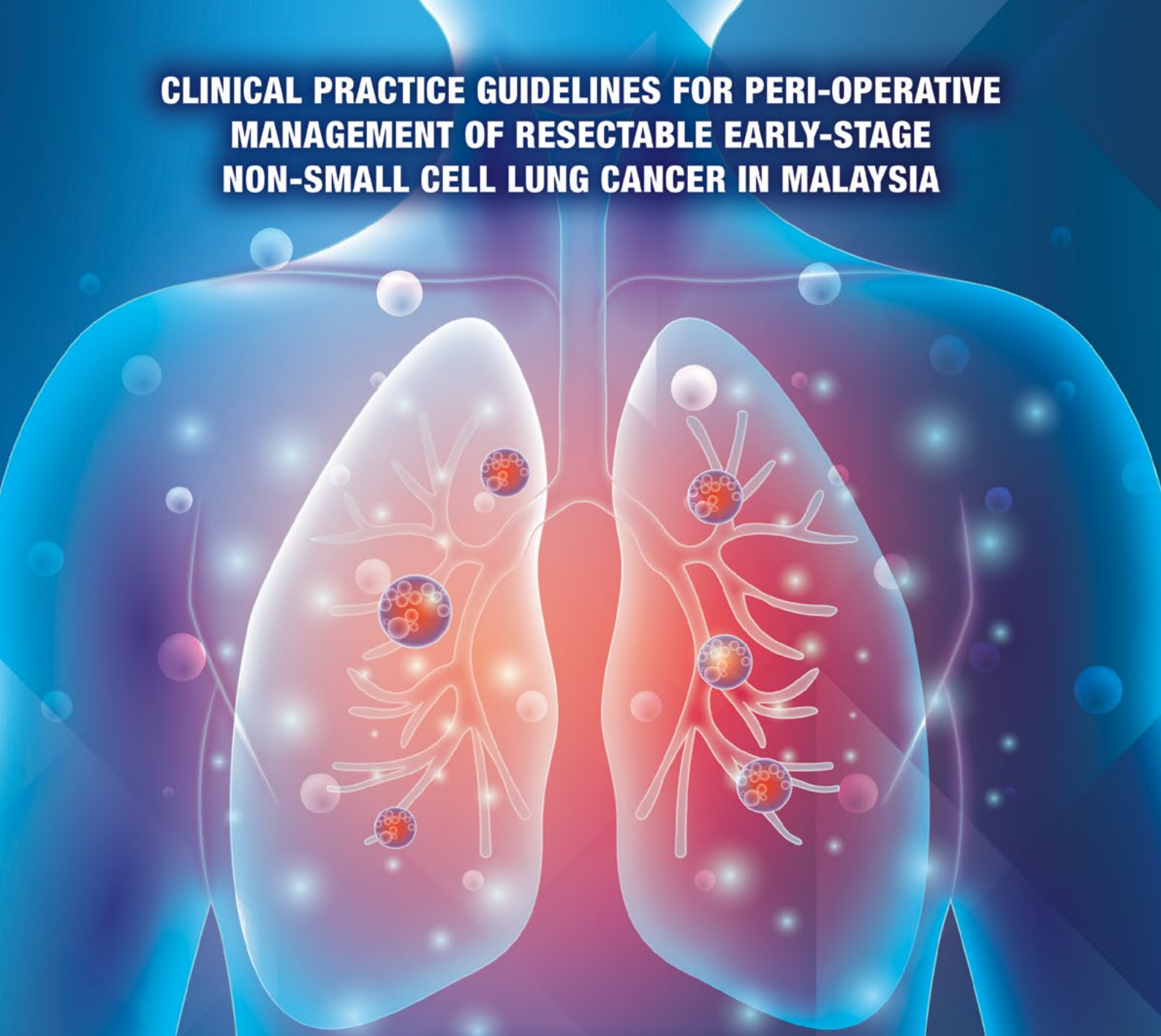
CLINICAL PRACTICE GUIDELINES FOR PERI-OPERATIVE MANAGEMENT OF RESECTABLE EARLY-STAGE NON-SMALL CELL LUNG CANCER IN MALAYSIA



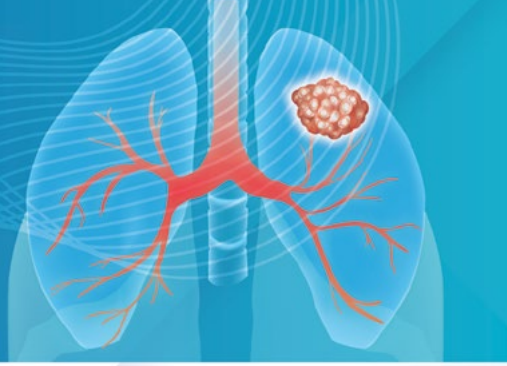
EXPERT CONSENSUS

SURGICAL CONSENSUS FOR SCREENING, DIAGNOSIS, STAGING, MULTIMODAL MANAGEMENT AND SURVEILLANCE OF EARLY-STAGE RESECTABLE NON-SMALL CELL LUNG CANCER (NSCLC) IN MALAYSIA

1st Edition
(April 2025)

MALAYSIAN THORACIC SOCIETY
Malaysian Association for Thoracic and Cardiovascular Surgery
LUNG CANCER NETWORK MALAYSIA
Malaysian Oncological Society
COLLEGE OF SURGEONS ACADEMY OF MEDICINE OF MALAYSIA

FOREWORD



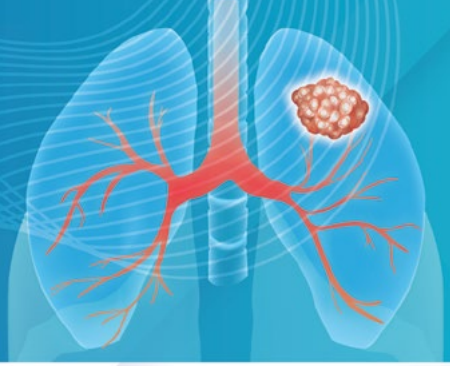
Lung cancer is the third most common cancer in Malaysia and remains one of the leading causes of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for the majority of cases. In recent years, advances in early detection, surgical techniques, and multidisciplinary care have significantly improved outcomes for patients diagnosed at an early, resectable stage. However, the complexity of care pathways necessitates clear, evidence-based guidance to ensure optimal outcomes.

These guidelines emphasize the critical role of low-dose CT screening in high-risk populations for early detection, provide a comprehensive overview of best practices for diagnosis including the importance of accurate histologic and molecular diagnosis, the necessity of precise staging to guide treatment planning, and underscoring the value of a multidisciplinary approach in tailoring multimodal strategies—including the growing emphasis and the evolution of minimally invasive surgical techniques, systemic therapies, and postoperative care—to individual patient needs. These recommendations are grounded in the latest clinical evidence and reflect the realities of modern practice across diverse healthcare settings,

I commend the efforts of the expert surgical consensus working group and the external reviewers in developing and contributing towards these guidelines, which will serve as a vital resource for clinicians navigating the complexities of decision-making and enhancing the quality of care provided to patients with early-stage resectable NSCLC in Malaysia.

Professor Dr Rosmawati Mohamed
MD (Birmingham), MRCP (UK), M Int Med (Mal), MBBS (Monash)
Master, Academy of Medicine of Malaysia

INTRODUCTION



This document comprises a surgical consensus of evidence-based guidelines to provide local recommendations on contemporary real-world best practices for screening, diagnosis, staging, multimodal management (including neoadjuvant, perioperative 'sandwich' and adjuvant therapy regimens), operative procedures and post-resection surveillance for early-stage resectable (stages IA-IIIB-N2) non-small cell lung cancer (NSCLC).

It is hoped that these guidelines endorsed by the Lung Cancer Network Malaysia, Malaysian Oncological Society, Malaysian Thoracic Society, Malaysian Association of Thoracic & Cardiovascular Surgery and the College of Surgeons, Academy of Medicine will elevate and standardise the perioperative management of early-stage resectable NSCLC in Malaysia, serve as a valuable educational and training tool for relevant medical professionals, and promote an inclusive, comprehensive multidisciplinary, multimodal approach for integrated holistic patient care, aimed at improving both patient outcomes and their quality of life with the best available evidence.

Given the rapid advances in the diagnostic landscape and evolving treatment paradigm for NSCLC, it is anticipated these guidelines will require review, revision and updating every five years or sooner.

Professor Dr Anand Sachithanandan *FRCSI (C-Th)*
Founding President, Lung Cancer Network Malaysia
Chair, Expert Surgical Consensus Working Group

Professor Dr Soon Sing Yang *FRCS (C-Th)*
Co-chair, Expert Surgical Consensus Working Group

Officially launched at 3rd National Lung Cancer Symposium, Kuala Lumpur – 26th April 2025.
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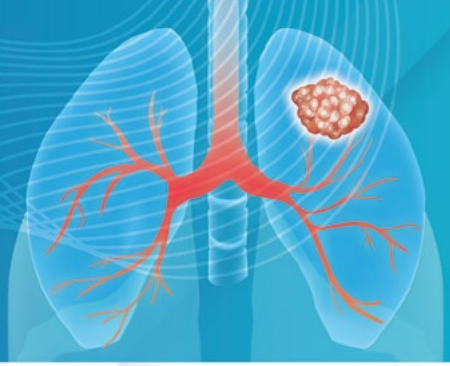
MESSAGE FROM COLLEGE OF SURGEONS OF MALAYSIA



College of Surgeons, Academy of Medicine of Malaysia

On behalf of the College of Surgeons, I am pleased to endorse the **Clinical Practice Guidelines for the Peri-Operative Management of Resectable Early-Stage Non-Small Cell Lung Cancer in Malaysia.**

This landmark document is a vital step forward in establishing a unified, evidence-based approach to lung cancer care in Malaysia. Covering five key domains—**screening, diagnosis and staging, neoadjuvant and peri-operative treatment, adjuvant treatment, and operative procedures with post-resection surveillance**—the guidelines offer a comprehensive roadmap to optimize patient outcomes across the entire care continuum.

I commend Professor Dr Anand Sachithanandan, Professor Dr Soon Sing Yang, and the Expert Surgical Consensus Working Group for their dedication and leadership in producing recommendations that are both internationally aligned and locally contextualized. Their efforts ensure the guidelines are both practical and impactful for Malaysian healthcare settings.

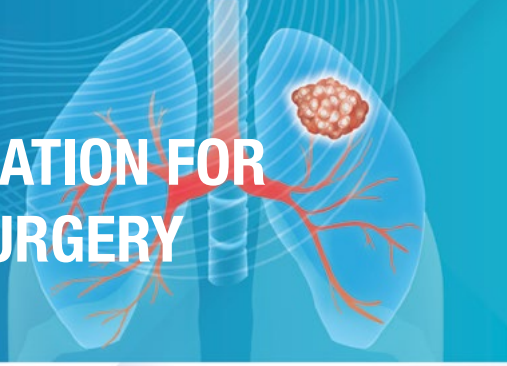
These guidelines are not only an important clinical reference but also serve as a valuable educational resource for surgical trainees and multidisciplinary teams. Emphasizing appropriate screening, timely staging, judicious use of neoadjuvant and adjuvant therapies, minimally invasive surgical approaches, and structured follow-up, this document sets the standard for high-quality thoracic oncology care.

I strongly encourage all surgical colleagues and allied specialists to incorporate these recommendations into their daily practice. Together, we can advance the standard of care and improve survival and quality of life for patients with early-stage NSCLC across Malaysia.

Yours faithfully
Dr Siow Sze Li
President
College of Surgeons, Academy of Medicine of Malaysia

College of Surgeons
Academy of Medicine of Malaysia

MESSAGE FROM MALAYSIAN ASSOCIATION FOR THORACIC AND CARDIOVASCULAR SURGERY



It gives me great pleasure to congratulate the expert surgical working group led by Dr Anand Sachithanandan and his esteemed collegues from cardiothoracic surgery, chest medicine and oncology for preparing and launching the Clinical Practice Guidelines for Perioperative Management of Resectable Early Stage Non Small Cell Lung Cancer in Malaysia.

