LITERATURE REVIEW

Monitoring and Evaluation of Therapy Response in Advanced-Stage Lung Cancer Treated with Systemic Therapy

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ABSTRACT

Lung cancer is the second most commonly diagnosed malignancy, with the highest mortality rate in the world. In Indonesia, lung cancer ranks third with 34,783 cases, contributing to the highest number of deaths due to cancer. Most patients are diagnosed at an advanced stage, requiring systemic therapy. Therapeutic modalities for lung cancer patients can include surgery, radiotherapy, and systemic therapy, with the choice of therapy determined by the histological type, disease stage, laboratory results, performance status (PS), and comorbidities. This situation requires regular monitoring and evaluation to reduce the symptoms and improve the patient's quality of life (QoL). Therapy response in systemic therapy patients can be evaluated through subjective, semi-subjective, and objective evaluations. Subjective evaluation involves monitoring QoL, focusing on cancer outcomes, and patients' well-being. Semi-subjective evaluation consists of monitoring the patient's weight and PS. Objective evaluation uses imaging equipment, such as computed tomography (CT) scans, fluoroscopy, magnetic resonance imaging (MRI), and positron emission tomography (PET) scans to monitor tumor progression.

INTRODUCTION

Lung cancer is the second most commonly diagnosed malignancy, with an incidence of 11.4% or 2,206,771 cases in 2020.[1] It is also the leading cause of cancer-related deaths, accounting for 1,796,144 fatalities or 18% of the total deaths.[1] In Indonesia, lung cancer ranks third with 34,783 cases, contributing to the highest mortality rate of 30,843 deaths or 13.2% of the total cancer-related deaths in 2020.[2] Lung cancer is broadly classified into two main types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Non-small cell lung cancer is the most common type, accounting for approximately 85% of all lung cancer cases, while SCLC accounts for the remaining 15%.[3] Lung cancer staging is critical for determining prognosis and guiding treatment decisions. Non-small cell lung cancer is divided into stages I to IV, with early stages being localized and potentially resectable, while stage IV indicates an advanced stage with distant metastases. In contrast, SCLC is categorized using a simplified two-tier system: limited-stage and extensive-stage.[4] Notably, 60% to 70% of lung cancer patients are diagnosed at an advanced or extensive stage.[5] For such cases, the treatment modality that can be administered is not surgery, but systemic therapy. Systemic therapy in lung cancer includes chemotherapy, targeted therapy, and immunotherapy, all of which continue to play crucial roles in the management of both NSCLC and SCLC. Systemic therapy aims to increase survival rates and improve patients' quality of life (QoL).[6] When administering systemic therapy, regular monitoring and evaluation are required to assess the patient's condition, manage therapy's side effects, and provide palliative therapy to improve QoL.[7] Considering the importance of evaluating and monitoring lung cancer patients

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undergoing systemic therapy, this literature review aimed to explore the monitoring and evaluation of therapy response in such patients.

SYSTEMIC THERAPY

Therapeutic modalities for lung cancer patients can include surgery, radiotherapy, and systemic therapy. Histological type, disease stage, laboratory results, performance status, and comorbidities determine the choice of therapy. Systemic therapy is the recommended treatment option for patients with advanced-stage lung cancer.[8] Over the last decade, significant advancements have been made in treating NSCLC, particularly by developing therapies directed at molecular targets such as mutations in the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK). Other targets have also been identified, such as reactive oxygen species (ROS) proto-oncogene 1 (ROS1), B-Raf proto-oncogene (BRAF), mesenchymal-epithelial transition (MET), human epidermal growth factor receptor 2 (HER2), neurotrophic tyrosine receptor kinase (NTRK), and rearranged during transfection (RET) mutations. Identifying oncogenic driver mutations is necessary to provide targeted therapy appropriate to the patient's condition.[9,10] Based on applicable guidelines, biomarker testing is crucial for diagnosing lung cancer.[10–14]

