Philippine Clinical Practice Guidelines for the

DIAGNOSIS, STAGING *and* MANAGEMENT *of* LUNG CARCINOMA

2021

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DISCLAIMER

This clinical practice guideline (CPG) is intended to be used by specialists and general practitioners who are primary care providers. Although adherence to this guideline is encouraged by the Department of Health (DOH), it should not restrict the clinicians in using their clinical judgment and considering patient's values, needs, and preferences while handling individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history, current physical status, and their responses to treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules to base legal action.

Developers of this CPG are aware of its limitations. Evidence summaries are based on the best available scientific evidence at the time of its formulation. As such, certain aspects of the interventions or diagnostic tests may not be completely addressed by the included studies.

This CPG is not intended to cover the entirety of the management of lung cancer. It provides recommendations on interventions where variability in clinical practice and some controversies in decision-making exist.

LIST OF ABBREVIATIONS AND ACRONYMS

ACCP	American College of Chest Physicians
ASCO	American Society of Clinical Oncology
ASTRO	American Society of Radiation Oncology
AUC	area under the curve
BTS	British Thoracic Society
CEA	carcinoembryonic antigen
CECT	contrast-enhanced computed tomography
CP	Consensus Panel
CPG	clinical practice guidelines
CRT	chemoradiotherapy
CT	computed tomography
CT-GAB	computed tomography-guided aspiration biopsy
CXR	chest x-ray
DFS	disease-free survival
DOH	Department of Health
EBUS	endobronchial ultrasound
EBUS-TBNA	endobronchial ultrasound-guided transbronchial needle aspiration
EGFR	estimated glomerular filtration rate
ERE	Evidence Review Experts
ERS	European Respiratory Society
ESGE	European Society of Gastrointestinal Endoscopy
ESMO	European Society of Medical Oncology
ESTS	European Society of Thoracic Surgeons
EtD	Evidence to Decision
EUS	endoscopic ultrasound
EUS-FNA	endoscopic ultrasound-guided fine needle aspiration
FDG	fluorodeoxyglucose
FDG PET-CT	fluorodeoxyglucose positron emission tomography-computed tomography
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HR	hazard ratio
IASLC	International Association for the Study of Lung Cancer
ICER	incremental cost-effectiveness ratio
IHC	immunohistochemistry
LA	lymphadenectomy
LDCT	low-dose computed tomography scan
LNS	lymph node sampling
MDT	multidisciplinary team
MLND	mediastinal lymph node dissection
MnDCT	minimal-dose computed tomography
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence – UK
NOS	not otherwise specified

NS	not significant
NSCLC	non-small cell lung carcinoma
OS	overall survival
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PhilHealth	Philippine Health Insurance Corporation
PICO	Population-Intervention-Comparator-Outcome
QoL	quality of life
RCT	randomized clinical trial
RR	risk ratio
SC	Steering Committee
SCLC	small cell lung carcinoma
SCTS	Society for Cardiothoracic Surgery
Sn	sensitivity
Sp	specificity
SRS	stereotactic radiosurgery
TKI	tyrosine kinase inhibitor
TNM	TNM Classification of Malignant Tumors
VATS	video-assisted thoracoscopic surgery
WBRT	whole brain radiotherapy

EXECUTIVE SUMMARY

In the Philippines, lung cancer is the most common cancer in males and the fourth most common cancer in females. It continues to pose a huge burden on patients and the whole healthcare system and considerable variation in practices in management have been observed among clinicians and institutions. This lung cancer CPG aims to give recommendations on aspects of lung cancer diagnosis and management where significant variability and controversy in clinical practice is observed in the country. It does not aim to cover all aspects of the management of lung cancer. It is intended to be used by general physicians and specialists, other healthcare professionals, policymakers to improve lung cancer management. Its target beneficiaries are the patients with lung cancer, and indirectly the whole of society in the Philippines.

This guideline is based on the current best available evidence (literature search up until April 2021), local resources, infrastructure, and the practice context in the country. Guideline recommendations were developed following a standard guideline development methodology outlined in the DOH CPG Manual 2018. Separate working groups were formed. Existing evidence were comprehensively searched and reviewed to address ten key questions. A multi-sectoral panel of representatives and experts crafted consensus recommendations. The GRADE method was used to determine the direction and strength of each recommendation.

Twelve recommendations were developed out of 10 clinical questions and their corresponding evidence summaries (Table 1). Of these, a majority were conditional recommendations and were based on low to very low certainty of evidence. Further research will very likely have an important impact in our confidence regarding the estimates of the effect of each intervention or accuracy of the diagnostic tests included in this CPG.

Table 1. Summary of Final Recommendations, 2021 Philippine Clinical Practice Guidelines on the Diagnosis, Staging, and Management of Lung Carcinoma

No.	Recommendations	Certainty of Evidence	Strength of Recommendation
1A	We suggest against the use of adjuvant chemotherapy after complete surgical resection among Stage IB non-small cell lung cancer.	Low ⊕⊕◯◯	Conditional
1B	There is insufficient evidence to recommend the use of adjuvant tyrosine kinase inhibitors after complete surgical resection among Stage IB non-small cell lung cancer.	Very low ⊕◯◯◯	None
2	There is insufficient evidence to recommend the use of neoadjuvant over adjuvant chemotherapy among patients with non-metastatic, non-small cell lung cancer.	Very low ⊕◯◯◯	None
3	Among fit patients with unresectable stage IIIA-IIIC non-small cell lung cancer, we suggest the use of concurrent over sequential chemotherapy and radiotherapy.	Low ⊕⊕◯◯	Conditional
4	We suggest against the use of cranial irradiation in addition to standard of care versus standard of care alone among non-small cell lung cancer patients (i.e., with or without EGFR mutations) with asymptomatic brain metastases.	Low ⊕⊕◯◯	Conditional
5	There is insufficient evidence to recommend the use of low-dose CT scan instead of standard contrast-enhanced CT as surveillance imaging in non-small cell lung cancer patients receiving curative intent treatment.	Very low ⊕◯◯◯	None
6A	We suggest the use of either CT-guided biopsy or VATS with biopsy for diagnosing central lesions.	Low ⊕⊕◯◯	Conditional
6B	We suggest the use of either CT-guided biopsy or VATS with biopsy for diagnosing peripheral lesions.	Low ⊕⊕◯◯	Conditional
7	We suggest the use of limited panel of two IHC markers over >2 panel IHC markers in establishing the histologic subtype of non-small cell lung cancer.	Low ⊕⊕◯◯	Conditional
8	We suggest the use of PET-CT over CT-Scan in the detection of mediastinal lymph node involvement among patients with stage I to IIIA non-small cell lung cancer.	Low ⊕⊕◯◯	Conditional
9	We suggest concurrent diagnostic and staging evaluation of mediastinal lymph nodes among patients with lung cancer.	Low ⊕⊕◯◯	Conditional
10	We suggest the use of either mediastinal lymph node dissection or lymph node sampling following surgical resection among patients with resectable non-small cell lung carcinoma.	Low ⊕⊕◯◯	Conditional

Chapter 1. INTRODUCTION

Lung cancer is the most common cancer in males and the fourth most common cancer in females in the Philippines. It is the number one cause of cancer deaths in both sexes in 2020, locally and globally.[1] It is detected in asymptomatic or symptomatic individuals as a lung mass or nodule on imaging. Individuals with pulmonary nodules should be evaluated and managed by estimating the probability of malignancy, performing imaging tests to better characterize the lesions, evaluating the risks associated with various management alternatives, and eliciting their preferences for management.[6] The location of the lesion and the cost of testing should be taken into consideration when discussing approach and intervention. Diagnostic procedures, like the PET-CT, bronchoscopy, imaging-guided biopsy, are not available nationwide. For this reason, a double set-up is sometimes practiced wherein surgery and biopsy for definitive pathologic diagnosis are done together.

There are two major types of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for about 85% of cases and are further classified into squamous cell carcinoma, adenocarcinoma, and large-cell carcinomas. Histological examination is required for primary tumor classification while special immunohistochemical staining is done to further distinguish among the subtypes. When immunohistochemical staining is not available, the sign-out diagnosis of poorly differentiated cancer is given, which introduces some uncertainty in treatment planning.

Treatment is based on pathology, location, and rate of spread. The most common treatments for lung cancer are basic supportive care, surgery, chemotherapy, radiotherapy, and palliative care. Careful treatment planning for best possible outcome is desired. In complicated clinical situations, treatment planning through a multidisciplinary team (MDT) is ideal.

Most treatments like chemotherapy and radiotherapy aim to destroy the cancer but damage healthy tissue as well causing numerous unwanted effects. Novel targeted therapies that attack specific targets on/in the tumor destroy the cancer with limited damage to healthy cells. However, patients with cancer mutations who are eligible for these drugs need to be identified through biomarker or molecular testing. These treatments are costly and not widely available, thereby limiting their use.

Due to these many limitations, practices on the use of diagnostics, referral to subspecialists, and choice of treatment are expected to vary from institution to institution. Because there is not one lung cancer treatment that is right for everyone, a thorough discussion between doctors and the patient is important when choosing how to best approach each case. Standard of care plus guidance from CPG would help ensure that every lung cancer patient gets the best possible care available. In 2020, DOH commissioned the Rizal Medical Center in Pasig, Metro Manila to formulate an evidence-based CPG on lung cancer to standardize the approach on the diagnosis and treatment of this disease.

Objectives of the CPG

This lung cancer CPG aims to give recommendations on prioritized topics in lung cancer diagnosis and management in the Philippines based on the current best available evidence, resources and infrastructure, and the local practice context.

Target audience

This document is envisioned to assist physicians, patients, healthcare providers, and policymakers in their decision-making.