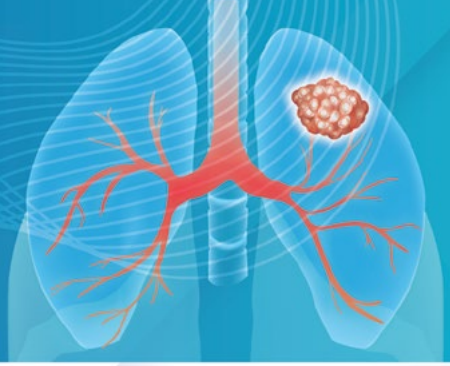
Indeed the release of this document is timely and long awaited. It has been supported by key stakeholder societies and will certainly be a landmark guide for health professionals in counselling and managing patients with this dreaded disease even better and provide high quality care with optimal outcomes. Furthermore I sincerely hope that the document will become a nidus for further collaboration with more multi disciplinary team meetings being held among doctors caring for these cohort of patients aiming towards excellence in healthcare.

The Malaysian Association of Thoracic and Cardiovascular Surgeons (MATCVS) as the sole flagbearer society for cardiothoracic surgeons in Malaysia is proud to endorse this document with some of our senior members being involved in the writing group. We hope this successful project further stamps our unquestionable commitment towards training of cardiothoracic surgeons capable of providing surgical management and overall best practice care for lung cancer patients in Malaysia in collaboration with other specialties.

Datuk Dr Basheer A Kareem
President
Malaysian Association for Thoracic & Cardiovascular Surgery (MATCVS)

Malaysian Association for Thoracic and Cardiovascular Surgery

MESSAGE FROM THE MALAYSIAN THORACIC SOCIETY



14th April 2025

Dear Professor Dr Anand Sachithanandan,

MALAYSIAN THORACIC SOCIETY (MTS) ENDORSEMENT FOR EARLY NSCLC SURGICAL GUIDELINES

On behalf of the Malaysian Thoracic Society (MTS) Executive Committee Members, I would like to inform you that MTS has agreed to endorse the surgical guidelines for the local management of early-stage resectable NSCLC.

Lung cancer remains one of the leading causes of cancer mortality in Malaysia, with the majority of patients presenting at advanced stages. This unfortunate reality is compounded by variations in diagnostic pathways and treatment practices across the country. As thoracic clinicians, we are all too aware of the pressing need for consistent, high-quality care anchored in best evidence and local feasibility.

The Malaysian Thoracic Society has long advocated for multidisciplinary, collaborative, and standardised approaches to thoracic disease management. This inaugural surgical consensus on early-stage resectable non-small cell lung cancer (NSCLC) is a testament to what can be achieved through united expertise and shared purpose. Developed by our leading thoracic surgeons and refined with input from respiratory physicians and oncologists, this document reflects both global evidence and local realities.

We strongly believe these guidelines will raise the standard of lung cancer care, promoting timely diagnosis, appropriate staging, and equitable access to curative treatment. It is our hope that this becomes a living document — one that not only informs practice but also inspires health system improvements.

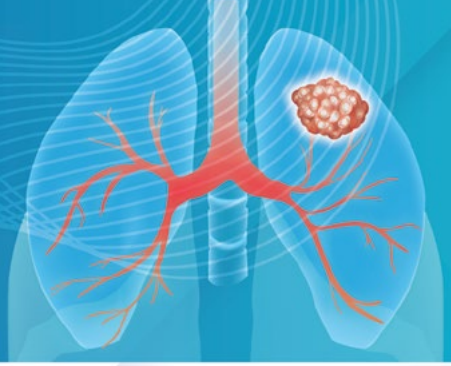
The Malaysian Thoracic Society is proud to support this important milestone and remains committed to championing initiatives that improve outcomes for patients with lung cancer.

Yours sincerely,

Professor Dr Ahmad Izuanuddin Ismail
President
Malaysian Thoracic Society

MALAYSIAN THORACIC SOCIETY

MESSAGE FROM MALAYSIAN ONCOLOGICAL SOCIETY



7th March 2025

Dear Professor Dr Anand Sachithanandan,

MOS ENDORSEMENT FOR EARLY NSCLC SURGICAL GUIDELINES

We thank you for your letter of invitation date 4th March 2025 and are pleased to inform that the Malaysian Oncological Society will endorse the evidence-based guideline (titled: Surgical consensus for screening, diagnosis, staging, multimodal management and surveillance of early-stage resectable non-small cell lung cancer (NSCLC) in Malaysia) which promotes a multi disciplinary and multi modal meticulous approach to tackle resectable lung cancer in Malaysia.

Once again, we would like to congratulate the Lung Cancer Network Malaysia for having developed a surgical consensus statement/clinical practice guidelines for the local management of early stage resectable NSCLC with the consensus view of a group of dedicated lung cancer surgeons (cardiothoracic & general thoracic) practising in MOH, university and private hospitals across Peninsula and East Malaysia

Thank you.

Yours sincerely,

Dr Muthukkumaran Thiagarajan
President (2025-2027)
Malaysian Oncological Society

Malaysian Oncological Society

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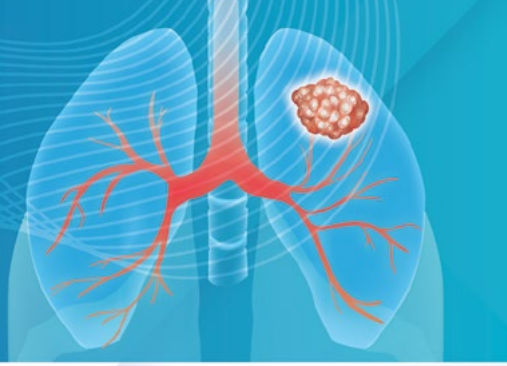
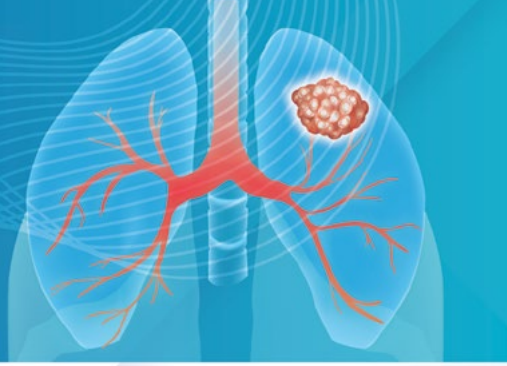
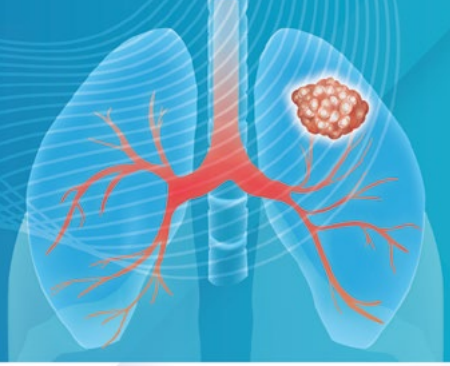




EXPERT SURGICAL CONSENSUS WORKING GROUP



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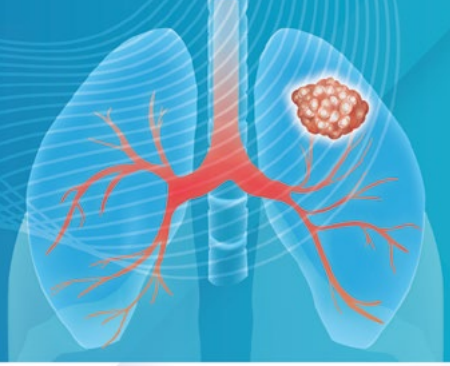
ABSTRACT



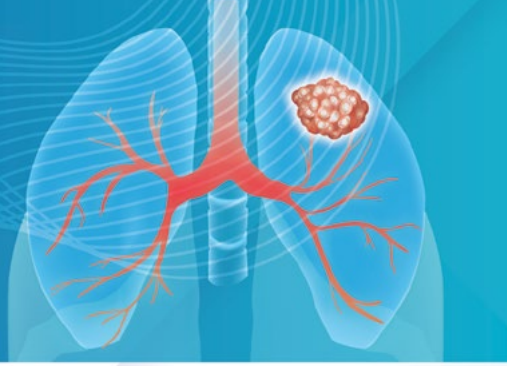
Lung cancer is the most frequently diagnosed cancer globally. In Malaysia, it ranks as the second most common cancer among men and third among women. Presently, no local clinical practice guidelines exist for lung cancer care in Malaysia. Given the lack of consensus regarding the perioperative management of early-stage non-small cell lung cancer (NSCLC), this document seeks to harmonise surgical practices among thoracic physicians and surgeons in Malaysia by recommending best practices for screening, diagnosis and staging, as well as multimodal management and surveillance in early-stage disease (stages I to IIIB-N2).

A local expert committee comprising nine high-volume actively practicing cardiothoracic or general thoracic surgeons gathered between February 2024 to July 2024 to deliberate existing evidence and formulate recommendations. A modified Delphi method comprising systematic review of published evidence and expert opinion based on local experience was utilised. The document was subsequently independently reviewed by two senior oncologists and two senior respiratory physicians, before incorporating their feedback into the final version.

These consensus statement guidelines will elevate and standardise the perioperative management of early-stage NSCLC in Malaysia, serve as a valuable educational and training tool for relevant medical professionals, and promote an inclusive, comprehensive multidisciplinary approach to integrated holistic patient care, aimed at improving both clinical outcomes and patients' quality of life with the best available evidence.

Keywords: Non-Small-Cell Lung Cancer, Perioperative, Surgical Consensus, Malaysia.

HIGHLIGHT



KEY RECOMMENDATIONS

1. Screening is recommended in high-risk non-smokers (age > 40 years) with a significant family history of lung cancer.
2. Any patient with suspected lung cancer should be seen by a relevant lung specialist within 2 weeks from the initial presentation.
3. Patients with early-stage resectable NSCLC should commence definitive treatment within 4 to 6 weeks of initial specialist consultation.
4. At the time of initial histological diagnosis, minimum genomic molecular profiling (EGFR, ALK, PD-L1 expression) should be performed as a reflex testing, where feasible for stage IIA-IIIB-N2 NSCLC.
5. All potentially resectable stage III and some stage II NSCLC should be discussed in a multidisciplinary setting for consideration for neoadjuvant treatment.
6. Curative resection should include adequate intraoperative mediastinal lymph node sampling or clearance of three mediastinal (N2) and one hilar (N1) station(s).

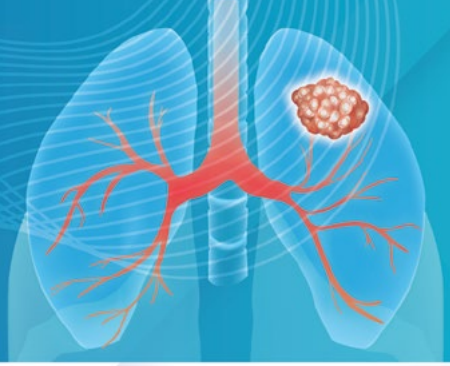
WHAT WAS RECOMMENDED AND WHAT IS NEW?

Alongside disease stage, tumour biology guides therapeutic options. Hence, all patients with potentially resectable stage III and selected stage II NSCLC should undergo evaluation by a multidisciplinary tumour board for neoadjuvant treatment consideration.

WHAT IS THE IMPLICATION, AND WHAT SHOULD CHANGE NOW?

Traditionally, genomic testing for early NSCLC is performed after surgery. However, in this new era of biomarker-driven neoadjuvant and perioperative therapy, upfront reflex testing upon initial histological diagnosis is imperative for guiding treatment decisions.

SURGICAL CONSENSUS RECOMMENDATIONS FOR EARLY-STAGE RESECTABLE NSCLC



SECTION 1: SCREENING

1. Screening should be offered to individuals aged 45 to 75 years with a tobacco smoking history of ≥ 20 years, including current or former smokers.
2. Screening is recommended in high-risk non-smokers (age > 40 years) with a significant family history (e.g., first-degree relative) of lung cancer.
3. LDCT thoracic imaging is the gold standard for lung cancer screening.