In NSCLC patients with oncogenic driver mutations, such as EGFR exon 19 deletion or exon 21 L858R mutation, first-line therapy typically involves osimertinib, a third-generation tyrosine kinase inhibitor (TKI). Alternative options include first- and second-generation TKIs, such as erlotinib, afatinib, gefitinib, and dacomitinib. For patients with EGFR mutations, such as S768I, L861Q, or G719X, treatment with afatinib or osimertinib is recommended. Additionally, patients with positive ALK mutations can be given ALK inhibitor therapy.[14] For patients without oncogenic driver mutations, the recommended systemic therapy is platinum doublet-based chemotherapy (e.g., carboplatin or cisplatin) combined with pemetrexed, particularly in patients with adenocarcinoma or large cell carcinoma.[15]

For patients with adenocarcinoma or large cell carcinoma with programmed death-ligand 1 (PD-L1) expression levels of 1% to 49%, a combination of platinum doublet-based chemotherapy with pemetrexed and immunotherapy can be considered.[6] Immunotherapy can also be considered if PD-L1 expression levels are 50% or above.[6] Meanwhile, for advanced stages of SCLC, the first-line chemotherapy regimen typically involves carboplatin combined with etoposide or irinotecan as a primary choice, with the option to include immunotherapy.[11]

TREATMENT EVALUATION

Regular and controlled examinations are required to monitor and evaluate patients undergoing systemic therapy. According to the European Society for Medical Oncology (ESMO), therapy response should be monitored after two to three cycles of chemotherapy or six to nine weeks after chemotherapy. Due to the heterogeneous nature of genetic mutations for patients receiving targeted therapy, evaluation and monitoring can be performed every 8 to 12 weeks, depending on the specific therapy.[12]

The Indonesian Society of Respirology (ISR) guidelines recommend evaluating and monitoring lung cancer patients not undergoing surgery every 8 to 12 weeks after chemotherapy.[15] The examinations include history taking, physical examination, computed tomography (CT) scan, laboratory examination, and other necessary examinations.[15]

The evaluation process encompasses the following aspects:[16]

1. Subjective responses in the form of initial complaints
2. Semi-subjective responses, namely, performance status and body weight
3. Objective responses, including physical examination (e.g., presence or absence of new nodules) and radiology using the Response Evaluation Criteria in Solid Tumors (RECIST)
4. Side effects of medication

A. SUBJECTIVE RESPONSE

The main goal of therapy in patients with advanced lung cancer is to maintain QoL. Systemic therapy plays a crucial role in controlling and reducing cancer symptoms. Evaluating QoL in patients undergoing systemic therapy facilitates the early detection of emerging symptoms, enabling timely interventions such as adjustments to medication, additional therapies, and psychosocial support.[17] Quality of life assessment in lung cancer patients generally encompasses cancer and patient outcomes. Cancer outcomes include the patient's response to treatment, duration of response, symptom-free period, and early detection of recurrence. Meanwhile, patient outcomes include the survival benefits achieved after treatment as measured by the increase in life expectancy and improvements in QoL before and after therapy.[18]

Quality of life is a broad, subjective, and multifaceted concept that includes the following dimensions:[18,19]

1. Physical health and symptoms
2. Functional status and daily living activities
3. Mental and social health, including social roles in the community

The monitoring and evaluation of complaints may vary among patients. Iyer, *et al*. (2014) identified the most common symptoms in lung cancer patients, including fatigue (98%), loss of appetite (98%), breathing problems (94%), cough (93%), pain (90%), and coughing up blood (70%).[20] The study also found that the severity of the symptoms was inversely correlated with the QoL.[20] Symptoms, such as loss of appetite, fatigue, pain, and shortness of breath, were the most significant contributors to reduced QoL.[20]

Subjective complaints and QoL in patients can be evaluated using standardized questionnaires. An example of the questionnaire is the EuroQol-5 Dimension (EQ-5D), which assesses five aspects of QoL, such as mobility, self-care, daily activities, comfort, and anxiety, and includes a visual analog scale (VAS) that only takes a few minutes to complete. The resulting health state index can be used for evaluation in patient care.[21] Another example is the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire, which assesses complaints and the QoL of lung cancer patients, including several aspects, such as symptoms, physical well-being, and emotional well-being, and has been developed comprehensively to evaluate lung cancer patients receiving treatment.[22]