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Chapter 2. GUIDELINE DEVELOPMENT METHODOLOGY

This CPG followed the standard methodology described in the 2018 Manual for Clinical Practice Guideline Development[7] by the DOH.

Guideline preparation

Three major working committees were formed: (1) the Steering Committee (SC/Lead CPG Developer), (2) Evidence Review Experts (ERE), and (3) Consensus Panel (CP). The SC identified ten (10) priority clinical questions based on various criteria such as variation in practices, new evidence, potential impact on practice, cost of interventions, and others. The ERE, composed of clinical epidemiologists or evidence-based practitioners, independently reviewed existing CPGs, created evidence summaries, and drafted evidence-based recommendations. The CP was composed of ten (10) multi-sectoral representatives who reviewed the evidence summaries and voted on recommendations during the *en banc* meetings. CP members were nominated by their individual organizations and screened by the SC.

Funding and management of conflicts of interest

This CPG was funded by the DOH. Although the funding body did not influence the contents of the CPG, only ten questions could be covered within the allocated budget. The SC formulated the guideline questions but had no participation in the evidence syntheses, drafting of the recommendations, and voting on final recommendations during the consensus panel meetings. All individuals involved in these guidelines were required to disclose potential conflicts of interest that have existed in the past 4 years. The SC assessed the individual interests for the CP panelists and decided that there were no substantial conflicts of interest that may introduce bias in their decision making (Appendix 1).

Evidence synthesis

After guideline questions were finalized, a systematic search of relevant studies was undertaken by at least two evidence reviewers. Other high-quality (i.e., AGREE II score > 75) international CPGs relevant to lung cancer diagnosis and management were also reviewed and included in the evidence summaries. Evidence reviewers appraised the directness, methodological quality, results, and applicability of each of the included studies for each guideline question. Estimates of effect for each outcome were then derived and draft recommendations were formulated based on the evidence. The overall certainty (quality) of evidence and strength of recommendations were rated using the GRADE method (Grading of Recommendations, Assessment, Development, and Evaluations).[8]

Consensus panel meetings

Virtual CP meetings were conducted in two sessions (May 20 and May 25, 2021) lasting two to three hours using Zoom videoconferencing. Prior to the actual meetings, evidence summaries were sent to the CP members and an orientation regarding the CPG process and interpretation of the evidence was given by a guideline methodologist. Outcomes considered critical and important for decision-making by healthcare providers and consumers were identified by the CP through an online survey. During individual perusal of the evidence summaries, the CP members were asked to fill out an Evidence-to Decision (EtD) questionnaire. A methodologist facilitated both CP meetings. Key findings for each guideline question were presented by an evidence reviewer. Using a nominal group technique, CP members were given the opportunity to address any issues or clarifications related to the evidence and explain the rationale behind their votes. For this CPG, the CP unanimously voted that only critical outcomes were to be considered in formulating the final recommendations.

Generation of recommendations

CP members voted on the direction (for or against) and strength (strong or conditional) of final recommendation based on the certainty of the evidence, balance between benefits and harms, values, preferences, and burden on patients, cost and resource implications, equity, acceptability, and feasibility. To guide discussions related to these factors, GRADE EtD summary tables were presented. Consensus was achieved when 75% of the CP members agreed on a proposed recommendation or decision. If no consensus was reached after three rounds of voting, a Delphi process was done as coordinated by the SC. A standardized language was used to indicate the direction and strength of each recommendation (e.g., *suggest* for conditional, *recommend* for strong recommendations).

Certainty of the evidence and strength of the recommendations

A certainty level or quality rating was determined for the entire body of evidence evaluated for each research question. The certainty of evidence represents the degree of confidence that the estimates of the treatment effect or test accuracy lie close to the actual effects of interest. For questions that had varying levels of certainty across outcomes, the lowest quality among the outcomes rated as critical was considered the as the final certainty level. Evidence based on randomized controlled trials (RCTs) was initially assigned a “high” quality, while evidence from observational studies was given a “low” rating.

The initial ranking of RCTs was downgraded in case of serious risk of bias, inconsistency between studies, indirectness, imprecision, and publication bias. On the other hand, the ranking of observational studies was upgraded when there was a large and consistent effect, a dose-response relationship between the outcomes and degree of exposure, or plausible confounders that are expected to diminish the observed effect.

The strength of recommendations was classified as either strong or conditional. A *strong recommendation* was given when the consensus panel was confident that the desirable effects of the intervention or test outweigh its undesirable effects, or vice versa. A *conditional recommendation* was given when the panel was less certain about the trade-offs because of the absence of high-quality evidence, imprecise estimates of benefit or harm, limited applicability of the recommendations to certain populations or settings, or when the anticipated benefits come at a high cost.

Table 2. Certainty in the effect estimates (quality of evidence) in GRADE

Certainty	Definition and Implications	Randomized trials	Observational studies
HIGH ⊕⊕⊕⊕	The group is very confident that the true effect lies close to that of the estimate of the effect. (Further research is very unlikely to change confidence in the effect estimate)	No serious flaws in study quality	Extremely strong association and no major threats to validity
MODERATE ⊕⊕⊕◯	The group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. (Further research is likely to have an important impact)	Serious flaws in design or execution; quasi-experimental design	Strong consistent association and no plausible confounders
LOW ⊕⊕◯◯	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect. (Further research is very likely to have an important impact)	Very serious flaws in design or execution	No serious flaws in study quality
VERY LOW ⊕◯◯◯	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. (The estimate of effect is very uncertain)	Very serious flaws and at least one other serious threat to validity	Serious flaws in design and execution

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Chapter 3. EVIDENCE AND FINAL RECOMMENDATIONS

1. Among patients with Stage IB non-small cell lung cancer who underwent complete tumor resection, should we use adjuvant systemic therapy (i.e., chemotherapy or targeted therapy with tyrosine kinase inhibitors) versus no adjuvant systemic therapy to improve disease-free and overall survival?

A. We suggest against the use of adjuvant chemotherapy after complete surgical resection among Stage IB non-small cell lung cancer.

Strength of recommendation: Conditional
Certainty of evidence: Low

Remarks: *Systemic therapy may be considered for Stage IB NSCLC patients who underwent complete surgical resection and possess high-risk features such as poorly-differentiated histopathology or lymphovascular invasion. Complete surgical resection refers to anatomic lung resection with at least a lymph node sampling or mediastinal lymph node dissection.*

B. There is insufficient evidence to recommend the use of adjuvant tyrosine kinase inhibitors after complete surgical resection among Stage IB non-small cell lung cancer.

Strength of recommendation: None
Certainty of evidence: Very low

The role of adjuvant systemic therapy for early stage (Stage IB) NSCLC has been controversial with no consensus among expert groups. The American Society of Clinical Oncology (ASCO) Cancer Care Ontario Guideline[9] does not endorse its use. However, the National Comprehensive Cancer Network (NCCN) guidelines consider giving adjuvant chemotherapy for patients with high-risk features.[10]

EVIDENCE TO DECISION

Benefits and harms

This review included nine RCTs enrolling Stage IB patients given adjuvant systemic therapy versus no systemic therapy after complete tumor resection. Lung cancer staging was based on both TNM Staging 7th and 8th edition.

Pooled results from RCTs show that both adjuvant chemotherapy (5 RCTs[11–14]) and systemic tyrosine kinase inhibitors (TKIs) (4 RCTs[15–19]) did not significantly improve overall survival (OS) and disease-free survival (DFS) among patients diagnosed with Stage IB NSCLC. Adverse

events associated with adjuvant chemotherapy for patients with early-stage NSCLC appeared to be temporary. Symptoms were comparable to baseline status by 9 months, except for sensory neuropathy and hearing loss.[20]

For TKIs, no published studies reported adverse events among early-stage NSCLC, EGFR-positive patients who underwent complete resection. Important toxicities associated with inhibition of EGFR pathway include a characteristic rash, diarrhea, and rare interstitial pneumonitis.[21]

The panel assessed the net benefit to vary on a case-to-case basis.

Certainty of evidence

Overall certainty of evidence of studies on adjuvant systemic therapy was rated low due to indirectness and inconsistency. Overall certainty of evidence of studies on TKIs was rated very low due to serious indirectness, inconsistency, and imprecision.

Methodologic issues in the studies were the following: (1) none of the included studies with mixed-stage population had subgroup analysis for Stage IB, (2) high-risk features were not consistently defined across studies, (3) the definition of 'complete surgical resection' was varied, and (4) some patients in the included studies who were classified as Stage IB would be classified as Stage IIA based on the current TNM staging system.

Other considerations

Cost

Among Stage IB patients with high-risk features and stage II NSCLC, adjuvant chemotherapy was found to be more cost-effective than standard health care interventions with an incremental cost-effectiveness ratio (ICER) of $464.61/life year gained.[22] No published study was found on the cost-effectiveness of adjuvant tyrosine kinase inhibitors among early-stage NSCLC, EGFR positive patients who underwent complete resection.

Recommendations from other groups

The NCCN Guidelines Version 4 recommends adjuvant chemotherapy for patients with completely resected stage IB tumors using the 8th Edition TNM Staging Classification with high-risk features (e.g., lymphovascular invasion, poor differentiation, or high standardized uptake value on PET) and recommends observation for all other cases.[10] Currently, there are no recommendations available for use of systemic TKIs among patients with Stage IB NSCLC with EGFR mutations after complete resection.