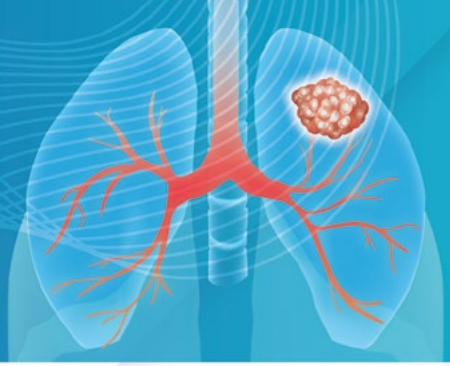
SECTION 2: DIAGNOSIS AND STAGING

1. Any patient with suspected lung cancer should be seen by a relevant lung specialist (respiratory physician, cardiothoracic/thoracic surgeon, oncologist) within 2 weeks from the initial presentation.
2. Patients with early-stage resectable NSCLC should commence definitive treatment (e.g., surgery/neoadjuvant therapy) within 4 to 6 weeks of initial specialist consultation.
3. At the time of initial histological diagnosis, minimum genomic molecular profiling (EGFR, ALK, PD-L1 expression) should be performed as a reflex testing, where feasible for stage IIA-IIIB-N2 NSCLC.
4. The mandatory staging modalities should include CE-CT of the thorax and whole-body PET-CT. If PET-CT is not available, a CE-CT of the abdomen and pelvis should then be performed.
5. CE-MRI of the brain is recommended for stage II and above, or where clinically indicated. If brain MRI is not feasible, CE-CT of the brain is acceptable.
6. Pathologic (cytohistological) confirmation of clinical N2 disease should be routinely performed prior to definitive therapy.

SECTION 3: NEOADJUVANT AND PERIOPERATIVE TREATMENT

1. All potentially resectable stage III NSCLC should be discussed in a multidisciplinary setting for consideration for neoadjuvant treatment.
2. For resectable stage II NSCLC, upfront resection is a reasonable strategy in many instances, unless there is a concern with the ability to achieve complete resection with a lobectomy.
3. Radiotherapy should not be recommended as part of pre-operative treatment for resectable NSCLC.

SURGICAL CONSENSUS RECOMMENDATIONS FOR EARLY-STAGE RESECTABLE NSCLC



SECTION 4: ADJUVANT TREATMENT

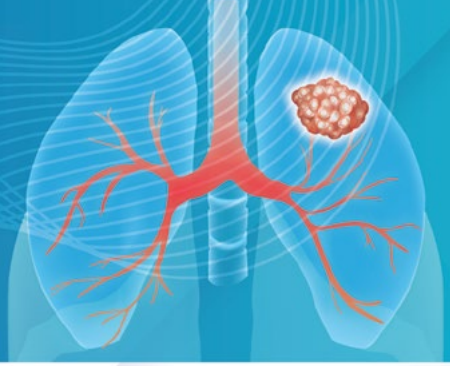
1. All patients with fully resected stage IB to IIIB (≤ N2) NSCLC should receive an oncology* consultation (within 4 weeks) to discuss adjuvant therapy options based on tumour genomic profiling from the initial biopsy or resected specimen for actionable driver alterations (EGFR and ALK) and PD-L1 expression.
2. All patients with fully resected (stage IB to IIIB) EGFR-mutant NSCLC (Del 19/L858) should be offered osimertinib 80 mg once daily +/- chemotherapy for at least 3 years, based on DFS/OS benefit from ADAURA** study.
3. All patients with fully resected (stage IB to IIIB) ALK-fusion positive NSCLC should be offered alectinib 600 mg twice daily +/- chemotherapy for at least 2 years, based on DFS/CNS-DFS benefit from ALINA** study.
4. Adjuvant immunotherapy with chemotherapy should be considered in resected stage IB to IIIB patients with PD-L1 ≥ 1% and no EGFR or ALK alterations but is not routinely recommended for those with PD-L1 < 1%.

SECTION 5: OPERATIVE PROCEDURES AND POST-RESECTION SURVEILLANCE

1. With R0 resection in mind, a minimally invasive approach is favoured for its lower post-operative morbidity and oncological non-inferiority to thoracotomy. However, its adoption depends on the surgeon's experience.
2. Lobectomy remains the standard of care for medically fit patients with early-stage NSCLC.
3. Sublobar resection may be an option in (a) patients with a smaller peripheral tumour < 2 cm, with proven lymph node-negative (N0), and/or (b) medically unfit patients (e.g., with limited lung function or significant comorbidities). Patients should be informed that a sublobar resection might be associated with a higher risk of locoregional recurrence.
4. Curative resection includes adequate intraoperative mediastinal lymph node sampling or clearance of three mediastinal (N2) and one hilar (N1) station(s).
5. Post-operative surveillance should be stage-dependent and conducted for a minimum of 5 years by a dedicated lung specialist (e.g., respiratory physician, cardiothoracic/thoracic surgeon, oncologist), using CT/PET-CT scan (stage I to II every 6 months for 3 years then annually for another two years, stage III every 3 to 6 months for 3 to 5 years, or as clinically indicated).

* Some respiratory physicians in Malaysia treat lung cancer; hence, the term "oncology consultation" encompasses consultations with oncologists or treating respiratory physicians.
** Both the ADAURA and ALINA studies recruited patients with stage IB-IIIA NSCLC (AJCC-UICC seventh edition).
ALK=anaplastic lymphoma kinase; **CE**=contrast enhanced; **CNS**=central nervous system; **CT**=computed tomography; **DFS**=disease-free survival; **LDCT**=low-dose computed tomography; **MRI**=magnetic resonance imaging; **NSCLC**=non-small cell lung cancer; **OS**=overall survival; **PET**=positron emission tomography; **TKI**=tyrosine kinase inhibitor.

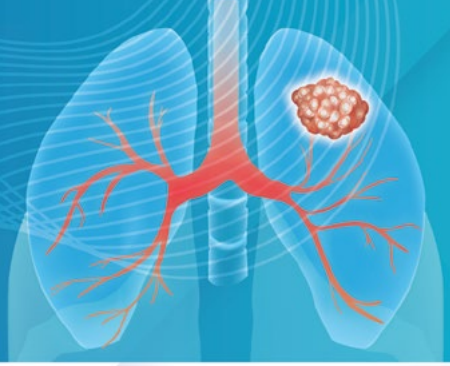
BACKGROUND



Lung cancer is the most frequently diagnosed cancer, with approximately 2.5 million new cases reported worldwide in 2022, accounting for 12.4% of all cancer diagnoses[1]. This trend is mirrored in Malaysia, where lung cancer ranks as the second most common cancer among men and third among women[2], representing about 10% of all malignancies[3]. It is estimated that non-small cell lung cancer (NSCLC) constitutes 85% of cases, of which approximately 25% are diagnosed at stages I and II[4-6]. However, up to 10% of patients with stage IA NSCLC will experience recurrence after curative surgery[7]. Locally, the Malaysian Study on Cancer Survival (MySCan) national registry data reported dismal results, with 1-year and 5-year relative survival of 63.3% and 37.1% for treated stage I disease, and 53.1% and 17.4% for stage II disease[8]. These poor outcomes underscore the need for a holistic approach and incorporation of emerging treatments to improve prognosis for early-stage resectable NSCLC.

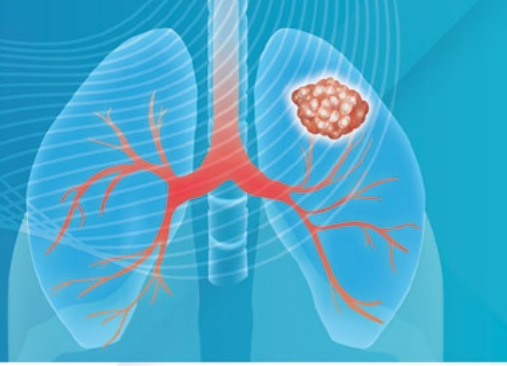
Numerous trials have demonstrated the efficacy of neoadjuvant, perioperative and adjuvant therapies in improving event-free survival (EFS), disease-free survival (DFS) and overall survival (OS) for early-stage disease. Recent trials for neoadjuvant and perioperative 'sandwich' immunotherapy regimes include CheckMate-816[9], AEGEAN[10], CheckMate-77T[11], KEYNOTE-671[12], and Neotorch[13]. Neoadjuvant/perioperative therapy before surgery can potentially reduce the delay in administering systemic therapy crucial for eradicating occult micro-metastases, which otherwise would only be given after surgery and reduce the size of locally advanced tumours[6,14], albeit with the potential risk of tumour progression in non-responders, precluding definitive curative-intent surgery and compromising surgical outcomes[15]. Adjuvant therapy trials including ADAURA[16], ALINA[17], ADJUVANT/CTONG-1104[18], IMpower010[19], and PEARLS/KEYNOTE-091[20] have shown promise in reducing postoperative relapse. However, many questions and concerns persist. Additionally, low-resource settings like Malaysia face unique challenges due to constraints in robust diagnostic tools and adequately trained personnel[21]. Hence, a tailored and pragmatic local approach to screening, early detection, diagnosis, treatment and surveillance of lung cancer patients is required.

BACKGROUND



Prior to this, there were no practice guidelines for the clinical management of lung cancer in Malaysia. Multidisciplinary teams, including oncologists, pulmonologists, thoracic surgeons, nuclear medicine and palliative care physicians, pathologists, radiologists and other allied healthcare professionals, are essential in providing personalised treatment plans and improving patient outcomes. This document seeks to harmonise surgical practices among thoracic physicians and surgeons in Malaysia by recommending best practices for screening, diagnosis and staging, as well as multimodal management and surveillance in resectable early-stage NSCLC (stages I to IIIB-N2). These recommendations integrate the best available scientific evidence with essential adaptations for local implementation, considering real-world factors such as geographical location, surgical setting, and the type of practice, all of which may influence the provision and timeliness of services. It seeks to ensure optimal patient outcomes by delivering high-quality, integrated, multidisciplinary, multimodal care. These guidelines do not address neuroendocrine tumours including small cell lung cancer, secondary lung cancers and advanced metastatic stage IIIC-IV NSCLC.

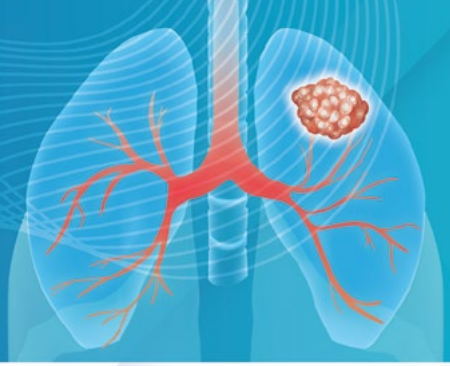
METHODS



The local expert committee comprised nine high-volume cardiothoracic or general thoracic surgeons practising in public, private, and university hospitals across Peninsula Malaysia and East Malaysia to provide a comprehensive and diverse local perspective of real-world surgical services and shortcomings. A series of three meetings were held from February to July 2024. In the first meeting, the experts were divided into five working groups to delve into various domains of early-stage resectable NSCLC, namely: i) screening, ii) diagnosis and staging, iii) neoadjuvant/perioperative immunotherapy, iv) adjuvant therapy with tyrosine kinase inhibitors (TKI) or immunotherapy, and v) operative metrics and post-operative surveillance. Each working group reviewed the available literature on clinical practices in Malaysia and the most recent available global clinical trial findings regarding early-stage lung cancer. The findings and recommendations were presented in the subsequent meetings for deliberation and consensus.

A modified Delphi method of formal group consensus comprising systematic review of published evidence together with expert opinion based on local experience was utilised. The key statement recommendations were initially drafted upon extensive discussion and deliberation among the expert panel. Each recommendation was subsequently rated independently using a five-point Likert scale to assess the level of agreement. Consensus was defined a priori as ≥ 75% of responses scoring 4 (agree) or 5 (strongly agree). As all recommendations met the predefined consensus threshold and achieved unanimous agreement (100%), they were adopted in the final guideline without the need for additional rounds. Upon draft completion, the document was independently and externally reviewed by two senior oncologists and two senior respiratory physicians, ensuring the guideline recommendations were appropriate for multidisciplinary team settings. Feedback from the external reviewers was incorporated into the final version of the consensus guidelines, as summarised in Table 1.