The choice between the EQ-5D and FACT-L for evaluating lung cancer patients depends on the specific objectives of the evaluation and the aspects of QoL under investigation. The EQ-5D is widely utilized in health economics research because it generates utility scores that can be employed to calculate quality-adjusted life years (QALYs) and is particularly suitable for cost-effectiveness evaluation. It is also helpful for extensive research and general health evaluations due to its simplicity and conciseness. However, the EQ-5D is not sensitive to specific lung cancer symptoms or problems, such as hemoptysis or dyspnea, and may overlook minor changes in the patient's condition.[21] The FACT-L, on the other hand, is specifically designed for lung cancer patients, making it highly effective in recording symptoms such as coughing, weight loss, and weariness that are particular to an illness and its treatments. Its sensitivity to changes in the patient's condition and its comprehensive evaluation of the QoL make it particularly valuable for clinical trials and studies focusing on treatment outcomes. However, the FACT-L requires more time to complete than the EQ-5D. Additionally, it is less suitable for economic assessments or cross-disease comparisons since it does not generate utility scores.[22]

B. SEMI-SUBJECTIVE RESPONSE

1. PHYSICAL EXAMINATION

During monitoring and evaluation, physical examination of the lungs may reveal abnormal findings such as lumps in the neck, armpit, or chest wall, signs of liver enlargement or ascites, and bone pain. The clinical signs observed in lung cancer patients depend on the location and size of the tumor, as well as the presence of metastases in other organs. Enlarged lymph nodes in the neck, supraclavicular region, and axilla indicate metastases. Abnormal shortness of breath may occur due to a large tumor mass, pleural effusion, or atelectasis. Venectasis (venous dilation) in the chest wall, accompanied by swelling (edema) of the face, neck, and arms, is associated with vena cava superior syndrome (VCSS). Thrombus in the veins of the extremities, characterized by edema accompanied by pain in the limbs and disruption of the hemostasis system (e.g., increased D-dimer levels), are symptoms of deep vein thrombosis (DVT). Metastases of the recurrent laryngeal nerve can cause hoarseness. Large tumor masses can invade the chest wall and brachial plexus, causing significant pain. Signs of a bone fracture may occur in cancer that metastasizes to the bones. Lastly, signs of neurological disorders may emerge if the cancer has spread to the spine or brain.[15,23]

2. WEIGHT

Chemotherapy can lead to several side effects, including nausea, vomiting, and reduced appetite because of diminished sensory functions such as smell and taste. These conditions may result in malnutrition, which increases the risk of infections and complications and weakens the immune response to therapy.[24] Gul, *et al*. (2021) indicated a relationship between nutritional status and the prognosis of lung cancer patients.[25] The study used the Controlling Nutritional Status (CONUT) assessment by calculating albumin levels, lymphocyte count, and cholesterol levels. Plasma albumin concentration is commonly used to assess nutritional status and liver function. The study observed a direct correlation between poor nutrition and low survival rates in patients.[25] This finding suggested the importance of nutritional management interventions. Interventions that can be given to patients include dietary consultations, food supplementation, and enteral or parenteral nutrition. The choice of nutritional support varies depending on the patient's condition, the disease progression, and the administered therapy.[26]

3. PERFORMANCE STATUS

Performance status (PS) is an assessment of a patient's functional abilities and capacity for self-care. This assessment plays a vital role in treatment selection and is an independent prognostic factor in patients with advanced lung cancer. Therefore, a thorough and accurate evaluation of PS is needed. Oncologists use different methods to assess PS before determining the choice of systemic therapy for cancer patients. The Eastern Cooperative Oncology Group (ECOG) and Karnofsky Performance Status (KPS) scale are the most commonly used tools.[27] The Karnofsky score, introduced in 1948, uses a linear scale from 0 to 100 based on the patient's ability to perform daily activities and the level of assistance required (Table 1).[27] On the other hand, the ECOG uses a five-point scale to assess PS and focuses on simple tools that can be used in routine clinical practice. This assessment was first developed in 1960 and is also known as the World Health Organization (WHO) performance status (Table 1).[27]