CONSENSUS ISSUES

The panelists decided to keep the recommendation as conditional for adjuvant systemic therapy because of (1) the low certainty of evidence, (2) potential net benefit for patients with stage IB NSCLC with high-risk features, and (3) to allow for health insurance coverage for patients who prefer to undergo this treatment. Some panelists commented that in clinical practice, patients with high-risk features (e.g., poorly-differentiated histopathology, lymphovascular invasion) are often advised adjuvant systemic therapy and some benefit from it. The following are some actionable issues that were mentioned:

a. The lack of a national cancer registry and an interoperable hospital information system which may help to determine the cost and cost-effectiveness of treatment
b. Lack of cost-effectiveness studies
c. Huge costs associated with treatment (surgery, chemotherapy)
d. The non-monetary cost of prolonged morbidity and loss of life
e. Lack of specialists in some regions of the country who are knowledgeable in the use of adjuvant therapy post-resection

For TKIs, the panelists decided not to make any recommendation for or against its use due to insufficient evidence.

GRADE EVIDENCE PROFILE

P Stage IB NSCLC with complete tumor resection
I Adjuvant systemic therapy (chemotherapy or targeted therapy with TKIs)
C No adjuvant systemic therapy
O OS, DFS

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		Treatment	Control	Relative (95% CI)	Absolute (95% CI)		
Adjuvant chemotherapy versus observation							
5-year OS	5	347/538 (64.5%)	330/539 (61.2%)	**RR 1.04** (0.96, 1.14)	**24 more per 1,000** (from 24 fewer to 86 more)	NS	MODERATE ⊕⊕⊕◯
5-year DFS	3	216/372 (58.1%)	177/375 (47.2%)	**RR 1.37** (0.94, 2.00)	**175 more per 1,000** (from 28 fewer to 472 more)	Trend towards observation (NS)	LOW ⊕⊕◯◯
Tyrosine kinase inhibitors versus observation							
5-year OS	2	-/0	-/0	**HR 1.22** (0.94, 1.58)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	Trend towards standard of care (NS)	MODERATE ⊕⊕⊕◯
5-year DFS	4	-/0	-/0	**HR 0.46** (0.16 to 1.30)	**0 fewer per 1,000** (from 1 fewer to 0 fewer)	Trend towards EGFR-TKI (NS)	VERY LOW ⊕◯◯◯
5-year DFS (subgroup analysis for Stage IB)	2	-/0	-/0	**HR 0.66** (0.27, 1.62)	**0 fewer per 1,000** (from 1 fewer to 0 fewer)	Trend towards EGFR-TKI (NS)	VERY LOW ⊕◯◯◯

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2. Among patients with non-metastatic non-small cell lung cancer, should we use neoadjuvant systemic therapy versus systemic adjuvant therapy to improve disease-free and overall survival?

There is insufficient evidence to recommend the use of neoadjuvant over adjuvant chemotherapy among patients with non-metastatic, non-small cell lung cancer.

Strength of recommendation: None
Certainty of evidence: Very low

Adjuvant or post-operative chemotherapy is the standard treatment used to improve cure rates for patients with completely resected Stage II to III disease. Chemotherapy should be initiated up to 8 weeks after surgery, but the time taken for surgical recovery may cause delay.[23] Compliance due to chemotherapy-related toxicity is also an issue of concern.[23]

Neoadjuvant chemotherapy, on the other hand, is given pre-operatively with the same intent.[24] The potential benefits of neoadjuvant chemotherapy include improved compliance, decreased likelihood of micrometastasis, and a reduced tumor size and improved operability.[24,25] However, it can cause delays in surgery, unnecessary pre-operative toxicity, and reduce tumor resectability.[25]

EVIDENCE TO DECISION

Benefits and harms

Only 1 RCT[26] evaluated DFS and OS for patients receiving both neoadjuvant systemic therapy followed by surgery and surgery followed by systemic adjuvant therapy. This study included 624 patients who were at stage IA with tumor size >2 cm, IB, II or T3N1 NSCLC. Post-hoc analysis showed no significant difference between the two interventions in terms of improving DFS and OS. Both the neoadjuvant and adjuvant chemotherapy treatments were well-tolerated. Some of the common adverse events reported were anemia, neutropenia, and fatigue. Incidence of Grade 3 or higher adverse events was similar in both treatment arms.

Certainty of evidence

Certainty of evidence is very low due to serious imprecision and very serious risk of bias resulting from allocation concealment and attrition bias.

Other considerations

Recommendations from other groups

The NCCN Guidelines recommend administration of adjuvant chemotherapy following surgery for Stage IIA (T2b, N0) to Stage IIIB (T2-4N0-1) NSCLC. Induction chemotherapy prior to surgical resection was recommended for Stage III (N2, M0) NSCLC. The preferred systemic therapy regimen consisted of cisplatin and pemetrexed for non-squamous lesions, and cisplatin and gemcitabine or cisplatin and docetaxel for squamous lesions. The carboplatin and paclitaxel regimen is only recommended for patients who are not able to tolerate cisplatin.[27]

The 2013 American College of Chest Physicians (ACCP) guidelines for treatment of clinical Stage III NSCLC stated that neoadjuvant therapy followed by surgery is neither clearly better nor clearly worse than definitive chemoradiation.[28] Moreover, for patients with completely resected pathologic stage IA and IB NSCLC, it is recommended that post-operative chemotherapy not be used. Adjuvant platinum-based chemotherapy is recommended for patients with completely resected Stage II A,B (N1) and good performance status.[29]

The European Society of Medical Oncology (ESMO) 2015 recommends adjuvant therapy for early and locally advanced stages II–III NSCLC with consideration of adjuvant therapy in those with Stage IB but with tumor sizes above 4 cm.[30]

CONSENSUS ISSUES

Due to the very low certainty and the limited number of studies found, the panel decided not to make any definitive recommendation for or against neoadjuvant systemic therapy. Clinicians should consider individual patient circumstances, availability of chemotherapeutic drugs, and the high costs prior to recommending pre- or post-operative chemotherapy for patients with non-metastatic NSCLC. The following ideas formed part of the discussion:

a. If for some reason surgery cannot be performed immediately, neoadjuvant chemotherapy may be considered.
b. Ideally, management is discussed in a multidisciplinary conference with the patient and family.
c. In a real-life setting, the cost of interventions, from diagnosis to recovery, is a large out-of-pocket expense and quite substantial for an average Filipino. Currently, both neoadjuvant and adjuvant chemotherapy are not covered by PhilHealth. These should be covered by the National Integrated Cancer Control Act (Republic Act 11215) and PhilHealth should expand its benefit packages to include chemotherapy for lung cancer.
d. Equal implementation in all regions of the Philippines will definitely improve equity.
e. With education and information dissemination among the stakeholders, these treatments should be readily acceptable as long as properly funded and accessible.

GRADE EVIDENCE PROFILE

P Non-metastatic NSCLC
I Neoadjuvant systemic therapy
C Systemic adjuvant therapy
O OS, DFS

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		Neoadjuvant systemic therapy	Adjuvant systemic therapy	Relative (95% CI)	Absolute (95% CI)		
5-year OS	1	117/199 (58.8%)	125/210 (59.5%)	**RR 0.99** (0.84, 1.16)	**8 more per 1,000** (from 95 fewer to 96 more)	NS	VERY LOW ⊕◯◯◯
5-year DFS	1	99/199 (49.7%)	102/210 (48.6%)	**RR 1.02** (0.84, 1.25)	**12 more per 1,000** (from 77 fewer to 120 more)	NS	VERY LOW ⊕◯◯◯

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3. Among patients with inoperable non-metastatic lung cancer (bulky Stage IIIA, B and C), should we use concurrent versus sequential systemic and radiation therapy to improve overall and progression-free survival?

Among fit patients with unresectable stage IIIA–IIIC non-small cell lung cancer, we suggest the use of concurrent over sequential chemotherapy and radiotherapy.

Strength of recommendation: Conditional
Certainty of evidence: Low

Remark: *Fit patients refer to young individuals with stable comorbidities and good functional status.*

Adding chemotherapy to radiotherapy in the treatment of unresectable stage III NSCLC has been found to increase median OS with common adverse events such as neutropenia, thrombocytopenia, and esophagitis.[31–33] Although both chemotherapy and radiotherapy confer a survival advantage, the optimal timing of chemotherapy and radiotherapy remains controversial.[33] Determining the optimal sequence for these patients may guide the clinician in choosing the appropriate treatment regimen for their patients.

EVIDENCE TO DECISION

Benefits and harms

Six RCTs[34–39] compared concurrent chemoradiotherapy (CRT) and sequential chemoradiotherapy for Stage IIIA–IIIB NSCLC. There was improved OS but no improvement in progression-free survival (PFS) with the use of concurrent CRT compared to the sequential CRT regimen.

Adverse events in both arms included pneumonitis, esophagitis, neutropenia, and mortality. A Cochrane meta-analysis conducted in 2010 also showed no differences in terms of treatment-related deaths, acute pneumonitis, neutropenia and anemia.[40] However, there were less cases of acute esophagitis for the sequential arm.[40] Another meta-analysis showed that concurrent chemoradiotherapy was associated with increased risk of grade 3 adverse events, such as esophagitis, nausea and vomiting, as well as reduced leukocyte and platelet counts.[41]

Considering the balance of benefit and risk, the panel believed that there is net benefit with CRT.

Certainty of evidence

Overall certainty of evidence of the included studies is low due to imprecision and risk of bias issues related to randomization and allocation concealment.

Other considerations

Cost

An economic analysis performed on 173 patients showed an average total cost per patient of €16,074 (₱929,858) in the sequential arm, and €15,245 (₱881,901) in the concurrent arm (*P*=0.15). Despite longer hospitalization due to toxicity, cost-minimization analysis favored the concurrent arm.[42]

Recommendations from other groups

The NCCN Guidelines state that concurrent CRT is more effective than sequential CRT for stage IIIA–IIIB NSCLC.[43] However, this comes at the expense of higher grade III–IV esophagitis. Sequential CRT may be administered to frail patients who may not tolerate the side effects of concurrent CRT.