SECTION 1: RECOMMENDATIONS FOR SCREENING



STATEMENT 1: Screening should be offered to individuals aged 45 to 75 years with a tobacco smoking history of ≥ 20 years, including current or former smokers.

The American Cancer Society (ACS) 2023 lung cancer screening guidelines recommend annual screening with low-dose computed tomography (LDCT) in persons aged 50 to 80 years who currently or formerly smoked with a minimum 20 pack-years smoking history[22]. The Malaysian expert panel recommends an earlier screening age range of 45 to 75 years, based on the latest Malaysian National Cancer Registry data, which demonstrated that lung cancer incidence rates here increased rapidly from age 45 years with a peak at age 70 years[3].

Cigarette smoking is well-established as the most prominent modifiable risk factor for lung cancer, contributing towards 85% of lung cancer deaths[23]. In Malaysia, male smokers are predominant with 43% of adult males reported as current smokers[24], translating to 92% of male lung cancer patients with a notable smoking history[25]. Although smoking burden is frequently measured in pack-years[26], lung cancer appears more strongly linked to smoking duration than to the average number of cigarettes per day[26-28]. Smoking intensity among males in Malaysia is high, characterised by prolonged duration and consumption of unfiltered contraband cigarettes. Hence, a rigid adherence to pack-years may underestimate the severity of the problem. In addition, the transition to vaping among young adults might present a real future risk that is currently unquantifiable. Nonetheless, pack-years remains a valuable predictor for smoking-related conditions, despite its limitations in accounting for prolonged or intense exposure[29]. In contrast, lung cancer in females is often attributed to non-smoking related risk factors[30,31], which will be discussed in the next statement. The expert panel has recommended removing the absolute pack-years criteria and instead focusing on a minimum smoking duration of 20 years.

Before initiating annual lung cancer screening for current smokers, the ACS recommends evidence-based smoking cessation counselling and interventions[22]. The panel concurs that it is crucial to have discussions with a healthcare professional on the benefits, limitations and harms of screening to facilitate informed decisions[22].

STATEMENT 2: Screening is recommended in high-risk non-smokers (age > 40 years) with a significant family history (e.g., first-degree relative) of lung cancer.

Despite the decline in smoking rates in some regions, paradoxically the proportion of lung cancer cases among never-smokers is on the rise, especially in women and younger individuals[32]. A Malaysian study reported that 60.3% of women with lung cancer were never-smokers[25]. Another local study found that the percentage of lung cancer patients who had never smoked was higher among those younger than 40 years (58.3% vs. 19.1%, $p < 0.001$)[32]. Lung cancer patients younger than 40 years had poorer WHO performance status and more advanced disease at presentation. The Taiwan Lung Cancer Screening in Never-Smoker Trial (TALENT) which screened high-risk never-smokers aged 55 to 75 years with LDCT of the chest identified a family history of lung cancer, particularly in first-degree relatives, as the most prominent risk factor[33].

Other risk factors contributing to lung cancer in non-smokers include exposure to second-hand smoke, a genetic predisposition, and chronic inflammation from chronic obstructive pulmonary disease and pulmonary tuberculosis, as well as exposures to 2.5 µm particulate matter (PM2.5) in air pollution, asbestos, silica, radon, heavy metals and polycyclic aromatic hydrocarbons[31,34]. Indoor air pollution is another major risk factor[31], evinced by the higher prevalence of lung cancer among East Asian female never-smokers, compared to other regions[30]. Sources of indoor air pollution includes charcoal burning in poorly ventilated homes, the use of wood and other solid fuels, and fumes from high-temperature wok cooking with unrefined vegetable oils[31]. While environmental exposures, such as second-hand smoke or PM 2.5, are relevant risk factors for lung cancer, they are often difficult to quantify accurately and objectively.

Since there are no specific evidence-based guidelines for lung cancer screening in non-smokers in Malaysia, the expert panel emphasises the importance of assessing family history of lung cancer, particularly in first-degree relatives, when considering population-based screening. Age is also a crucial individual risk factor to consider, with screening generally recommended to begin at age 45 for average-risk individuals. For those with a family history of lung cancer, screening should start at age 40 or at the age when the youngest affected family member was diagnosed, whichever comes first.

STATEMENT 3: Low-dose computed tomography thoracic imaging is the gold standard for lung cancer screening.

Lung cancer screening with non-contrasted LDCT chest imaging has demonstrated a meaningful stage-shift from advanced to localised disease, leading to reduced lung cancer-specific mortality[35,36], primarily due to early cancer detection and improved control[37]. A recent United States Veterans Health Administration study provides real-world evidence of the benefits of LDCT screening with a higher proportion of early-stage disease detection and significantly improved OS and lung cancer-specific survival at five years[38]. The MySCan 2018 report documented a 5-year relative survival rate of 37.1% for lung cancer detected at stage I; however, this rate drops to 7.5% at stage III and 6.3% at stage IV[8]. Around 95% of lung cancer cases in Malaysia are diagnosed at stage III or IV disease[2], highlighting the urgent need for effective lung cancer screening.

The NELSON trial conducted in Belgium and Netherlands has shown that volumetric lung cancer screening with LDCT reduces mortality in high-risk individuals compared to those who were not screened, with a cumulative rate ratio for lung cancer mortality of 0.76 (95% CI 0.61 to 0.94; $p = 0.01$) at year 10[35]. LDCT screening reduced the risk of lung cancer death by 24% in men at 10 years, with a more substantial risk reduction of 33 to 59% observed in women during 6- to 10-year follow-up[35]. Similar outcomes were observed in the US National Lung Screening Trial (NSLT), where LDCT resulted in a 20% reduction in lung cancer mortality (95% CI 6.8 to 26.7; $p = 0.004$)[36]. Out of 45 studies included in a systematic review, 39 studies (86.7%) concluded lung cancer screening with LDCT was cost-effective, especially for individuals aged 55 to 75 with a smoking history of at least 20 pack-years[39]. A real-world study from National Taiwan University Hospital showed a notable improvement in five-year survival rates with LDCT, increasing from 22.1% between 2006 and 2011 to 54.9% between 2015 and 2020[37].

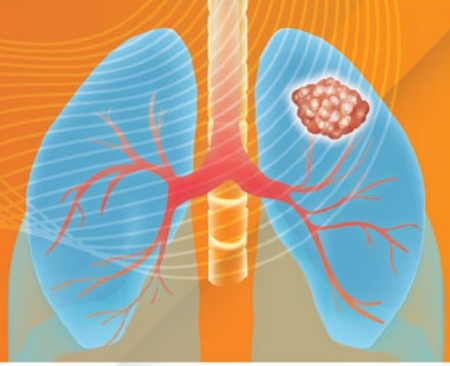
Lung-RADS (Lung Imaging Reporting and Data System) is a classification system used to standardise the reporting and management of lung nodules detected in LDCT screenings[22]. Indeterminate nodules are those that cannot be clearly classified as benign or malignant based on initial imaging. Patients with Lung-RADS 1 (no nodules and benign lesion) and Lung-RADS 2 (small nodules that are benign in appearance or behaviour) are advised to return for regular screening in 12 months[22]. Meanwhile, patients with Lung-RADS 3 findings (nodule $\geq$ 6 mm to $<$ 8 mm on baseline screening, or 4 mm to $<$ 6 mm on repeat screening) should undergo LDCT every six months[22].

Suspicious lesions classified as Lung-RADS 4A (larger or growing nodules) require follow-up with an LDCT in three months. Lung-RADS 4B and 4X are highly suspicious for lung cancer and usually necessitate immediate further evaluation and/or tissue sampling[22]. Individuals with indeterminate nodules should be referred to and closely followed up by dedicated lung specialists to ensure timely imaging and appropriate surveillance.

While LDCT is a highly performant method for lung nodule detection, chest x-ray imaging still plays an important role in nodule diagnosis in primary care and resource-limited settings[40,41]. The integration of artificial intelligence (AI)-enabled imaging modalities powered by deep learning algorithms is expected to assist radiologists and general physicians by enhancing diagnostic sensitivity, reducing workload and improving turnaround times, thereby improving efficiency and accuracy of lung cancer screening[40,42]. For instance, an AI model developed using NLST data helped determine appropriate screening intervals without delaying diagnosis[43]. Meanwhile, a Malaysian pilot project that incorporated AI-assisted chest radiography for lung cancer screening in the primary care setting led to improved detection of indeterminate pulmonary nodules[40]. It is hoped that AI will expand lung cancer screening by combining increased accessibility through reduced cost, remote deployment and quicker turn-around times with enhanced diagnostic sensitivity to enable swift interpretation of imaging results, especially for underserved or remote communities.

Presently, radiological imaging remains the most reliable method for lung cancer screening. However, biomarkers like circulating tumour deoxyribonucleic acid (ctDNA) are expected to enhance future screening strategies. Carcinoembryonic antigen (CEA), a relatively inexpensive and widely available serum tumour marker, holds prognostic and risk-stratification value[44-46]. A recent local study demonstrated that approximately 40% of Malaysians with non-squamous resectable NSCLC had an elevated baseline CEA and this was associated with an inferior DFS despite complete resection and extensive nodal dissection[47]. Though non-specific, CEA may serve as a valuable biomarker in the diagnostic work-up of suspected or confirmed NSCLC, helping personalise scan intervals for surveillance of indeterminate pulmonary nodules.

SECTION 2: RECOMMENDATIONS FOR DIAGNOSIS AND STAGING



STATEMENT 1: Any patient with suspected lung cancer should be seen by a relevant lung specialist (respiratory physician, cardiothoracic/thoracic surgeon, oncologist) within 2 weeks from the initial presentation.

Advancements in lung cancer management have expanded treatment options, including minimally invasive surgery, chemotherapy (e.g., immunotherapy and oral targeted therapy), radiotherapy, and palliative care. With increasingly complex treatment for confirmed or suspected lung cancer, the American College of Chest Physicians (ACCP)[48] and the National Comprehensive Cancer Network (NCCN)[49] emphasise the importance of multidisciplinary care. This approach is further validated by the successful outcomes observed in the multidisciplinary management of other cancer types, including reductions in waiting times, changes in management strategies, improvements in patient satisfaction, and in some cases, extended survival times[50].

Delays can arise at multiple points, including the time between symptom onset and the first visit to a general practitioner, referral to a specialist, diagnostic testing, and the start of definitive treatment[50]. The British Thoracic Society (BTS) recommends that patients with suspected lung cancer should be promptly referred to a lung specialist, with the specialist consultation taking place within one week and diagnostic testing completed within two weeks[51]. As part of the 'National Health Service (NHS) Cancer Plan', the UK government implemented the two-week rule in 2000, requiring that patients with suspected cancer be seen by a relevant specialist within two weeks of referral by their general practitioner[52]. A recent guideline by the Portuguese lung cancer expert panel on unresectable stage III NSCLC recommends that patients referred to a specialist or a diagnostic assessment programme should be seen within two weeks[53]. Reducing the delay between referral and consultation is crucial for enabling earlier treatment initiation in lung cancer patients[54].

Increased time-to-treatment initiation (TTI) is independently associated with poorer survival in non-metastatic NSCLC. A TTI of less than 45 days is considered a reasonable clinical time frame for improved outcomes[55]. Data from a Taiwan national survey reaffirms the strong association between TTI and mortality rates for NSCLC, particularly for stage I/II disease, reiterating the importance of a timely diagnosis and prompt initiation of therapy for early-stage curable tumours[56]. Therefore, ensuring timely treatment initiation is crucial for improving survival outcomes in early-stage NSCLC patients.

Early-stage Resectable NSCLC Peri-operative Guidelines. (Malaysia).

STATEMENT 2: Patients with early-stage resectable NSCLC should commence definitive treatment (e.g., surgery/neoadjuvant therapy) within 4 to 6 weeks of initial specialist consultation.

Several international study groups have stressed the importance of establishing standards for timely care of patients with known or suspected lung cancer. The BTS recommends completing all diagnostic tests within two weeks of the initial request, with treatment initiation timelines varying based on the selected treatment approach[51]. These include initiating chemotherapy within seven working days after the decision to proceed, starting radical radiotherapy within four weeks of referral, and ideally limiting the time between being placed on a surgeon's waiting list and thoracotomy to four weeks, with a maximum of eight weeks from the first specialist consultation for uncomplicated operable cases[51].