Table 1. Assessment criteria for performance status according to Karnofsky and the World Health Organization (WHO)[27]

Karnofsky Score	WHO	Limitation
90-100	0	Normal to minor complaints/signs, able to perform everyday activities, limited or unable to perform strenuous activities
70-80	1	Some complaints, able to perform everyday activities with up to 100% effort, unable to perform everyday activities but able to take care of themselves, able to be active for more than 50% of their waking hours
50-60	2	Able to take care of themselves or occasionally requiring help, able to be active for more than 50% of their waking hours, confined to bed/chair for more than 50% of their waking hours
30-40	3	Unable to perform activities, requiring special care or assistance to take care of themselves, seriously ill, requiring hospital treatment, confined to bed/chair
10-20	4	Severely ill, confined to the bed, requiring hospital treatment, and requiring active assistance from others
0	5	Dead

C. OBJECTIVE RESPONSE RADIOLOGIST

There are several principles for objectively monitoring therapy response in lung cancer patients:[28]

1. The timing of diagnostic examinations must be adjusted to the pathogenesis and progression of lung cancer
2. Diagnostic examination should be directed at the location most likely to exhibit progression or metastasis, and the examination must have high positive and negative predictive values
3. Diagnostic examination should lead to available therapies that significantly improve healing, prolong life expectancy, or alleviate symptoms

Monitoring the therapy response in lung cancer patients is recommended after two to three cycles of chemotherapy or six to nine weeks after administering immunotherapy or targeted therapy. This evaluation should use the same diagnostic examination as the initial examination to detect the presence of tumor lesions. According to the cancer type, the diagnostic examination should also include organs that may exhibit metastases. Lesion measurement during monitoring must follow the RECIST guidelines for patients undergoing chemotherapy and targeted therapy and the Immune Response Evaluation Criteria in Solid Tumors (iRECIST) guidelines for patients undergoing immunotherapy.[29,30] However, routine diagnostic examination in patients with lung cancer has limitations, as it may increase the patient's anxiety and impose an additional financial burden.[28]

Monitoring and evaluation of the therapy response in lung cancer patients often involve radiographic examinations as follows:

1) Chest X-ray

Chest X-ray is inexpensive and widely accessible, but relatively less sensitive than other radiographic examinations.[31] According to the ISR guidelines, therapy response can be evaluated by assessing changes in tumor size on chest X-ray after the second cycle of chemotherapy, with subsequent evaluations performed monthly.[15] According to the RECIST guidelines, therapy response can be evaluated using the same modalities employed during the initial tumor diagnosis, including a chest X-ray. However, a chest X-ray can only be used if the lesion is visible and surrounded by aerated lung tissue. The minimum measurable tumor lesion diameter for evaluation by chest X-ray is 20 mm or larger.[32]

2) Thoracic computed tomography (CT) scan and magnetic resonance imaging (MRI)

Thoracic CT scan is the primary radiographic modality for diagnosing lung cancer and determining disease stage. It is used as an initial diagnostic tool for patients suspected of having lung cancer, with its scope extended to the adrenal glands to assess possible metastases. Further examinations, such as head or abdomen CT scans, can be performed if necessary.[13] According to the ISR guidelines, the evaluation of therapy response to NSCLC using a thoracic CT scan can be performed after three cycles of chemotherapy.[15] For patients undergoing targeted therapy, the monitoring and evaluation schedule aligns with that for chemotherapy, occurring every three months or three cycles.[17] Similarly, the ESMO recommends that the

evaluation of therapy response be performed after two to three cycles of chemotherapy in patients with advanced-stage.[30] For patients with extensive-stage SCLC, the ESMO recommends performing a CT scan every two to three months, especially for those eligible for further treatment.[11] Thoracic MRI is an alternative when a thoracic CT scan with contrast cannot be performed. Moreover, MRI is the primary tool to detect metastases in the brain and spine.[13]