The ESMO recommends concurrent CRT as the preferred option among fit patients due to the five-year survival advantage at the cost of higher rates of esophagitis. The 10% increase in early mortality for patients in the concurrent arm is also a concern for its use.[44–46] ESMO recommends the sequential approach for elderly patients and those with comorbidities.[45,46]

CONSENSUS ISSUES

The costs of concurrent CRT in local settings may be substantial for an average Filipino. Current management protocols in specialist lung care centers already use this concurrent CRT and reserve sequential CRT for patients who cannot tolerate the adverse effects of the former. As such, concurrent CRT may be feasible to implement and acceptable to key stakeholders provided that radiation facilities are made widely available and as long as it is covered by social health insurance.

GRADE EVIDENCE PROFILE

P Inoperable NSCLC (bulky Stage IIIA, B, C)
I Concurrent systemic and radiation therapy
C Sequential systemic and radiation therapy
O OS, PFS

Outcomes	Studies	Relative Effect (95% CI)	Interpretation	Certainty of evidence
OS	6	**HR 0.81** (0.71, 0.92)	Benefit for concurrent chemoradiotherapy	MODERATE ⊕⊕⊕◯
PFS	4	**HR 0.87** (0.74, 1.02)	No significant difference	LOW ⊕⊕◯◯

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4. Among non-small cell lung cancer patients (i.e., with or without EGFR mutations) with asymptomatic brain metastases, should we use cranial irradiation in addition to standard of care versus standard of care alone to improve quality of life and progression-free survival?

We suggest against the use of cranial irradiation in addition to standard of care versus standard of care alone among non-small cell lung cancer patients (i.e., with or without EGFR mutations) with asymptomatic brain metastases.

Strength of recommendation: Conditional
Certainty of evidence: Low

Approximately 30% of patients with lung cancer develop brain metastasis at some point during their illness, with silent brain metastasis occurring in 12%–18% of patients at the time of initial presentation.[47] The presence of brain metastases impacts quality and length of survival. The mainstay of treatment for brain metastases has been corticosteroids, antiepileptic medication, whole brain radiotherapy (WBRT), radiosurgery, and surgery provided alone or in combination.[48]

WBRT has long been used as treatment for brain metastases; however, it is limited by its long-term side effects. Several studies have shown a significant decline in neurocognitive function among patients receiving WBRT, particularly in the areas of memory and learning.[49,50] Stereotactic radiosurgery (SRS) is less invasive, involving delivery of high dose of radiation, which allows for precise tumor targeting while minimizing the irradiation to the adjacent normal tissue.[47]

EVIDENCE TO DECISION

Benefits and harms

Three RCTs[47,51,52] investigated the effect of cranial irradiation on the quality of life (QoL) and PFS of patients with NSCLC with asymptomatic brain metastases. The addition of cranial irradiation either in the form of stereotactic radiosurgery (SRS) or whole brain radiotherapy (WBRT) to standard of care did not confer a significant survival advantage in terms of extracranial PFS and overall PFS for the treatment of asymptomatic brain metastasis. One study showed significant greater deterioration in QoL parameters (i.e., global health status, physical and cognitive functions) when upfront WBRT was used versus upfront chemotherapy.[52] The panel weighed the net benefit to be with standard of care alone over the addition of cranial irradiation to standard of care.

Certainty of evidence

The certainty of evidence is low due to serious risk of bias, indirectness, and imprecision.

Other considerations

Cost

Cost-effectiveness analysis showed that chemotherapy using icotinib was more cost-effective compared to WBRT-chemotherapy for overall PFS and intracranial PFS.[53]

Recommendations from other groups

The 2012 American Society of Radiation Oncology (ASTRO) guideline suggests SRS without WBRT for patients with up to 4 brain metastases in solid cancer irrespective of cranial symptoms.[54] The 2014 ESMO Consensus Conference on Lung Cancer recommends that treatment with an EGFR TKI may be considered for patients with EGFR-mutated NSCLC and with brain metastases.[55] Radiotherapy can safely be given concomitantly to EGFR TKI.[56]

The 2020 National Comprehensive Cancer Network (NCCN) recommends SRS over surgery for patients with small, asymptomatic lesions that do not require surgery and for patients with lesions that are not surgically accessible.[55] The optimal treatment strategy of brain metastases for patients with a poor prognosis is highly individualized and may call for best supportive care, WBRT, SRS, or trials of CNS-active systemic agents depending on the clinical scenarios. In NSCLC patients with EGFR mutations and brain metastasis, upfront systemic therapy alone may be considered in carefully selected, asymptomatic patients.[55]

CONSENSUS ISSUES

The preservation of QoL among patients with metastatic NSCLC is quite important to most patients. Thus, treatment (cranial RT) for asymptomatic brain metastasis that does not offer survival benefit but reduces QoL was deemed difficult to justify. Cranial irradiation was also said to be quite expensive. This recommendation also reflects current practice in the country, making it highly acceptable to all stakeholders and feasible to implement.

GRADE EVIDENCE PROFILE

P NSCLC patients with asymptomatic brain metastases
I Cranial irradiation in addition to standard of care
C Standard of care alone
O QoL, PFS

Outcome	Studies	Effect	Certainty of evidence
Extracranial PFS	1 (n=98)	median extracranial PFS was comparable at 5.4 months for both treatment groups (P=0.824)	MODERATE ⊕⊕⊕◯
Overall PFS	2 RCT (n=196)	No statistically significant differences in PFS between the primary chemotherapy arm (3.6 months) vs WBRT-first arm (4.4 months); log-rank P= 0.62] Icotinib associated with longer PFS compared to WBRT and chemotherapy (median 6.8 vs 3.4 months, respectively; HR 0.44, 95% CI 0.31–0.63, P < 0.0001)	MODERATE ⊕⊕⊕◯
QoL	1 RCT (n=48)	After WBRT, global health status was found to be statistically significantly impaired with decreased mean score of 48 from 65. Physical and cognitive function were also more impaired for WBRT.	LOW ⊕⊕◯◯
Brain functional outcome/ cognitive function	2 RCT (n=256)	No statistically significant differences in the neurocognitive function score between the two treatment groups [MoCA-K (p=0.9932), K-IADL (p=0.4252), Barthel ADL scores (p=0.9657), K-MMSE (p=0.3798) and MMSE (p=0·663)]	LOW ⊕⊕◯◯
Toxicity Profile/ Adverse Effect	2 RCT (n=206)	Grade 3 or 4 neutropenia occurred more frequently in the WBRT-first arm compared to the primary chemotherapy arm (79% vs 40%; P = .014) Adverse events of grade 3 or worse were reportedly more common in patients treated with WBRT and chemotherapy versus patients treated with icotinib (38% versus 8%)	LOW ⊕⊕◯◯
Cost-Effectiveness Analysis	1 RCT	CEA for overall PFS also showed more benefit with icotinib over WBRT-chemotherapy • ICER $13,484.21/QALY • ACER: $36,562.63/QALY • net benefit: –$9,836.41.7	LOW ⊕⊕◯◯

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5. Among patients who have completed definitive cancer treatment (i.e., surgery or chemotherapy & radiotherapy), should we do surveillance imaging using CT scan with IV contrast compared with low-dose CT scan to improve overall survival?

There is insufficient evidence to recommend the use of low-dose CT scan instead of standard contrast-enhanced CT as surveillance imaging in non-small cell lung cancer patients receiving curative intent treatment.

Strength of recommendation: None
Certainty of evidence: Very low

Follow-up and surveillance of patients with lung cancer receiving definitive treatment is usually through contrast-enhanced standard dose CT scan (CECT). It allows detection of lung nodules and parahilar and mediastinal nodes,[58] but introduces additional risks from repetitive exposure to radiation and dye. Non-enhanced low-dose CT scan (LDCT) for lung cancer screening has been shown to prolong survival and the possibility of using it for surveillance was explored. [57]

EVIDENCE TO DECISION

Benefits and harms

No RCT was found directly comparing LDCT versus CECT as surveillance imaging modality for patients with NSCLC who have received curative-intent treatment. There was also no published study on the safety and cost-effectiveness outcomes of LDCT compared to CECT.

One prospective cohort study involving NSCLC patients who underwent complete surgical resection showed better OS for either CT or PET scan compared to clinical examination with carcinoembryonic antigen determination (CEA) and CXR every 3 months.[59] In this study, CECT and LDCT were used sequentially (CECT every 6 months for 2 years then LDCT annually) thus a comparison of the two CT modalities is not possible. Another cohort study showed that minimal-dose CT (MnDCT) is superior to CXR in terms of detecting asymptomatic recurrence, which translated to increased survival among patients who received 2nd curative intent treatment.[60] The panel assessed net benefit with the use of CECT.

Certainty of evidence

The overall certainty of evidence provided by these two studies was rated very low due to concerns related to serious indirectness and risk of bias.

Other considerations

Cost

There was no cost-effectiveness study for CECT versus LDCT in the follow-up of lung cancer patients undergoing curative intent treatment. In government hospitals (National Kidney and Transplant Institute and Philippine Heart Center), the costs of LDCT and CECT are around ₱6,000 and ₱8,500, respectively. In private hospitals (St Luke's Medical Center and The Medical City), the procedures cost around ₱11,000 and ₱13,000 for LDCT and CECT, respectively.

Recommendations from other groups

For patients with NSCLC and SCLC receiving curative intent or definitive treatment, the 2020 ASCO and 2017 ESMO both recommend the use of chest CT scan (preferably with contrast) every 6 months until 2 years, then a low-dose non-contrast CT scan yearly thereafter.[61,62] On the other hand, the NCCN (NCCN NSCLC Guidelines version 4.2021,[63] and NCCN SCLC Guidelines Ver 3.2021[64]) recommend chest CT scan with or without contrast every 3–6 months for the first 2 years followed by an annual LDCT scan. The recommendations from these three groups were all based on low quality evidence.