The NHS Cancer Plan also set a goal of 31 days from diagnosis to the start of treatment, and 62 days from referral to treatment[52]. The Swedish Lung Cancer Study Group recommends that 80% of patients should have diagnostic tests completed within four weeks of consultation with a respiratory physician, with treatment beginning within two weeks thereafter[57]. The Canadian guidelines suggest a maximum of four weeks between the initial primary care visit and diagnosis, followed by surgery within two weeks[58]. The expert panel recognises considerable variation exists in the provision of cancer services across different sectors of the Malaysian healthcare system. However, a meticulous and timely work-up within a maximum interval of four to six weeks is achievable, if prioritised. This is imperative given the impact of TTI on patient outcomes.

STATEMENT 3: At the time of initial histological diagnosis, minimum genomic molecular profiling (EGFR, ALK, PD-L1 expression) should be performed as a reflex testing, where feasible for stage IIA-IIIB-N2 NSCLC.

Oral tyrosine kinase inhibitors targeting genomic driver alterations have made biomarker testing essential for personalised treatment in patients with NSCLC harbouring actionable driver alterations. Guidelines recommend biomarker testing in advanced NSCLC to identify alterations in EGFR, ALK, ROS1, BRAF, NTRK, MET, RET, KRAS, HER2 and NRG1, as well as PD-L1 expression[59-61]. While stage I to III NSCLC is potentially curable, relapse after surgical resection is common, and adjuvant therapies offer considerable potential to minimise recurrence and improve survival.

With the US Food and Drug Administration and European Medicines Agency approval of adjuvant osimertinib for EGFR-mutated resected NSCLC, as per ADAURA study findings[16], molecular testing on diagnostic or resection specimens is crucial for stage IB-IIIA cases. The choice between single-gene testing and next-generation sequencing depends on factors such as costs, reimbursement, approved treatment, patient needs, tissue availability, and laboratory capabilities[62].

Reflex molecular testing refers to the automatic ordering of predefined biomarkers upon an NSCLC diagnosis, eliminating the need for a separate oncologist request[62,63]. This approach has several advantages, like improving testing rates, earlier initiation of systemic treatments based on biomarker status, and higher mutation detection rates[63-65]. Reflex testing also diminishes the need for clinicians to select patients based on clinical characteristics[62]. For pathologists, it is more efficient to conduct testing while the case is active instead of revisiting the stored samples later, which can lead to material loss from tissue degradation or repeated cutting of sample blocks[62].

The recent Asian Thoracic Oncology Research Group (ATORG) guidelines recommend preoperative testing for PD-L1, EGFR and ALK in clinical stage II-IIIA NSCLC[66]. However, no consensus was reached for stage IB (as per American Joint Committee on Cancer [AJCC]-Union for International Cancer Control [UICC] eighth edition), as these patients were excluded from perioperative chemoimmunotherapy trials. Therefore, it may be reasonable to defer testing to the resected surgical specimen for stage IB if adjuvant therapy is being considered.

The recent guidelines from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology (CAP/IASLC/AMP) suggest that pathologist-initiated reflex testing is reasonable but should be an individualised institutional decision[67]. The main challenges in adopting reflex testing are likely to be the cost and securing reimbursement, especially in publicly funded healthcare systems where payment may depend on the documented disease stage[62]. Given the high local prevalence of actionable mutations in resectable NSCLC, the expert panel emphasised the importance of establishing the genomic tumour biology before resection. This approach is pivotal to refine patient selection and initiate early, appropriate treatment strategies in this new era of biomarker-driven perioperative multimodal therapy. However, it is essential that testing is done promptly so as not to delay definitive and potentially curative surgery.

STATEMENT 4: The mandatory staging modalities should include contrast-enhanced computed tomography (CE-CT) of the thorax and whole-body positron emission tomography CT (PET-CT). If PET-CT is not available, a CE-CT of the abdomen and pelvis should then be performed.

The NCCN guidelines recommend CE-CT of the chest and upper abdomen as part of the initial evaluation and staging of NSCLC[68]. Given that CT is more affordable than PET scans, it remains the most common imaging method for staging[69]. Although CT is the recommended imaging modality for detecting pulmonary nodules, nodule features like shape, edge characteristics, cavitation, and location have not been reliable in distinguishing between benign and malignant nodules[70], leaving PET scans to play a valuable role in this area.

The use of 2-deoxy-2-[18F]fluoro-D-glucose (18F-FDG) PET-CT is recommended by NCCN, if not previously conducted, as part of the pre-treatment evaluation for stage I to IV NSCLC[71]. While CE-CT and FDG PET-CT are routinely used for staging NSCLC[72], PET alone is recognised as an accurate, non-invasive diagnostic tool that is highly sensitive and specific for malignant nodules[73]. PET works by identifying metabolically active tissue, as malignant nodules show higher glucose uptake and 18F-FDG enhancement compared to benign nodules[73]. However, several benign conditions, such as infections, granulomatous disease, and tuberculosis, can also show increased metabolic activity[74]. Conversely, some NSCLC subtypes, such as lepidic adenocarcinoma, may have poor FDG uptake resulting in a false negative finding[75].

The Tumour, Node, Metastases (TNM) staging system is the current standard for assessing the anatomic extent of lung cancer[76]. The ninth TNM edition based on a comprehensive analysis of an international database with over 75,000 patients came into clinical use in January 2025[77]. Taking NCCN's recommendation into consideration, the expert panel suggests CE-CT of the thorax and whole-body FDG PET-CT as the mandatory staging modality. In cases where PET-CT is not feasible, CE-CT of the abdomen and pelvis should be conducted as the minimum alternative modality. While bone scans may serve as a viable option for assessing bone metastases, particularly in resource-limited settings, their sensitivity and specificity are generally lower compared to PET-CT[78,79].

STATEMENT 5: Contrast-enhanced magnetic resonance imaging (CE-MRI) of the brain is recommended for stage II and above, or where clinically indicated. If brain MRI is not feasible, CE-CT of the brain is acceptable.

Brain metastases are a common complication in patients with NSCLC, with around 20% presenting with intracranial involvement at diagnosis[80] and up to 40% developing cerebral metastases during their disease progression[81]. Risk factors for brain metastases include non-squamous histology, younger age (≤ 50 years), adenocarcinoma subtypes, preoperative chemotherapy, and advanced tumour stage[82-85]. Staging of the brain may change the management pathway, either avoiding non-curative surgery or enabling aggressive management of oligometastatic disease[86].

Screening for brain metastases in NSCLC is recommended from stage II onwards for patients receiving treatment with curative intent[68,87]. The NCCN advises using CE-MRI of the brain for pre-treatment evaluation in stage II to IIIA, with optional screening for stage IB[68]. The National Institute for Health and Care Excellence (NICE) supports CE-CT of the brain for stage II NSCLC, followed by brain MRI if the CT suggests metastases[87]. For stage III patients and beyond, guidelines recommend MRI during initial staging[68,87-90]. When MRI is not feasible, a CE-CT brain scan is recommended[68,88,90]. Although MRI is more sensitive, CE-CT is often used in daily practice due to MRI contraindications or limited access[91-93]. For patients with suspected intracranial pathology, MRI should follow an initial abnormal CT or be used as the first-line test if available[87,89].

Screening patients for brain metastases is crucial, as its diagnosis can significantly impact the treatment plan for a patient with otherwise early-stage disease. This may involve abandoning treatment with radical intent and initiating systemic treatment (with or without local treatment for the brain metastases) or pursuing radical treatment for both the thoracic disease and the limited number of brain metastases.

STATEMENT 6: Pathologic (cytohistological) confirmation of clinical N2 disease should be routinely performed prior to definitive therapy.

Occult pathological N2 (pN2) lymph nodes are sometimes discovered intra-operatively despite accurate staging[94]. The prevalence of pN2 NSCLC varies between 7 to 21%[95-99], frequently detected in patients with clinical stage I NSCLC who undergo resection[100]. Factors associated with a higher risk of upstaging include female sex, adenocarcinoma, large tumour size, delayed time from diagnosis to surgery, positive resection margins, and a greater number of lymph nodes examined[100,101]. PET-CT risk factors include a high maximum standard uptake value of the primary tumour and the presence of a micro papillary and solid pattern[102]. These risk factors underscore the importance of patient selection and thorough staging to ensure those who could benefit from further evaluation and potential neoadjuvant therapy are appropriately identified.

Central and bulky tumours present unique challenges due to their size and proximity to the mediastinum. These tumours often have more extensive lymph node involvement and pose complex anatomical considerations. Consequently, imaging alone may not provide sufficient accuracy in staging, necessitating histological confirmation through biopsy or surgical sampling to avoid misclassification. The expert panel advises extending nodal examinations to include nodes that are located one station higher than those known or suspected to be malignant. For example, in cases with clinically positive N1 nodes, routine sampling of N2 nodes is recommended, as this represents a significant risk factor for nodal upstaging[101].

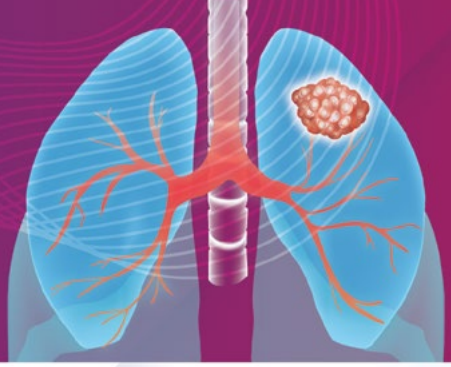
Current lung cancer diagnostic guidelines advocate invasive mediastinal nodal staging methods to ensure more accurate staging prior to surgical resection, including endoscopic techniques such as endobronchial ultrasound (EBUS) or endoscopic ultrasound (EUS) with fine-needle aspiration, video-assisted mediastinoscopy or left anterior mediastinotomy (for stations 5 & 6 lymph nodes)[68,90,103]. The European Society of Thoracic Surgeons (ESTS) guidelines recommend preoperative mediastinal staging for central tumours, N1 nodes, and tumours larger than 3 cm (particularly those of adenocarcinoma subtype with high standardised uptake value)[103]. Similarly, the NCCN recommends that most patients with clinical stage I or II lung cancer undergo mediastinal staging, preferably mediastinoscopy, as the initial step before planned resection (68). The NCCN recommends invasive mediastinal staging for patients with a strong clinical suspicion of N2 or N3 nodal disease[68], while ACCP advises that for patients with intermediate suspicion of N2 or N3 involvement, invasive staging of the mediastinum should be performed instead of relying solely on imaging[90].

Routine histological confirmation of clinical N2 disease is a critical step in the management of lung cancer, particularly for patients with central or bulky tumours. Invasive mediastinal nodal staging provides precise staging, which is essential for treatment planning and improving patient outcomes, as treatment strategies and prognosis differ based on disease stage. The expert panel feels every effort should be made to confirm or exclude microscopic histological mediastinal N2/N3 nodal disease where clinical suspicion is high, starting with the least invasive approach locally available.

The panel recognises that 'resectability' can be highly subjective and even contentious, particularly for T4 tumours, multi-station N2, and even single-station bulky N2 disease. Resectability is largely dependent on surgical expertise in terms of technical skill and operative judgement, as well as an understanding of tumour biology. The assessment of resectability is influenced by the experience of the individual surgeon or institution, which often reflects surgical case mix and volumes. Complex, high-risk or borderline cases are best evaluated by experienced thoracic surgeons within a multidisciplinary team setting. Whilst contemporary and future advances in neoadjuvant and perioperative therapy may redefine 'resectability', with the primary oncological goal of surgery being an R0 resection which includes negative margins and adequate systematic mediastinal lymph node dissection, the panel considers N3 disease (contralateral mediastinal/hilar or ipsilateral supraclavicular lymph node involvement) unresectable, even in medically operable patients.

Similarly, the panel noted that while neoadjuvant chemoimmunotherapy may enhance resectability in some cases through potential downstaging, the goal of neoadjuvant therapy should not be to convert upfront unresectable disease for surgical resection, as there is no compelling evidence presently to support this strategy. Instead, such patients are better served with definitive chemoradiation +/- adjuvant immunotherapy or oral targeted therapy based on their tumour biology; there should be no delay in initiation of non-surgical therapy.