3) Positron emission tomography (PET) scan

F-fluorodeoxyglucose positron emission tomography (FDG-PET) can be used to evaluate and monitor the response of lung cancer patients receiving chemotherapy and radiotherapy. Patients with lung cancer experience increased glucose metabolism, resulting in increased uptake of FDG, which can be detected using PET scans. Compared to CT scans, PET scans can detect cancer lesion activity in areas beyond the lungs. They can also identify disease progression in lung cancer images complicated by atelectasis, consolidation, and radiation-induced fibrosis. An increase in FDG levels in patients after the first cycle of chemotherapy indicates a poor prognosis for the patient's survival rate.[33] Positron emission tomography scans effectively predict therapy response in patients undergoing chemotherapy, which can be evaluated by comparing the image of the lesion with the level of FDG uptake. Additionally, PET scans can differentiate between active tumor lesions and those undergoing necrosis or fibrosis.[31]

Response Evaluation Criteria in Solid Tumors

Tumor progression is determined using a measurement scale based on the RECIST criteria. These criteria have been widely accepted as objective standards for measuring and monitoring tumor size and evaluating therapy response.[32] However, there is ongoing debate over using RECIST criteria to evaluate therapy response to targeted therapies. While the RECIST criteria remain a key reference, clinical examinations are necessary to detect potential worsening.[30]

Lung cancer evaluations use the RECIST 1.1 assessment (Table 2). The criteria focus on changes in tumor size based on target lesions, non-target lesions, and the presence or absence of new lesions.[34] Updates in RECIST 1.1 include a minimum measurable lesion of 1 cm, five total target lesions and a maximum of two per organ, and the classification of lymph nodes smaller than 1 cm as a complete response. Another study highlighted limitations of this measurement, particularly in measuring tumors with irregular or spiculated shapes.[35]

Table 2. Assessment of tumor progression based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria[32]

Response	Target Lesion	Non-Target Lesion	New Lesion
Complete response (CR)	All target lesions disappear	All non-target lesions disappear	None
Partial response (PR)	Tumor size reduces by ≥30% from baseline (over four weeks)	There is no development of non-target lesions	None
Progressive disease (PD)	Tumor size increases by ≥20% compared to the smallest tumor size of the previous examination	There is progression from non-target lesions	New lesion
Stable disease (SD)	Not meeting the CR, PR, and PD criteria	There is no development of non-target lesions	None

In patients undergoing immunotherapy, therapy response is evaluated using the iRECIST criteria, which modify RECIST 1.1. Unlike chemotherapy, immunotherapy elicits different responses that necessitate tailored assessment criteria. Immunotherapy can increase survival rates in patients and cause a unique condition in the body known as pseudoprogression.[36] This condition is defined as an increase in the size of the primary tumor or the appearance of new lesions, followed by tumor regression. Pseudoprogression does not indicate a worsening of tumor development, as confirmed by histopathological biopsy, which revealed infiltration and recruitment of various immune cells, such as T or B lymphocytes, in the tumor. This can lead to ineffective discontinuation of therapy due to errors in defining progressive disease in patients.[37]

Table 3. Differences between Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and iRECIST[21]

	RECIST 1.1	iRECIST
Dimension	Unidimensional	Same with RECIST
Definition of measurable lesions	Diameter length above 10 mm using computed tomography scan with calipers; 20 mm using chest X-ray	Same with RECIST
Lymph nodes that can be measured	>15 mm on short axis	-
Measured target lesions	Five total target lesions (two per organ); other non-target lesions	Same with RECIST
Additional criteria	The total longest diameter of the target lesion or short axis for lymph nodes	The total longest diameter of the target lesion or short axis for lymph nodes; separate measurement of new lesions
New lesion	Classified as a progressive disease	Unconfirmed progressive disease necessitating further examination
Progressive disease	≥20% increase in the sizes with an absolute increase of ≥5 mm compared with the smallest tumor size of the previous examination; the presence of new lesions	≥20% increase compared with the size of the smallest tumor of the prior examination; the presence of new lesions; classified as an unconfirmed progressive disease; confirmation or re-examination after four to eight weeks