CONSENSUS ISSUES

The panel agreed that recurrence of primary lung cancer after completed definitive treatment is part of natural course of the disease and surveillance is important. Current evidence was deemed insufficient for LDCT to replace CECT as the imaging of choice for this purpose. As this is a non-contrast study, LDCT could miss lymph nodes and the lower radiation dose used makes characterization of suspected pulmonary nodules less accurate. Missing on these lesions would mean delay in investigation and treatment, especially if the recurrence is still resectable. LDCT is also not widely available in the country.

Whether LD or CECT is used, the cost of repeated imaging over a period of years is considered quite costly to the common Filipino. This may negatively impact feasibility of its implementation. Equity may be a significant issue as CT equipment as well as experts who interpret these tests may not always be available across the country or accessible to disadvantaged groups.

GRADE EVIDENCE PROFILE

P Patients who completed definitive cancer treatment
I CT scan with IV contrast / contrast-enhanced CT
C Low-dose CT
O OS

	Outcomes	Basis	Effect Estimate (95% CI)	Interpretation	Certainty of evidence
OS	CXR q3 months for 2 years then q6 months	1 (n=358)	2.1±1.5 yrs (1.51, 2.69)	Increased OS with the use of Chest CT scan or PET/CT scan vs. CXR (3.6 ± 1.5 years vs. 2.1 ± 5 years, *p* < 0.002)	VERY LOW ⊕◯◯◯
	CECT q6 months for 2 years then annual LDCT		3.3±1.7 yrs (2.71, 3.89)		
	PET/CT annually		3.8±1.4 yrs (3.41, 4.19)		
	CXR	1 (n=271)	Sn=21.2% (11.1, 34.7%)	MnDCT increased detection rates of asymptomatic disease who are candidates of a 2nd curative intent treatment leading to increased survival (65 vs. 25 months, P<0.001)	VERY LOW ⊕◯◯◯
	MnDCT		Sn=94.2% (84.1, 98.8%)		

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6. Among patients with pulmonary mass for biopsy, should we use CT-guided aspiration biopsy versus video-assisted thoracic surgery with biopsy in diagnosing cancer for both central and peripheral lesions?

A. We suggest the use of either CT-guided aspiration biopsy or video-assisted thoracic surgery with biopsy for diagnosing central lesions.

B. We suggest the use of either CT-guided aspiration biopsy or video-assisted thoracic surgery with biopsy for diagnosing peripheral lesions.

Strength of recommendation: Conditional
Certainty of evidence: Low

Remarks: *Separate recommendations were made for central and peripheral lesions since CT-GAB and VATS with biopsy have different indications.*

CT-guided biopsy (CT-GAB) is a common and relatively less invasive method of acquiring a tissue diagnosis for pulmonary masses compared to video-assisted thoracic surgery (VATS) with biopsy. However, the latter is preferred for patients with high risk of malignancy, or patients with an intermediate risk and with a non-diagnostic or suspicious biopsy result.[65] Both procedures have been shown to have high diagnostic accuracy.

EVIDENCE TO DECISION

Benefits and harms

There was no study that directly compared CT-GAB and VATS with biopsy. Thirty-two diagnostic studies on the use of CT-GAB for the diagnosis of lung masses were found,[66–97] while there were 9 diagnostic studies that tackled the use of VATS with biopsy for the same purpose.[98–106] In the diagnosis of lung masses (both central and peripheral lesions), CT-GAB had a similar diagnostic accuracy (i.e., overall diagnostic yield, sensitivity, specificity, diagnostic yield, likelihood ratios) with VATS. In the sole study that distinguished between central and peripheral lesions, the diagnostic yield was also found to be similar.[66]

Pneumothorax was reported among patients who underwent CT-GAB, with incidence ranging from 5.6% to 51.8% across 31 studies.[66–88, 90–97] Alveolar hemorrhage was also noted in 1% to 62.1% of patients from 27 studies. Likewise, patients subject to VATS with biopsy may experience intraoperative and post-operative complications such as bleeding, air leakage, hemothorax, chylothorax, atrial fibrillation, asthma, pneumonia, pneumonia and hypoxia.[98–106]
Most of the panel members believed that the balance between benefit and harm with the use of either diagnostic procedure will vary on a case-to-case basis.

Certainty of evidence

The overall certainty of evidence is low due to indirectness and serious risk of bias.

Other considerations

Cost

In private institutions in the Philippines, the typical cost of CT-GAB of lung masses is approximately ₱70,000, while VATS with biopsy costs around ₱250,000–₱300,000. Costs for both procedures are lower in the public setting.

Recommendations from other groups

The British Thoracic Society (BTS) guidelines[107] on the investigation and management of pulmonary nodules stated that percutaneous lung biopsy may be offered if the result will alter treatment plan (Grade C). In 2013, the ACCP[108] included transthoracic needle aspiration (usually CT-guided) as part of the work-up, especially for peripheral lesions.

CONSENSUS ISSUES

The panel decided to make separate recommendations for central and peripheral lesions as CT-GAB and VATS with biopsy have different indications for use and are not often compared with each other. Either method may be used for the diagnosis of lung cancer, but many variables can affect the choice of diagnostic method: lesion size (i.e., <1 cm or >1 cm), lesion location, presence of mediastinal lymph nodes or distant metastasis, patient characteristics, local availability of specialists and equipment, expertise, adequacy of tissue sample, invasiveness of the procedure, and cost.

It was pointed out that not all peripherally-located lesions may be sampled using CT-GAB (e.g., peri-diaphragmatic or sitting on fissures). Each lesion must be evaluated on a case-to-case basis. The choice of method to use for peripheral lesions should be determined by the interventional radiologist who will perform the biopsy. It was suggested that a multidisciplinary team be involved in the diagnosis of lung cancer.

When considering cost and availability alone, CT-GAB was favored over VATS with biopsy. It was considered acceptable to key stakeholders, and would be feasible to implement in urban centers. However, inequity is highly possible whichever biopsy procedure is used because of high cost and unavailability of equipment and expertise in many places in the Philippines.

GRADE EVIDENCE PROFILE

P Patients with pulmonary mass for biopsy
I CT-GAB, VATS with biopsy
C Surgery with histopathology; clinical course and follow-up; histology of another primary mass in another site; other non-histopathology work-up
O Diagnosing lung cancer for both central and peripheral lesions (diagnostic yield, sensitivity, specificity, likelihood ratios)

Method	No. of Studies	Sn (95% CI)	Sp (95% CI)	LR+ (95% CI)	LR- (95% CI)	Certainty of evidence
CT-GAB	28 (8,146 samples)	0.93 (0.92, 0.94)	0.99 (0.97, 1.00)	87 (27, 282)	0.07 (0.06, 0.08)	Low
VATS with biopsy	6 (507 patients)	0.95 (0.93, 0.97)	0.96 (0.92, 0.98)	26.1 (11.9, 57.2)	0.05 (0.03, 0.08)	Low

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7. Among patients diagnosed with lung cancer but with uncertain histology on biopsy, should we use two-panel immunohistochemistry [adenocarcinoma marker (TTF1 or Napsin A) and a squamous cell marker (p40 or p63)] versus higher panel immunohistochemistry [both adenocarcinoma markers (TTF1 and Napsin A) and other markers like p63, synaptophysin, chromogranin and CK5/6] in establishing the histology of the lung cancer?

We suggest the use of limited panel of two IHC markers over higher panel IHC markers in establishing the histologic subtype of non-small cell lung cancer.

Strength of recommendation: Conditional
Certainty of evidence: Low

Knowledge of definite histology of lung cancer is crucial for appropriate choice of definitive treatment. Immunohistochemistry (IHC) study is done when the morphologic features do not clearly point to a particular subtype, often encountered in small tissue specimens and cytologic samples.[109] Two or more IHC markers are used; at least one for adenocarcinoma and at least one for squamous cell carcinoma. Neuroendocrine markers are used only when there is neuroendocrine differentiation observed on histologic evaluation.[110] As the amount of tissue available for testing is limited, and testing for driver mutations and/or PD-L1 may be needed, it is important to determine if there is diagnostic advantage of higher panel over two panel IHC.

EVIDENCE TO DECISION

Benefits and harms

Compared to panels with only two IHC markers, panels with more than two IHC markers did not demonstrate superior sensitivity or specificity in establishing the histologic subtype of NSCLC, including specimens with poorly differentiated or not otherwise specified (NOS) histology.[111–127] Most of the panel members assessed net benefit with the use of two-panel IHC test.

Certainty of evidence

The overall certainty of evidence for diagnostic accuracy is low. Most of the studies had moderate risk of bias due to uncertainties in the process of patient selection and in the use of pre-specified thresholds for the index tests. Majority of the included studies also had a moderate to high concern for indirectness due to differences in patient population.

Other considerations

Cost

A two-stain IHC strategy may offer a cost-saving benefit (₱2,000–₱3,000 per additional stain and ₱300 per stain as reader's fee, based on current rates obtained from Philippine General Hospital). It also allows for conservation of tumor tissue for other molecular tests that are used to guide therapy. For some patients, it may avoid the need for a re-biopsy, and its attendant cost and risk of complications.

Recommendations from other groups

The International Association for the Study of Lung Cancer (IASLC) recommends the use of a limited panel consisting of p40 and TTF-1 for the subtyping of NSCLC.[110] While the choice and number of markers ultimately depends on clinical findings and the probability for a specific histologic type, majority of cases do not require more than two markers. They cite the higher sensitivity and AUC of TTF-1 compared to Napsin A for the diagnosis of adenocarcinoma.[115] On the other hand, p40 has been demonstrated to be more specific than p63 for squamous cell carcinoma, with similar sensitivity.[124] CD56, synaptophysin and chromogranin are recommended only when morphologic features that suggest neuroendocrine differentiation are identified.[110]

CONSENSUS ISSUES

The panel favored the two-panel IHC markers because higher panels did not seem to have higher diagnostic advantage and were more costly. The lower cost of two-panel test also led the panel to conclude that this may be more acceptable to the stakeholders, are more feasible to implement, and would lead to less inequity.