SECTION 3: RECOMMENDATIONS FOR NEOADJUVANT AND PERIOPERATIVE TREATMENT



STATEMENT 1: All potentially resectable stage III NSCLC should be discussed in a multidisciplinary setting for consideration for neoadjuvant treatment.

Stage III NSCLC presents a heterogeneous range of tumour and nodal involvement, necessitating diverse management strategies and a multidisciplinary approach[104]. With recent treatment developments and evolving guidelines, selecting the most appropriate therapy has become increasingly complex for clinicians[104]. As such, a multimodal approach involving a multidisciplinary team, including thoracic surgeons, respiratory physicians, oncologists, radiologists, nuclear medicine physicians and pathologists, is essential[104,105].

The expert panel emphasises that a thoracic surgeon must first evaluate the resectability of the locally advanced tumour before any decision is made regarding systemic therapy. The ideal timing for surgery following neoadjuvant immunotherapy has yet to be clearly established. However, phase two and three neoadjuvant and perioperative chemoimmunotherapy trials scheduled surgery within six weeks after the last dose of three to four cycles of neoadjuvant chemoimmunotherapy to minimise the potential impact of delayed resection on survival[106]. Taking this into consideration, the expert panel opined that surgery should be performed within two to four weeks of completion of chemoimmunotherapy, to prevent dense adhesion of lympho-vascular structures in the chest. Adjuvant chemotherapy with or without radiotherapy is optional.

STATEMENT 2: For resectable stage II NSCLC, upfront resection is a reasonable strategy in many instances, unless there is a concern with the ability to achieve complete resection with a lobectomy.

Surgery remains the cornerstone of treatment for early-stage resectable NSCLC, with lobectomy being the standard and optimal resection strategy for medically operable patients[105]. A recent real-world study from France involving 19,452 patients with stage IA lung carcinoma supports lobectomy as the reference treatment for resectable disease[107]. While upfront surgery may be considered for patients with stage IIIA/IIIB NSCLC, assessing technical resectability and optimising adjuvant therapy can present

challenges[108]. The expert panel recommends initiating neoadjuvant therapy when an R0 resection with lobectomy is not feasible after evaluation by a thoracic surgeon, aiming to downstage and downsize the disease to achieve complete resection with a lobectomy, avoiding the morbidity and risk of a pneumonectomy or an incomplete resection.

The addition of immunotherapy to chemotherapy has been shown to improve outcomes in patients with resectable NSCLC. Recent trials, including CheckMate-816[9], CheckMate-77T[11], KEYNOTE-671[12], AEGEAN[10] and Neotorch[13] have shown improved EFS and impressive pathological complete response (pCR) rates when immunotherapy was added to the neoadjuvant protocol compared to a placebo. Despite these advancements, OS data remains limited[9,10,13], though the KEYNOTE-671 study reported a significant survival benefit with perioperative pembrolizumab compared to placebo (HR 0.72, 95% CI 0.56 to 0.93) at the second interim analysis with a median follow-up of 36.6 months[109]. The CheckMate-816 trial demonstrated a five-year OS benefit, supporting a neoadjuvant-only strategy for patients who achieved a pCR (95.3 % vs. 55.7%; HR 0.11, 95% CI 0.04-0.36) or pre-surgical ctDNA clearance (75% vs. 52.6%)[110]. These findings may help refine which patients will derive an additional benefit from adjuvant therapy as part of a peri-operative 'sandwich' protocol. Among patients receiving neoadjuvant immunotherapy plus chemotherapy, 77 to 83% successfully underwent surgery, with R0 resection rates of 92 to 96%[9,10,12,13]. However, up to 22.3% of patients failed to be optimised for curative surgery despite neoadjuvant therapy, partly due to disease progression[9], highlighting a potential drawback with this approach.

The expert panel appreciates that the treatment paradigm for stage II disease is evolving and presently, the optimal management strategy remains undefined. This is reflected in the 2024 IASLC recommendations for early-stage resectable NSCLC, which reported a lack of consensus (65% agreement) for neoadjuvant chemoimmunotherapy followed by surgery versus upfront surgery in patients with resectable clinical stage II NSCLC, regardless of PD-L1 expression[111]. While neoadjuvant treatment remains a safe and potentially valuable option, concerns persist about the strength and sufficiency of current evidence[111]. Similarly, ATORG advises that neoadjuvant chemoimmunotherapy is an optional approach for patients with upfront resectable stage IB-II (EGFR and ALK negative) NSCLC, irrespective of PD-L1 status, if there are no medical contraindications[66].

The magnitude of EFS benefit seen in the neoadjuvant and perioperative trials was most evident in stage III disease, although a recent meta-analysis did show favourable EFS for neoadjuvant chemoimmunotherapy over neoadjuvant chemotherapy in stage II disease (HR 0.71, 95% CI 0.55 to 0.92)[6], particularly in patients with a tumour PD-L1 level > 1%.

It is hoped that improvements in EFS will translate into OS benefit; however, apart from KEYNOTE-671 and CheckMate-816, this has yet to be demonstrated. In general, the best outcomes were observed in patients with a strong immunopathological response, with pCR rates ranging from 17.2 to 35.1% (9-13). Conversely, 7 to 22.3% of patients in the chemoimmunotherapy arm across various randomised trials were not resected, some of whom might have benefited from upfront surgery[6].

Given the limited robust OS data and the absence of direct head-to-head comparisons between neoadjuvant therapy followed by surgery against upfront resection with adjuvant therapy, the expert panel considers upfront resection a reasonable approach for stage II disease, provided an R0 resection can be achieved with a lobectomy or a lesser resection. However, the panel acknowledges the heterogeneity of stage II NSCLC, particularly in patients with T3N0 disease (tumours with possible chest wall, pericardial or phrenic nerve involvement, or a separate tumour in ipsilateral lobe), central or larger tumours (5 to 7 cm) near fissures or where pathologic lymph node sampling was not feasible due to technical reasons. In cases where local expertise is limited or there is a risk of clinical under-staging, an oncology opinion should be sought—ideally in a multidisciplinary setting—to evaluate the potential benefit of neoadjuvant or perioperative therapy.

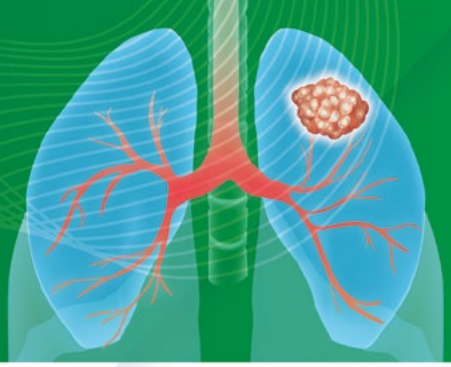
Current evidence does not conclusively support the superiority of any single therapeutic approach. Therefore, real-world factors such as affordability, pharmacological toxicity (including immune-related adverse events), increased surgical complexity, and the risk of disease progression precluding curative-intent surgery must be carefully weighed when evaluating the risk-benefit for individual patients with stage II NSCLC outside a trial setting. Neoadjuvant therapy can be considered for patients with marginally resectable tumours following multidisciplinary team discussion. In cases where EGFR or ALK tests are unavailable, or immunotherapy is unaffordable or intolerable, neoadjuvant chemotherapy can be an alternative option. Upon completing neoadjuvant therapy and appropriate restaging, the case should be re-presented at the tumour board to seek a surgical opinion regarding resectability. With emerging evidence, the treatment paradigm for stage II disease will continue to evolve, necessitating periodic review and updates to recommendations.

STATEMENT 3: Radiotherapy should not be recommended as part of pre-operative treatment for resectable NSCLC.

Existing literature argues against the routine use of radiotherapy in early-stage resectable NSCLC. For stage II N0 NSCLC, radiotherapy has shown no benefit and has even been linked to worse outcomes, such as decreased OS and increased mortality[112]. Similarly, in patients with stage III NSCLC, pre-operative radiotherapy has not demonstrated a significant survival advantage and is associated with higher rates of chemoradiotherapy-related toxicities[113,114]. A systematic review and meta-analysis comparing studies of stage IIIA (N2) NSCLC patients reported no survival benefit from adding radiotherapy to chemotherapy in the neoadjuvant setting[115]. This lack of survival benefit is likely due to the locoregional effects of radiotherapy, which does not address systemic micro-metastatic disease, leading to disease relapse and death.

Additionally, neoadjuvant radiotherapy is associated with increased post-operative morbidity and mortality, with morbidity ranging from 40 to 60% and mortality between 4 to 20%[116-122]. Common radiation-related complications occur in about 40% of patients, primarily affecting the lungs (e.g., pneumonia, atelectasis, prolonged air leakage) or the heart (e.g., arrhythmia)[120,122,123]. Given the absence of survival benefits and the high risk of complications, the expert panel advises against the use of radiotherapy in the pre-operative setting for resectable NSCLC.

SECTION 4: RECOMMENDATIONS FOR ADJUVANT TREATMENT



STATEMENT 1: All patients with fully resected stage IB to IIIB (≤ N2) NSCLC should receive an oncology consultation (within 4 weeks) to discuss adjuvant therapy options based on tumour genomic profiling from the initial biopsy or resected specimen for actionable mutations (EGFR and ALK) and PD-L1 expression.

As with the neoadjuvant setting, patients should be evaluated by a multidisciplinary team to discuss adjuvant therapy options, ideally within a tumour board setting[111]. In Malaysia, some respiratory physicians treat lung cancer; hence, the term "oncology consultation" encompasses consultations with oncologists or treating respiratory physicians. Beyond TNM staging, adjuvant therapy may be particularly beneficial for patients with high-risk microscopic features, such as lymphovascular invasion, visceral pleural invasion, spread through the air space, and a micropapillary or solid predominant pattern[124]. Although this has not been specifically studied in early-stage NSCLC, adjuvant chemotherapy for patients with pathologic stage I lung carcinoma significantly improved both recurrence-free survival and overall survival in high-risk groups[124].

The IASLC recommends that patients considered for adjuvant systemic therapy should be tested for at least EGFR and ALK alterations, as well as PD-L1 status. If feasible, biomarker testing for additional oncogenic drivers is encouraged in early-stage patients, as ongoing trials focus on specific driver mutations, and PD-1 and PD-L1 checkpoint inhibitors have limited efficacy in these populations. There should be no role for immunotherapy in patients harbouring actionable genomic alterations. While TKIs can be administered following adjuvant chemotherapy based on physician judgement, chemotherapy is essential alongside adjuvant immunotherapy to achieve optimal benefit[111].

The recommendations in this section were based on the eighth edition of the AJCC-UICC Staging Manual. With notable updates in the latest ninth TNM edition, some stage IIIA subgroups are now reclassified as stage IIB (T1 N2a) or upstaged to stage IIIB (T2a N2b and T2b N2b).

STATEMENT 2: All patients with fully resected (stage IB to IIIB) EGFR-mutant NSCLC (Del 19/L858) should be offered osimertinib 80 mg once daily +/- chemotherapy for at least 3 years, based on DFS/OS benefit from ADAURA study.

The most prevalent genomic alteration identified in NSCLC here involves the EGFR gene, either as a deletion at exon 19 (Del-19) or point mutation at exon 21 (L858)[125], affecting 20 to 65% of the population in Asian countries[126]. The ADAURA trial, a phase III, double-blind, placebo-controlled study that assigned patients to receive either osimertinib (80 mg once daily) or placebo for three years, demonstrated a significantly longer DFS in resected EGFR-mutant stage IB-IIIA NSCLC patients (AJCC-UICC seventh edition) treated with adjuvant osimertinib compared to placebo (HR 0.2, 95% CI 0.14 to 0.3)[16]. At two years, 90% of patients with stage II to IIIA disease in the osimertinib group were alive and disease-free (95% CI 84 to 93), compared to 44% in the placebo group (95% CI 37 to 51) (HR 0.17, 95% CI 0.11 to 0.26)[16]. This DFS benefit was observed across all subgroups, including stage IB disease, and was independent of prior adjuvant chemotherapy[16]. Central nervous system (CNS) DFS at two years was 98% in the osimertinib group (95% CI 95 to 99) vs. 85% in the placebo group (95% CI 80 to 89) (HR 0.18, 95% CI 0.1 to 0.33)[16]. Five-year OS was 88% with osimertinib vs. 78% with placebo (HR 0.49, 95% CI 0.33 to 0.73)[127].

