Registry and the Malaysian Lung Cancer Registry lack detailed information on diagnostic and staging modalities as well as treatment methods used in patients with different disease stages. There is a shortage of accredited molecular testing laboratories in the country resulting in a long turnaround time for diagnostic samples, especially in the public sector.

Strategies for Smoking Cessation

The mQuit program was introduced as an integrated quit-smoking service offered in both public and private facilities in Malaysia.²² The program has recorded just above 30% success rate in helping smokers to quit, whereas most of the remaining participants merely reduced the amount of cigarettes smoked.²³ Banning the sale of cigarettes to minors, outlawing tobacco advertisements, displaying graphic warnings on cigarette packages, and prohibiting smoking in public areas and eateries are the antismoking strategies in force in Malaysia.

Summary

Funding limitations for treatments pose a significant challenge in lung cancer management in Malaysia. Increasing local awareness about lung cancer is important to help high-risk patients get screened and reduce the percentage of late-stage disease presentation. Efforts to tackle the high smoking prevalence, a major risk of lung cancer, are also underway.

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