GRADE EVIDENCE PROFILE

P Patients diagnosed with lung cancer but with uncertain histology on biopsy
I Two-panel IHC marker
C Higher panel IHC marker
O Establish histology

	IHC panel	No. of studies	Sn (95% CI)	Sp (95% CI)	LR+ (95% CI)	LR- (95% CI)	Certainty of Evidence (Sn)	Certainty of Evidence (Sp)
General	*Two markers*							
	Napsin A, CK5/6	3 (n=914)	0.86 (0.70,0.94)	0.64 (0.44,0.79)	2.36 (1.49,3.74)	0.23 (0.12,0.44)	Low	Low
	Napsin A, p40	3 (n=912)	0.91 (0.88,0.93)	0.61 (0.40,0.79)	2.33 (1.39,3.90)	0.15 (0.11,0.22)	High	Moderate
	Napsin A, p63	2 (n=650)	0.88 (0.79,0.94)	0.61 (0.38,0.81)	2.29 (1.33,3.96)	0.19 (0.11,0.32)	Moderate	Low
	TTF-1, CK5/6	5 (n=1,056)	0.99 (0.90,1.00)	0.14 (0.04,0.38)	1.15 (0.97,1.37)	0.05 (0.01,0.39)	Moderate	Low
	TTF-1, p40	2 (n=832)	0.93 (0.91,0.95)	0.44 (0.19,0.73)	1.67 (0.98,2.85)	0.16 (0.08,0.32)	High	Moderate
	TTF-1, p63	7 (n=1,215)	0.88 (0.81,0.92)	0.46 (0.29,0.63)	1.61 (1.22,2.14)	0.27 (0.20,0.37)	High	Low
	More than two markers							
	TTF-1, 34bE12, CK5/6, p63, S100A7	1 (n=44)	0.88 (0.73,0.95)	0.30 (0.11,0.60)	1.26 (0.82,2.37)	0.40 (0.08,2.45)	Low	Low
	TTF-1, CK5/6, CK7, p63	2 (n=155)	0.98 (0.06,1.00)	0.60 (0.32,0.84)	2.45 (0,13323.80)	0.04 (0,191.67)	Low	Low
	TTF-1, CK5/6, p63	1 (n=82)	0.74 (0.63,0.83)	0.88 (0.53,0.98)	6.17 (1.34,41.5)	0.30 (0.17,0.70)	Low	Low
	Napsin A, CK5/6, p63	1 (n=82)	0.82 (0.72,0.90)	0.75 (0.35,0.97)	3.28 (1.11,30.00)	0.24 (0.10,0.80)	Low	Low
	TTF-1, Napsin A, CK5/6, p63	2 (n=119)	0.87 (0.79,0.92)	0.77 (0.48,0.92)	3.76 (1.39,10.18)	0.17 (0.10,0.30)	Moderate	Low
	TTF-1, Napsin A, CK5/6	1 (n=82)	0.68 (0.56,0.78)	0.75 (0.35,0.97)	2.72 (0.86,26)	0.43 (0.23,1.26)	Low	Low
	TTF-1, Napsin A, CK5/6, p40	1 (n=568)	0.94 (0.92,0.96)	0.30 (0.20,0.42)	1.34 (1.15,1.66)	0.20 (0.10,0.40)	High	Low
	TTF-1, Napsin A, p63	1 (n=82)	0.84 (0.73,0.91)	0.75 (0.35,0.97)	3.36 (1.12,30.33)	0.21 (0.09,0.77)	Low	Low
poorly differentiated NSCLC or NOS	*Two markers*							
	Napsin A, CK5/6	1 (n=82)	0.65 (0.53,0.76)	0.75 (0.35,0.97)	2.60 (0.82,25.33)	0.47 (0.25,1.34)	Moderate	Low
	Napsin A, p63	1 (n=82)	0.81 (0.70,0.89)	0.75 (0.35,0.97)	3.24 (1.08,29.67)	0.25 (0.11,0.86)	Moderate	Low
	TTF-1, CK5/6	2 (n=176)	0.68 (0.52,0.81)	0.75 (0.27,0.96)	2.67 (0.63,11.39)	0.43 (0.26,0.71)	Low	Low
	TTF-1, p63	2 (n=176)	0.78 (0.70,0.85)	0.78 (0.35,0.96)	3.49 (0.84,14.47)	0.28 (0.17,0.45)	Moderate	Low
	More than two markers							
	TTF-1, 34bE12, CK5/6, p63, S100A7	1 (n=44)	0.88 (0.73,0.97)	0.30 (0.07,0.65)	1.26 (0.78,2.77)	0.40 (0.05,3.86)	Moderate	Low
	TTF-1, CK5/6, CK7, p63	1 (n=103)	0.66 (0.55,0.76)	0.60 (0.32,0.84)	1.65 (0.81,4.75)	0.57 (0.29,1.41)	Moderate	Low
	TTF-1, CK5/6, p63	1 (n=82)	0.74 (0.63,0.84)	0.88 (0.47,1.00)	6.17 (1.19,84.00)	0.30 (0.16,0.79)	Moderate	Low
	Napsin A, CK5/6, p63	1 (n=82)	0.82 (0.72,0.90)	0.75 (0.35,0.97)	3.28 (1.11,30.00)	0.24 (0.10,0.80)	Moderate	Low
	TTF-1, Napsin A, CK5/6, p63	2 (n=119)	0.87 (0.79,0.92)	0.77 (0.48,0.92)	3.76 (1.39,10.18)	0.17 (0.10,0.30)	Moderate	Low
	TTF-1, Napsin A, CK5/6	1 (n=82)	0.68 (0.56,0.78)	0.75 (0.35,0.97)	2.72 (0.86,26.00)	0.43 (0.23,1.26)	Moderate	Low
	TTF-1, Napsin A, p63	1 (n=82)	0.84 (0.73,0.91)	0.75 (0.35,0.97)	3.36 (1.12.30.33)	0.21 (0.09,0.77)	Moderate	Low

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8. Among patients with clinical Stage I to non-bulky IIIA non-small cell lung cancer, should we do CT scan versus PET-CT scan in determining mediastinal lymph node involvement?

We suggest the use of PET-CT over CT-Scan in the detection of mediastinal lymph node involvement among patients with stage I to IIIA non-small cell lung cancer.

Strength of recommendation: Conditional
Certainty of evidence: Low

Determination of nodal status, especially mediastinal lymph node involvement is an important prognostic factor in NSCLC patients and is essential in the peri-operative therapy decision. Radiologic imaging, as well as endoscopic and surgical technique, has been utilized to detect the clinical N (nodal) category. Ascertaining an accurate radiologic imaging technique helps in mitigating risks and costs associated with invasive procedures.[125]

EVIDENCE TO DECISION

Benefits and harms

PET-CT has higher sensitivity [63% (95% CI 26, 89) vs 59% (95% CI 42,74)] and specificity[94% (95% CI 59, 99) vs 84% (95% CI, 42, 97)] in detecting mediastinal lymph node involvement for clinical stage I to non-bulky IIIA NSCLC (see GRADE table).[126–128] In patients who underwent CECT, mild hypersensitivity reaction occurred in less than 3%; moderate to severe allergic reactions in less than 0.04%, Contrast-induced nephropathy occurred in around 5% of hospitalized patients with normal renal function.[129] Potential harm of FDG PET-CT is radiation-induced effects. Allergic reactions to FDG have also been reported in a case report.[130] Most of the panelists considered net benefit with the use of PET-CT.

Certainty of evidence

Certainty of evidence was deemed low due to risk of bias (unknown blinding of pathologists for the reference standard), and imprecision (wide confidence intervals on sensitivity for both CT and PET-CT in all studies).

Other considerations

Cost

The cost of CECT scan across institutions may range from ₱4,000 to ₱9,000.[131] Whole body PET-CT, which is usually available in private institutions, will cost between ₱40,000 and

₱100,000.[132] CT scan is more widely available compared to PET-CT in the Philippines. As of April 2021, only ten institutions offer PET-CT in the country, a majority of which is found in Metro Manila (Makati – 2, Ortigas – 1, Taguig – 1, Quezon City – 2, San Juan – 1, Manila – 1, Cebu – 2).[132]

Recommendations from other groups

The ESMO guidelines does not explicitly distinguish between CT and PET-CT in the diagnosis of mediastinal involvement. It is indicated that in patients with abnormal mediastinal and/or hilar lymph nodes at CT and/or PET, endosonography is recommended over surgical staging.[133]

National Institute for Health and Care Excellence (NICE) and NCCN provide more emphasis on the role of PET-CT in the pre-treatment plan for patients with NSCLC. NICE guidelines mention that in assessing mediastinal and chest wall invasion, physicians must be aware that CT alone may not be reliable. Patients who potentially have treatment with curative intent should be offered PET-CT.[134]

NCCN states that subsequent pathologic confirmation is then deemed necessary if there is evidence of mediastinal lymph node involvement. Invasive mediastinal staging is also suggested before surgical staging for patients with clinical stage I or II lung cancer (Level of Recommendation: 2A).[135]

CONSENSUS ISSUES

Despite the large costs and limited availability of PET-CT, the panel chose to recommend this diagnostic procedure for detection of nodal involvement because of its higher diagnostic accuracy compared to CT. The panel also concluded that it is probably acceptable to stakeholders and may be feasible to implement with government support in procurement of equipment. By making the recommendation, the panel hopes that it will spur efforts to increase the availability of PET-CT in the country.