Given the significant and clinically meaningful improvement in DFS (including CNS-DFS) and OS compared to placebo observed in the ADAURA study, adjuvant oral therapy with osimertinib, a third-generation TKI, is recommended for all patients with fully resected stage IB to IIIB NSCLC harbouring an EGFR sensitising mutation (Del19 or L858R), for a minimum of three years post-surgery, with or without platinum-based chemotherapy.

STATEMENT 3: All patients with fully resected (stage IB to IIIB) ALK-fusion positive NSCLC should be offered alectinib 600 mg twice-daily +/- chemotherapy for at least 2 years, based on DFS/CNS-DFS benefit from ALINA study.

The second most common mutation encountered in NSCLC is ALK rearrangement, found in 2 to 7% of early-stage NSCLC and predominantly affects younger patients, most of whom are non-smokers or light smokers[128,129]. These tumours have a high propensity for brain metastasis, with up to 60% of patients developing CNS metastases during their disease course[130]. The recent phase III ALINA study demonstrated significantly improved DFS in patients with fully resected ALK-positive stage IB-IIIA NSCLC (AJCC-UICC seventh edition) who received adjuvant alectinib (600 mg twice daily) for two years compared

to those who received platinum-based chemotherapy[131]. At two years, DFS was 93.8% in the alectinib group vs. 63% in the chemotherapy group in patients with stage II or IIIA disease (HR 0.24, 95% CI 0.13 to 0.45), and at three years, 88.3% vs. 53.3%, respectively[131]. The DFS benefit was consistent across the subgroups, including stage IB disease, with a median DFS of 41.3 months in the chemotherapy subgroup vs. not reached in the alectinib subgroup (HR 0.24, 95% CI 0.13 to 0.43)[131]. Subgroup analyses showed the DFS benefit was independent of disease stage and smoking history[131]. While an improvement in CNS-DFS was observed (HR 0.22, 95% CI 0.08 to 0.58), OS data remains immature at the time of writing[131].

Based on the statistically significant and clinically meaningful improvement in DFS (including CNS-DFS) compared to adjuvant chemotherapy, observed consistently across all subgroups in the ALINA study, all patients with fully resected stage IB to IIIB ALK-fusion positive NSCLC should be offered adjuvant therapy with alectinib, a second-generation TKI, for at least two years, with or without platinum-based chemotherapy following surgery.

STATEMENT 4: Adjuvant immunotherapy with chemotherapy should be considered in resected stage IB to IIIB patients with PD-L1 ≥ 1% and no EGFR or ALK mutations but is not routinely recommended for those with PD-L1 < 1%.

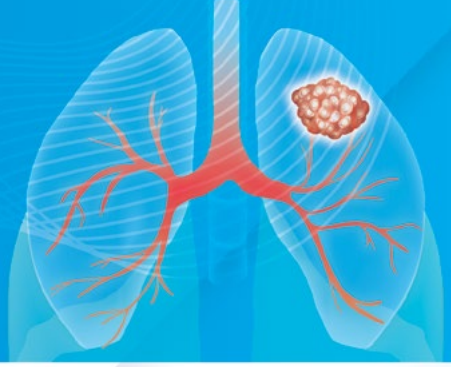
Recent trials have investigated the impact of tumour PD-L1 expression on treatment outcomes with adjuvant immunotherapy. The phase 3 IMpower010 trial randomised patients with completely resected stage IB to IIIA NSCLC (AJCC-UICC seventh edition) to receive adjuvant atezolizumab (1,200 mg every 21 days for 16 cycles) or best supportive care (BSC) after chemotherapy[19]. The primary endpoint was met, with atezolizumab significantly improving DFS compared to BSC in patients with stage II to IIIA and PD-L1 ≥ 1% (HR 0.66, 95% CI 0.5 to 0.88), as well as in all patients with stage II to IIIA disease (HR 0.79, 95% CI 0.64 to 0.96) and stage IB to IIIA (HR 0.81, 95% CI 0.67 to 0.99) (19). However, no DFS benefit was observed in patients with PD-L1 < 1% (HR 0.97, 95% CI 0.72–1.31), while those with PD-L1 ≥ 50% showed the most significant benefit (HR 0.43, 95% CI 0.27 to 0.68)[19]. At a median follow-up of 45.3 months, OS remained not estimable for stage IB to IIIA (HR 0.995, 95% CI 0.78 to 1.28); OS data showed a favourable trend in patients with stage II to IIIA and PD-L1 ≥ 1% (HR 0.71, 95% CI 0.49 to 1.03), but significant OS benefit was seen only in those with PD-L1 ≥ 50% (HR 0.42, 95% CI 0.23 to 0.78) (132). Notably, OS data suggested potential harm for patients with PD-L1 < 1% (HR 1.36, 95% CI 0.93 to 1.99)[132].

The phase 3 PEARLS/KEYNOTE-091 trial randomised patients with completely resected stage IB to IIIA NSCLC (AJCC-UICC seventh edition) to receive either pembrolizumab 200 mg or placebo. In the overall trial population, adjuvant pembrolizumab showed a significant improvement in DFS (HR 0.76, 95% CI 0.63 to 0.91). However, PD-L1 subgroup analyses yielded mixed results: no benefit was observed for PD-L1 < 1% (HR 0.78, 95% CI 0.58 to 1.03), a benefit was seen for PD-L1 1 to 49% (HR 0.67, 95% CI 0.48 to 0.92), and no benefit was found for PD-L1 ≥ 50% (HR 0.82, 95% CI 0.57 to 1.18). This anomalous latter finding has been attributed to an over-performance of the placebo group in the PD-L1 > 50% cohort. At the time of data cut-off, median OS was not reached in either group (HR 0.87, 95% CI 0.67 to 1.15)[20].

Both IMpower010 and PEARLS/KEYNOTE-091 did not exclude resected stage IB to IIIA NSCLC patients with EGFR mutations or ALK aberrations[20,132]. However, the sample sizes for patients with these driver mutations were small, with some patients having an unknown molecular profile. In IMpower010, subgroup analysis for EGFR mutations showed no DFS benefit (HR 0.99, 95% CI 0.6 to 1.62)[19], while a DFS benefit was observed in the EGFR-mutant group in PEARLS/KEYNOTE-091 (HR 0.44, 95% CI 0.23 to 0.84)[20]. Similarly, in IMpower010, patients with ALK rearrangements did not benefit from adjuvant atezolizumab (HR 1.04, 95% CI 0.38 to 2.9)[19], with data for PEARLS/KEYNOTE-091 not reported, likely due to low patient numbers. Given the small sample sizes for these groups, the data should be interpreted with caution. Additionally, the negative findings of the phase 3 BR.31 trial, which evaluated adjuvant durvalumab in resected stage 1B-IIIA NSCLC, cast doubt over the benefit and efficacy of adjuvant immunotherapy when the trial did not demonstrate a significant DFS benefit over placebo in patients with EGFR/ALK wild-type tumours and PD-L1 tumour proportion score > 25% (trial primary endpoint)[133].

Nevertheless, based on the earlier trial results, the expert panel recommends considering adjuvant immunotherapy with chemotherapy for resected stage IB to IIIB patients with PD-L1 ≥ 1% and no EGFR or ALK mutations. Adjuvant immunotherapy is not routinely recommended for resected stage IB to III patients with PD-L1 < 1% due to minimal therapeutic benefit and the risk of adverse outcomes. Separately, it remains to be seen whether adjuvant immunotherapy can be safely de-escalated in patients whose tumours achieve a pCR after neoadjuvant therapy and who are ctDNA negative post-resection, suggesting no minimum residual disease (MRD) and hence a cure. Presently, concerns exist regarding the sensitivity and negative predictive value of commercially available ctDNA assays to facilitate this adaptive MRD-based approach.

SECTION 5: RECOMMENDATIONS FOR OPERATIVE PROCEDURES AND POST-RESECTION SURVEILLANCE



STATEMENT 1: With R0 resection in mind, a minimally invasive approach is favoured for its lower post-operative morbidity and oncological non-inferiority to thoracotomy. However, its adoption depends on the surgeon's experience.

Video-assisted thoracoscopic surgery (VATS) was introduced in the 1990s as a minimally invasive alternative to conventional lung cancer surgery, reducing the need for large incisions and ribs-spreading[134]. The VIOLET trial demonstrated that VATS lobectomy leads to improved physical function at five weeks, shorter postoperative hospital stays, fewer serious complications after discharge, reduced hospital readmissions, and less pain, contributing to enhanced quality of life at one year[135]. The study also suggests that despite more modest air leaks and bleeding, the operative outcomes with VATS lobectomy is comparable to open thoracotomy[135].

While VATS has tremendously reduced post-surgical morbidity, allowing more patients who were previously unfit or unwilling to undergo surgery to pursue a curative operation[134,136-138], close monitoring for complications remains essential. Up to 32% of patients may experience residual pain lasting up to 59 months (range 35 to 79 months) after a curative VATS lung resection[139]. Additionally, around 53% of VATS patients report paraesthesia distinct from nociceptive wound pain, with a median observation time of 19 months[140]. Considering the need to reduce surgical access trauma, multiport VATS has evolved into two-port or uniport VATS, which unlike robot-assisted surgery, requires no expensive equipment and has a minimal learning curve for experienced VATS surgeons[141,142]. With skilled execution, VATS lobectomy can lead to better patient compliance with adjuvant chemotherapy, with minimal delay or dose adjustments[143-145].

Robotic-assisted thoracic surgery (RATS) is an exciting emerging trend, offering excellent intra-operative visualisation that facilitates more thorough lymph node dissection, enhanced ergonomic movement, and potentially less tissue trauma. However, longer-term outcomes in terms of oncologic efficacy, safety and cost-effectiveness are still awaited. In a resource-constrained setting like Malaysia, providing value-based healthcare remains a major consideration. The expert panel believes that while surgical innovation is vital for advancing the specialty and improving patient outcomes, RATS for resectable NSCLC should only be performed by accredited, fully trained surgeons in high-volume centres with appropriate on-site proctoring and mentoring, with clinical outcomes audited.

STATEMENT 2: Lobectomy remains the standard of care for medically fit patients with early-stage NSCLC.

Reducing resected lung volume helps minimise surgical trauma and physiological respiratory insult. Traditionally, curative lung cancer resection involves a lobectomy, which is the anatomical resection of one or more lung lobes. In contrast, a sublobar resection involves either the non-anatomical removal of a wedge or the anatomical resection of the lung segment containing the tumour. While segmentectomy is expected to significantly reduce post-operative complications and preserve lung function[146,147], an initial randomised trial by the 1995 Lung Cancer Study Group showed that sublobar resection for T1 N0 NSCLC demonstrated no additional benefits in perioperative morbidity and mortality or late post-operative pulmonary function compared to lobectomy (148). In fact, the study reported a higher death rate and locoregional recurrence rate in patients who underwent sublobar resection than lobectomy[148].

When sublobar resections were categorised as segmentectomies versus wedge resections, the segmentectomy group showed lower rates of locoregional recurrences and improved cancer-related survival rates[149]. Nonetheless, emerging evidence prompted the Lung Cancer Study Group to revise its position in 2010, recommending the selective use of sublobar resection for small tumours and those with favourable histologic profiles, accompanied by adequate surgical margins, proper evaluation of hilar and mediastinal lymph nodes, and appropriate use of adjuvant therapy[150]. As a result, lobectomy with systematic mediastinal lymph node dissection remains the gold standard for lung cancer resection, while sublobar resection is considered a reasonable option for high-risk, compromised patients[151].