GRADE EVIDENCE PROFILE

P Patients with clinical Stage I to non-bulky IIIA NSCLC
I CT scan, PET-CT scan
C Biopsy, histopathology
O Determining mediastinal lymph node involvement

Method	No. of studies	Sn (95% CI)	Sp (95% CI)	Certainty of Evidence
PET-CT	3 (n=425)	**0.63** (0.26, 0.89)	**0.94** (0.59, 0.99)	Low
CT	3 (n=425)	**0.59** (0.42, 0.74)	**0.84** (0.42, 0.97)	Low

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9. Among patients diagnosed with lung cancer with suspicious mediastinal lymph node involvement, should we do concurrent diagnostic and staging evaluation of the mediastinal lymph nodes (i.e., endobronchial ultrasound or thoracoscopy with biopsy) versus sequential staging using PET-CT and diagnostic lymph node biopsy to improve patient outcomes (i.e., overall survival, disease-free survival)?

We suggest concurrent diagnostic and staging evaluation of mediastinal lymph nodes among patients with lung cancer.

Strength of recommendation: Conditional
Certainty of evidence: Low

The conventional sequential approach of imaging with PET-CT and different variations of biopsy for staging are effective, but this usually takes time. The alternative strategy of concurrent endoscopic evaluation and biopsy offers a shorter timeline, but may entail unnecessary higher costs.[136] Not all tertiary centers in the Philippines currently offer endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS), but the choice between a sequential versus a concurrent approach poses a true equipoise and will be relevant in the future of lung cancer management in the country.

EVIDENCE TO DECISION

Benefit and harms

There was indirect evidence from an RCT comparing various strategies (including bronchoscopy, radiology-guided biopsy sampling, PET-CT, and mediastinoscopy) with EBUS or EUS with biopsy in suspected lung cancer and with mediastinal lymph nodes.[137] The concurrent diagnostic approach had a longer mean survival (HR 0.60, 95% CI 0.37, 0.98) compared to the sequential approach. The EBUS group received a decision twice as fast as the comparator, both in the intention to diagnose and the confirmed NSCLC groups (14 days vs. 28 days and 15 days vs. 30 days, respectively). The panel assessed net benefit with the use of concurrent diagnostic and staging evaluation.

Certainty of evidence

The certainty of evidence is low, considering the inherent sources of bias and indirectness.

Other considerations

Cost

The EBUS approach was not more expensive than the conventional approach. It may be considered more cost-effective since similar costs resulted to earlier treatment decision for the EBUS group.[137]

Recommendations from other groups

The 2019 NICE guidelines recommend to offer PET-CT prior to treatment for all people with lung cancer who could potentially have treatment with curative intent, and to offer endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for biopsy of paratracheal and peri-bronchial intra-parenchymal lung lesions. Specific to the section on intra-thoracic lymph node assessment, it identified PET-CT as the preferred initial diagnostic test followed by EBUS-TBNA or EUS-FNA to patients with suspected lung cancer who have enlarged intrathoracic lymph nodes (lymph nodes ≥10 mm short axis on CT) and who could potentially have treatment with curative intent.[138]

The 2015 guidelines of the European Society of Gastrointestinal Endoscopy (ESGE), in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) stated that endosonography is recommended over surgical staging for mediastinal nodal staging in patients with suspected or proven NSCLC with abnormal mediastinal and/or hilar nodes at CT and/or PET-CT.[139] In 2013, the ACCP recommended performing EBUS-TBNA and/or EUS-FNA in patients with high suspicion of N2,3 involvement either by discrete mediastinal lymph node enlargement or PET uptake.[140] None of the previous guidelines reported difference of clinical outcomes with the use of the PET-CT, EBUS-TBNA and/or EUS-NA.

CONSENSUS ISSUES

Based on the presented evidence, the panel also concluded that moderate savings may be attained with EBUS since it may lead to earlier diagnosis. For the same reason, it may be acceptable to stakeholders. However, feasibility of implementation may be a concern since the technology is not widely available.

GRADE EVIDENCE PROFILE

P Patients diagnosed with lung cancer with suspicious mediastinal lymph node involvement
I Concurrent diagnostic and staging evaluation of the mediastinal lymph nodes
C Sequential staging using PET-CT and diagnostic lymph node biopsy
O Mean survival

Outcome	No. of studies	Study results (95% CI)	Certainty of Evidence	Interpretation
Mean survival	1 (n=96)	**HR 0.60** (0.37, 0.98)	Low	Significant favoring the EBUS group

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10. Among patients with resectable (i.e., Stage I to IIIA) non-small cell lung cancer, should we do complete mediastinal lymph node dissection versus lymph node sampling to improve disease-free and overall survival?

We suggest the use of either mediastinal lymph node dissection or lymph node sampling following surgical resection among patients with resectable non-small cell lung carcinoma.

Strength of recommendation: Conditional
Certainty of evidence: Low

Mediastinal lymph node dissection (MLND) is the removal of all lymph node-bearing tissue in the mediastinum,[141] while lymph node sampling (LNS) only samples suspicious mediastinal lymph nodes at levels specified by the surgeon.[142,143] Choosing between MLND and LNS in patients with resectable NSCLC affects the extent of lymph node evaluation for staging purposes, operating time, and post-operative complications.[141]

EVIDENCE TO DECISION

Benefit and harms

The pooled hazard ratio from four RCTs showed no statistically significant difference between MLND and LNS in terms of OS.[144–147] Pooled risk ratios for local tumor recurrence and distant metastasis during follow-up were also similar for the two intervention groups. Only one study reported DFS which was similar for the two methods.[145] The panel assessed that net effects of the interventions may vary on a case-to-case basis.

Certainty of evidence

Certainty of evidence is rated low due to substantial heterogeneity across studies and imprecision of results.

Other considerations

Cost

PhilHealth case rates for procedures relevant to pulmonary resection with lymph node evaluation are presented in Table 3.[148]

Table 3. PhilHealth case rates for selected procedures related to pulmonary resection with lymph node evaluation.

Procedure Description	Case Rate	Professional Fee	Health Care Institution Fee
Resection of lung	53,400	29,400	24,000
Thoracic lymphadenectomy, regional, including mediastinal and peritracheal nodes	37,800	21,000	16,800
Mediastinotomy with exploration, drainage, removal of foreign body, or biopsy; transthoracic approach, including either transthoracic or median sternotomy	23,300	12,600	10,700
Mediastinoscopy, with or without biopsy	14,960	7,560	7,400

Recommendations from other groups

According to the ESTS, lobe-specific systematic nodal dissection in patients with peripheral squamous T1 cancers is acceptable due to the low probability of unforeseen N2 disease.[142] Systematic lymph node dissection in all patients undergoing resection was also recommended in the guidelines on the management of patients with lung cancer by the BTS and the Society for Cardiothoracic Surgery (SCTS).[149] The NCCN 2020 CPG in Oncology for NSCLC recommends either MLND or systematic LNS as appropriate for early-stage NSCLC, so long as lymph nodes are sampled from all mediastinal stations.[150]

CONSENSUS ISSUES

Due to the endorsement of international guidelines for standard practice and there being no statistically significant difference between the two methods on all outcomes, the panel concluded that MLND and LNS would probably be acceptable to stakeholders. The interventions were also assessed as probably feasible to implement as no extraordinary equipment is required. However, feasibility may be affected by the availability of experts in the facility where the procedure will be performed.

GRADE EVIDENCE PROFILE

P Patients with resectable (i.e., Stage I to IIIA) NSCLC
I MLND
C LNS
O OS, DFS; local recurrence; distant metastasis

Outcome	No. of studies	Study results (95% CI)	Certainty of Evidence	Interpretation
OS	4 (n=1,778)	**HR 0.77** (0.56, 1.07; p=0.13)	Low	Not significant
DFS	1 (n=169)	**HR 0.82** (0.54, 1.27; p=0.34)	Low	Not significant
Local recurrence	4 (n=1,778)	**RR 0.92** (0.67, 1.27; p=0.62)	Moderate	Not significant
Distant metastasis	4 (n=1,778)	**RR 0.88** (0.74, 1.04; p=0.14)	Moderate	Not significant

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Chapter 4. RESEARCH GAPS

During the development of this CPG, the need for more research on lung cancer became more apparent. There are at least 12 ongoing trials registered in ClinicalTrials.gov on tyrosine kinase inhibitors for early-stage NSCLC (targeting the EGFR, HER2, and other pathways).[151-162] There were trials comparing systemic adjuvant and neoadjuvant therapy for improvement of survival outcomes by the Chinese Society of Lung Cancer,[163] National Cancer Centre in Korea,[164] and The Samsung Medical Centre[165] but these were withdrawn due to poor patient recruitment. Among studies listed in clinicaltrials.gov relevant to NSCLC, MLND, and LNS, there is one ongoing RCT in China[169] comparing MLND to no lymph node dissection in survival among NSCLC patients, and one non-randomized trial in Canada[170] comparing targeted LNS to systematic LNS in terms of diagnostic yield.