Historically, major lung resections were always preceded by bronchoscopic evaluation; however, the contemporary value of routine bronchoscopy in the pre-operative work-up of smaller peripheral tumours is debatable. Despite advances in radiological imaging, the expert panel believes that conventional bronchoscopy (flexible and/or rigid) should still be performed by the operating surgeon pre-operatively. This allows for evaluation of resection margins, exclusion of occult endobronchial pathology that may not be evident on imaging, and pulmonary toileting to facilitate re-expansion of the remaining lung, especially for patients with larger or less peripheral tumours. Additionally, newer techniques performed by skilled bronchoscopists, including navigation bronchoscopy, robotic-assisted bronchoscopy, endobronchial ultrasound and fluoroscopy (e.g., dye marking or fiducial placement), may assist in lesion localisation and planning of lung-conserving sublobar resections.

STATEMENT 3: Sublobar resection may be an option in (a) patients with a smaller peripheral tumour < 2 cm, with proven lymph node-negative (N0), and/or (b) medically unfit patients (e.g., with limited lung function or significant comorbidities). Patients should be informed that a sublobar resection might be associated with a higher risk of locoregional recurrence.

Existing evidence supports the use of sublobar resection for patients with small, peripheral tumour (less than 2 cm) and limited lung function[151-153]. A systematic review involving 43,469 patients reported a higher complication rate in the lobectomy group, especially among older adults (range 0 to 48%) and those with comorbidities (0 to 46.6%), though a higher recurrence rate was observed in the sublobar resection group (3.6 to 53.4% vs. 6.2 to 32%)[154]. The systematic review concludes that sublobar resections are most suitable for elderly patients or those with existing comorbidities or reduced lung function, while lobectomy remains the standard of care for medically fit patients or those with a higher recurrence risk[154].

A recent phase III Japanese non-inferiority trial (JCOG0802) comparing segmentectomy over lobectomy for clinical stage IA disease (tumour diameter ≤ 2 cm; consolidation-to-tumour ratio > 0·5) demonstrated superior five-year OS in the segmentectomy group (94.3 % vs. 91.1%) with comparable relapse-free survival (RFS) (88% vs. 87.9%)[155]. However, a higher local relapse rate was observed in segmentectomy patients (10.5% vs. 4.5%)[155]. At one-year follow-up, the difference in local relapse between the two groups was 3.5% ($p < 0.0001$), which remained below the pre-defined threshold for clinical significance of 10%[155].

Major guidelines outline clear recommendations for selecting patients suitable for sublobar resection. The ACCP guidelines suggest anatomical sublobar resection instead of a lobectomy for patients at higher risk of perioperative mortality (156). Since sublobar resection offers survival benefits over non-surgical therapy for stage I NSCLC[157,158], the ACCP also recommends it over non-surgical therapy in patients with clinical stage I NSCLC who may tolerate surgery but not lobectomy due to reduced lung function or comorbid conditions[156]. Similarly, the European Society of Medical Oncology (ESMO) guidelines advise that anatomical segmentectomy is acceptable for pure ground glass opacity lesions, adenocarcinomas in situ, or with minimal invasion[88]. However, sublobar resection should be performed using a minimally invasive approach to maximise its

benefits[141]. A wide sublobar wedge resection can offer adequate local control and RFS for peripheral ground-glass opacity-dominant lung cancers (≥ 2 cm and with consolidation tumour ratio ≥ 0.25 on CT imaging), achieving excellent long-term outcomes with a 10-year RFS of 98.6% and a 10-year OS of 98.5%[159].

The expert panel recommends that non-surgical options, such as stereotactic body radiotherapy or local ablative therapies (radiofrequency/microwave), be considered by a multidisciplinary tumour board for patients deemed borderline medically operable, even for a sublobar wedge resection.

STATEMENT 4: Curative resection includes adequate intraoperative mediastinal lymph node sampling or clearance of three mediastinal (N2) and one hilar (N1) station(s).

Both the NCCN and ACS Commission on Cancer standards advise that any curative-intent resection for NSCLC must include sampling nodes from at least three distinct mediastinal nodal stations (stations 2 to 9) and one or more hilar station (stations 10 to 14)[160]. Adherence to station-based sampling improved recurrence-free survival (RFS) in the Veterans Health Administration cohort study, along with improvements in overall survival and increased likelihood of pathological upstaging[161]. This highlights the importance of promoting consistent adherence to intraoperative systematic lymph node sampling guidelines to improve patient outcomes following curative-intent lung cancer resection[161].

Following favourable survival outcomes observed in the Veterans Health Administration cohort study, adequate lymph node sampling was incorporated as one of the five surgical quality metrics, together with timely surgery (within 12 weeks of radiographic suspicion), use of a minimally invasive approach, anatomic resection, and securing a negative surgical margin[162]. Similarly, adherence to these intraoperative quality metrics correlated with improved OS and RFS[162], reinforcing their importance as surgical benchmarks for optimal patient care.

STATEMENT 5: Post-operative surveillance should be stage-dependent and conducted for a minimum of 5 years by a dedicated lung specialist (e.g., respiratory physician, cardiothoracic/thoracic surgeon, oncologist), using CT/PET-CT scan (stage I to II every 6 months for 3 years then annually for another two years, stage III every 3 to 6 months for 3 to 5 years, or as clinically indicated).

Post-operative surveillance for recurrence or detection of a second metachronous primary tumour is crucial to ensure optimal long-term prognosis for stage I to III NSCLC patients who undergo curative-intent surgical resection. As most recurrences occur within the first two years post-surgery, guidelines recommend that patients undergo a chest CT scan with or without contrast for the initial post-surgery surveillance for the first two to five years[68,163]. Patients with a prior history of lung cancer have a higher risk of a new primary lung cancer than the general at-risk population (163); hence, annual LDCT is recommended for the surveillance of new primary lung cancers following the initial post-surgery surveillance period[68].

Current guidelines from the ACCP and American Society of Clinical Oncology (ASCO) recommend follow-ups every six months for the first two years, followed by annual visits[163,164]. Radiological follow-ups should incorporate CT scans of the adrenals within the initial two years, accompanied by LDCT of the chest[163]. PET-CT scans, however, are not preferred by ASCO for routine surveillance due to high costs and additional radiation, with no proven benefit over CT as a surveillance tool[163,165]. Nonetheless, PET-CT scans may prove helpful when post-treatment changes hinder effective CT evaluation[163]. Meanwhile, the ESMO guidelines recommend surveillance every six months for the first three years using contrast-enhanced chest and abdominal CT, with PET scans as required[166]. Beyond this period, follow-up frequency may be tailored to individual patient's needs[166]. The frequency of follow-ups, whether every six months for the first two or three years, should be tailored based on patients' existing risk factors and resource availability.

The role of circulating biomarkers in surveillance continues to be a topic of debate. ASCO advises against using circulating biomarkers, including CEA, as a surveillance strategy for detecting recurrence in resected early-stage NSCLC patients (163). Although blood-based biomarkers offer theoretical advantages and have demonstrated value in other solid tumours, data supporting their routine use in NSCLC surveillance remain inconsistent, underscoring the need for further research to define their role in reliably detecting recurrence[163]. A recent local study, however, demonstrated the utility of CEA as a prognostic and surveillance tool for disease recurrence in Malaysians with early-stage

non-squamous NSCLC following resection[47]. An elevated pre-resection baseline CEA may serve as a surrogate for biologically aggressive disease, correlating with inferior DFS despite curative R0 resection and extensive intra-operative nodal sampling. Such patients may benefit from meticulous post-resection surveillance and consideration of adjuvant therapy beyond conventional TNM criteria.

According to ASCO guidelines, routine brain MRI surveillance for recurrence is not recommended in patients who have completed curative-intent treatment for NSCLC[163]. While no randomised trials have assessed brain MRI specifically for surveillance in NSCLC, studies on prophylactic cranial irradiation did not show a survival benefit despite reducing brain metastasis rates[163]. Therefore, routine brain MRI in asymptomatic patients is unlikely to provide meaningful clinical benefit[163]. Given this, brain MRI should be approached with caution in surveillance strategies.

Additionally, ASCO advises that patients unsuitable or unwilling to undergo further treatment may be omitted from surveillance; while age should not exclude patients from surveillance imaging, factors such as overall health status, comorbidities, and patient preferences should be considered[163]. Considering the existing evidence, the expert panel opines that a routine surveillance brain MRI is not required for asymptomatic non-ALK mutant patients with resected stage I/II disease and a normal PET-CT scan. For symptomatic patients or those with resected stage III and/or ALK-positive NSCLC, a contrasted brain MRI is a reasonable surveillance investigation, alongside PET-CT, at the discretion of the treating oncologist. Similarly, the expert panel suggests that in patients with an elevated baseline pre-resection serum CEA, surveillance with serial measurements may be beneficial to monitor treatment response and detect recurrence early. This approach may also help personalise surveillance scan intervals.

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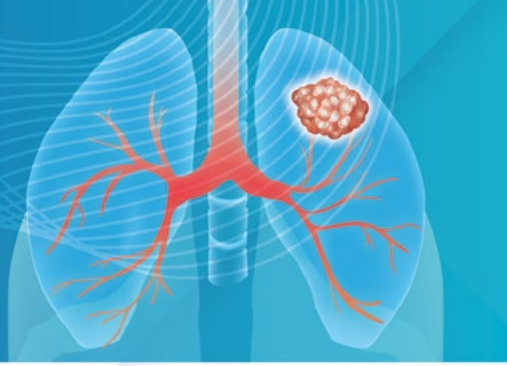

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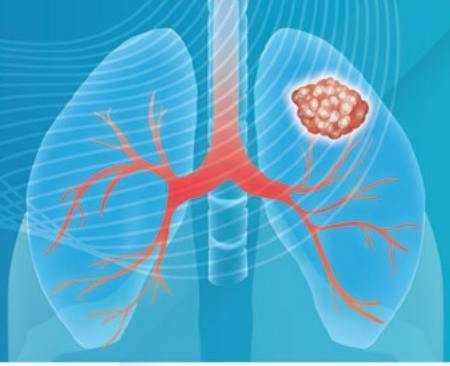

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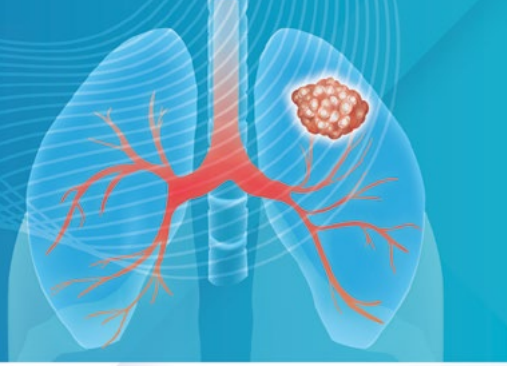
ABBREVIATIONS



18F-FDG	2-deoxy-2-[18F]fluoro-D-glucose
ACCP	American College of Chest Physicians
ACS	American Cancer Society
AI	Artificial intelligence
AJCC-UICC	American Joint Committee on Cancer-Union for International Cancer Control
AMP	Association for Molecular Pathology
ASCO	American Society of Clinical Oncology
ATORG	Asian Thoracic Oncology Research Group
BTS	British Thoracic Society
CAP	College of American Pathologists
CEA	Carcinoembryonic antigen
CE-CT	Contrast-enhanced computed tomography
CE-MRI	Contrast-enhanced magnetic resonance imaging
CI	Confidence interval
CNS	Central nervous system
CT	Computed tomography
ctDNA	Circulating tumour deoxyribonucleic acid
DFS	Disease-free survival
EBUS	Endobronchial ultrasound
EFS	Event-free survival
ESMO	European Society of Medical Oncology
ESTS	European Society of Thoracic Surgeons
EUS	Endoscopic ultrasound
HR	Hazard ratio
IASLC	International Association for the Study of Lung Cancer
LDCT	Low-dose computed tomography
Lung-RADS	Lung Imaging Reporting and Data System
MRD	Minimum residual disease
MySCan	Malaysian Study on Cancer Survival
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
NSLT	National Lung Screening Trial
OS	Overall survival
pCR	Pathological complete response
PET	Positron emission tomography
PM2.5	2.5 μm particulate matter
RATS	Robotic-assisted thoracic surgery
RFS	Recurrence-free survival
TALENT	Taiwan Lung Cancer Screening in Never-Smoker Trial
TKI	Tyrosine kinase inhibitors
TNM	Tumour, Node, Metastases staging system
TTI	Time-to-treatment initiation
VATS	Video-assisted thoracoscopic surgery

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