The following research topics for future study were identified:

a. Adjuvant chemotherapy for early stage NSCLD and subgroups with high-risk features
b. Comparison of neoadjuvant and systemic adjuvant therapy for NSCLC
c. Comparison of concurrent versus sequential systemic (tyrosine kinase inhibitors and immunotherapy) and radiation therapy for locally-advanced lung cancer in adults, or specifically in the geriatric subgroup
d. Epidemiology of lung cancer in Filipinos
e. Clinical course of lung cancer after treatment
f. Clinical course of patients with brain metastasis from primary lung cancer
g. Cost-effectiveness studies on recommended treatments
h. Use of surveillance imaging after curative intent treatment
i. Survival outcome with different methods of biopsy done in the Philippines
j. Comparison of CT-guided with VATS with biopsy as the surgical reference standard
k. Network meta-analysis to compare CT-guided biopsy, VATS with biopsy, and other modalities
l. CT-GAB for early disease prior to definitive surgery
m. Utility of a multidisciplinary team in the diagnosis of lung cancer
n. Comparison of two-panel versus higher panel IHC in diagnosis of lung cancer
o. CT scan vs. PET-CT scan for detection of mediastinal lymph node involvement
p. Utility of concurrent diagnostic and staging evaluation vs sequential staging using PET-CT and diagnostic lymph node biopsy
q. Comparison of survival in NSCLC for MLND vs. LNS

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Chapter 5. MONITORING AND EVALUATION

Dissemination

The SC will submit the full-text manuscript of this CPG to the Department of Health. The Disease Prevention and Control Bureau of DOH will transmit copies of this CPG to PhilHealth, health maintenance organizations, and pharmaceutical industry partners. DOH will release a memorandum to notify all stakeholders of the publication.

This CPG will be presented during conferences and annual conventions of medical societies. Copies of this CPG with the endorsement of relevant medical institutions will be sent to medical schools and libraries to integrate the recommendations in their training curricula, with the support of the faculty members and heads of hospital-based departments, including but not limited to surgery, radiology, pathology, and internal medicine.

The SC will develop a simplified version of this CPG and make it available in a format ready for reproduction and dissemination to patients in clinics and hospitals.

Implementation

The SC will develop a program of monitoring to determine the best practices of relevant stakeholders in terms of diagnosis and management of lung carcinoma. Monitoring the use of this CPG may also be a subject of research by interested parties.

Updating of the guidelines

Considering the level of certainty in the body evidence found for each guideline question, we anticipate that these guidelines will need regular updating. We will update these guidelines after 3 years or earlier should new important evidence become available.

Chapter 6. AUTHORSHIP, CONTRIBUTIONS, ACKNOWLEDGEMENT

This project would not have been possible without the initiative and funding from the DOH. The DOH neither imposed any condition nor exerted any influence in formulating the final recommendations.

Steering Committee. The steering committee was indispensable in creating working groups and coordinating the preparatory work, evidence review, and formulation of the recommendations. It organized the consensus panel and facilitated the *en banc* meeting. The SC was responsible for the overall organization and management and is accountable for the overall quality of this clinical practice guideline.

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Technical Working Group. Asia-Pacific Center for Evidence Based Healthcare, Inc. undertook extensive technical work in (1) searching and summarizing the evidence while ensuring objectivity in each stage of the process, (2) presenting the evidence in the panel meeting, and (3) documenting and writing the final output.

> *Dr. Evelyn O. Salido (Lead), Dr. Aldrich Ivan Lois Burog (Technical Coordinator), Dr. Marc Evans M. Abat, Dr. Reginald B. Balmeo, Dr. Melissa A. Dator, Louie F. Dy, Dr. Vaneza Leah A. Espino, Dr. Joseff Karl U. Fernandez, Dr. Rich Ericson C. King, Dr. Nathaniel S. Orillaza Jr., Dr. Rogelio N. Velasco Jr., Dr. Mithi Kalayaan S. Zamora (Evidence Reviewers), Mr. Howell Henrian G. Bayona, Ms. Isabel Teresa O. Salido (Technical Writers), Dr Leonila F. Dans (Technical Adviser)*

Consensus Panel. This CPG is invaluable because of the involvement and active participation of the panelists from various sectors of healthcare who dedicated their time and effort to share their expertise, experience, and knowledge in scrutinizing the scientific evidence with consideration of other critical factors such as patient values and preferences and current healthcare system in the Philippines. The Panel is composed of the following individuals:

> *Dr. Cheryl Moana Marie Añonuevo (nurse practitioner), Aaron Bernabe (patient representative), Dr. Clarito U. Cairo Jr.(Department of Health), Dr. Lenora C. Fernandez (patient representative), Dr. Guia Elena Imelda R. Ladrera (Philippine College of Chest Physicians), Dr. Imelda M. Mateo (Philippine College of Physicians), Dr. Anna Marie M. Pascual-Panganiban (Philippine Society of Medical Oncology, Dr. Djhoanna Aguirre-Pedro (Philippine Academy of Family Physicians), Dr. Dennis C. Villanueva (Philippine Society of Vascular and Interventional Radiology), and Dr. Edmund E. Villaroman (Thoraco-Vascular Society).*

This project would not have been successful without the leadership and guidance of Dr. Evelyn O. Salido, Dr. Leonila F. Dans, and Dr. Maria Rica Lumague.

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Appendix 1. DECLARATION OF CONFLICTS OF INTEREST

Steering committee

Name	Area of Expertise	Affiliation	Summary of Disclosure or other relevant interest
Michelle Angela Tan-Reyes, MD	Adult Pulmonology	Rizal Medical Center	None declared
Marcelo Severino B. Imasa, MD	Medical Oncology	Lung Center of the Philippines, St. Luke's Medical Center Quezon City	• Payment from AstraZeneca as consultant/expert advisor (2019–2021) • Past research grants and non-financial support from AstraZeneca (2019–2021) and Roche (2017–2020)
Bernadette Marie Q. Dy-Olaer, MD	Medical Oncology	Philippine Society of Medical Oncology	None declared
Arabelle Coleen P. Ofina, MD	Family Medicine	Asian Hospital and Medical Center, Ospital ng Makati, Makati Medical Center	Non-financial: board member of Philippine Society of Hospice and Palliative Medicine

Consensus panel

Name	Area of Expertise	Affiliation	Summary of Disclosure or other relevant interest
Cheryl Moana Marie Añonuevo, RN	Nurse advocate	Asian Hospital and Medical Center, Philippine Nurses Association	None declared
Aaron Bernabe	Patient advocate	Not applicable	None declared
Clarito U. Cairo Jr., MD, FPSVI, FPCOM	Public Health, Occupational Medicine	Department of Health	Non-financial interest: Medical Officer IV of Department of Health – Program Manager of Cancer Control
Lenora C. Fernandez, MD, FPCP, FPCCP, FACCP	Internal Medicine – Pulmonology, patient advocate	Division of Pulmonary Medicine, Department of Medicine, University of the Philippines Manila – Philippine General Hospital	Non-financial: consultant for AstraZeneca regarding the prevalence of lung cancer
Guia Elena Imelda R. Ladrera, MD	Internal Medicine – Medical Oncology	Philippine College of Chest Physicians	Payment from AstraZeneca for • research on Osimertinib (2018–present) • consulting (2019) • speakership (2019)
Imelda M. Mateo, MD, MBAH, FPCP, FPCCP	Internal Medicine – Pulmonology	Philippine College of Physicians; Amang Rodriguez Memorial Medical Center	Non-financial: • Medical Center Chief II of Amang Rodriguez Memorial Medical Center (government institution) • consensus panelist for other CPGs (COVID-19 Living CPG) • Vice President of the Philippine College of Chest Physicians (PCCP) • Treasurer of the Philippine College of Physicians (PCP) • Vice President of Action on

Name	Area of Expertise	Affiliation	Summary of Disclosure or other relevant interest
			Smoking & Health (ASH) Philippines
Anna Marie M. Pascual-Panganiban, MD	Internal Medicine – Medical Oncology	Philippine Society of Medical Oncology	Payment from AstraZeneca, Boehringer, Roche, Eli-Lilly for being a speaker (2000–present) for lectures
Djhoanna Aguirre-Pedro, MD, FPAFP, FPSHPM	Family Medicine, Hospice and Palliative Medicine	Philippine Academy of Family Physicians	None declared
Dennis C. Villanueva, MD, FPCR, FPSVIR	Diagnostic and Interventional Radiology	Philippine Society of Vascular and Interventional Radiology; St Luke's Medical Center	None declared
Edmund E. Villaroman, MD	Surgery	Thoraco-Vascular Society	Payment from Johnson & Johnson Phils., Medtronic as lecturer/expert consultant (2013–present)

Evidence reviewers

Name	Area of Expertise	Affiliation	Summary of Disclosure or other relevant interest
Marc Evans M. Abat, MD, FPCP, FPCGM	Internal Medicine – Geriatrics	Philippine General Hospital	None declared
Reginald B. Balmeo, MD	Pediatrics – Pulmonology	Lucena United Doctors Hospital and Medical Center	None declared
Melissa A. Dator, MD, MBA, DPPS, DPSN	Pediatrics – Nephrology	Ateneo School of Medicine and Public Health	None declared
Louie F. Dy	Medical Intern	University of the Philippines Manila College of Medicine	None declared
Vaneza Leah A. Espino, MD	Pediatrics – Pulmonology	Perpetual Help Medical Center Las Piñas	None declared
Joseff Karl U. Fernandez, MD	Internal Medicine – Medical Oncology	Philippine General Hospital	None declared
Rich Ericson C. King, MD	Internal Medicine	Philippine General Hospital	None declared
Nathaniel S. Orillaza Jr., MD	Orthopedic Surgery	University of the Philippines Manila	Senior editor of the Journal of ASEAN Federation of Endocrine Societies
Rogelio N. Velasco Jr., MD	Internal Medicine	Philippine General Hospital	None declared
Mithi Kalayaan S. Zamora, MD	Internal Medicine – Pulmonology	Diliman Doctors Hospital	None declared
Maria Vanessa Sulit, RN, MSc	Clinical Epidemiology	Asia Pacific Center for Evidence-Based Healthcare	Non-financial interest: Coordinator, Asia-Pacific Center for Evidence-Based Healthcare, Inc. Engage in CPG and EBM work and trainings
Aldrich Ivan Lois Burog, MD, MSc (cand.)	Clinical Epidemiology	University of the Philippines Manila	None declared
Evelyn O. Salido, MD, MSc	Internal Medicine-Rheumatology Clinical Epidemiology	University of the Philippines Manila	None declared