OTHER LABORATORY EXAMINATIONS

TUMOR MARKERS

Tumor markers are biochemical indicators of the presence or absence of tumors. They can be produced by the tumor or non-tumor cells in response to the tumor. Tumor markers play several roles: diagnostic, prognostic, predictive, and monitoring. Their use in monitoring evaluates the success of therapy and follow-up.[38] Several markers commonly used in diagnosing lung cancer include carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), squamous cell carcinoma (SCC) antigen, cytokeratin-19 fragment (CYFRA21-1), progesterone-releasing peptide (ProGRP), and neuron-specific enolase (NSE). Additionally, these markers can be used to monitor and evaluate therapy response. Combining several tumor markers can increase the sensitivity and accuracy of disease progression monitoring.[39]

Liquid Biopsy

Liquid biopsy is a non-invasive examination using blood, sputum, and urine to detect the presence or absence of tumor cells in the bloodstream. This examination can be used for screening, initial diagnosis, monitoring, and identifying molecular diversity in lung cancer. An advantage of liquid biopsy is its ability to detect mutations in cancer tissue, identify the mechanisms of resistance to therapy that occur, and predict response to therapy. The four biomarkers commonly used include circulating tumor cells (CTCs), cell-free deoxyribonucleic acid (cfDNA), exosomes, and metabolites.[40]

Circulating tumor cells are cancer cells released from the primary tumor or metastases into the bloodstream. These markers are more frequently detected in advanced-stage cancer and serve as a prognostic factor and a tool for monitoring response to systemic therapy.[31] Cell-free DNA is a DNA fragment circulating in the bloodstream. In lung cancer, the tumor mass undergoes apoptosis and necrosis, resulting in a DNA fraction known as cell tumor DNA (ctDNA) that provides insights into the genetic heterogeneity of different types of tumors. It can also facilitate monitoring therapy response and identify resistance to treatment.[40]

According to the ESMO, ctDNA has several advantages over CTCs. One example of ctDNA is the EGFR mutation from T790M, which indicates the presence of a mutation and can serve as a monitoring marker in patients who have received first-line TKI therapy. The absence of the T790M mutation in the blood indicates a positive response to therapy and is a good prognostic indicator. In patients who previously responded well to TKI therapy and no mutations were detected in the blood, re-detection of ctDNA can indicate relapse and correlate poorly with the patient's clinical and radiological findings. For patients who receive immunotherapy, detecting tumor mutational burden (TMB) suggests an improvement in the patient's clinical condition.[12]

Liquid biopsy presents a viable alternative to biopsy because of its ease of examination and avoidance of tissue biopsy. However, this examination is not widely adopted as a routine diagnostic and monitoring tool for lung cancer because of its high cost, limited availability, and the need for extensive research and consensus on standardization in diagnosis and therapy.[6,12,40]

SUMMARY

Lung cancer is the second most commonly diagnosed malignancy, with the highest mortality rate in the world. Most patients present at an advanced stage that requires systemic therapy. This situation requires regular monitoring and evaluation to reduce the

symptoms and improve the patient's QoL. Three approaches can be employed in evaluating and monitoring patients undergoing systemic therapy: subjective, semi-subjective, and objective evaluations. Subjective evaluation involves monitoring the patient's QoL, focusing on cancer and patient outcomes. Cancer outcomes include patient response to treatment, duration of response, symptom-free period, and early detection of recurrence, while patient outcomes include the survival benefits achieved. Semi-subjective evaluation involves the monitoring of the patient's weight and performance status. Monitoring body weight is a clinical predictor and prognostic factor for evaluating disease progression. At the same time, performance status plays a vital role in treatment selection and is an independent prognostic factor for patients with advanced cancer. Finally, objective evaluation involves using imaging tools such as CT scans, chest X-rays, MRI, and PET scans to monitor tumor progression. Using assessment criteria such as RECIST 1.1 or iRECIST simplifies the determination of progression and aids in deciding subsequent therapeutic strategies.

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Authors' Contribution
Conceptualization of the framework and methodology: AF, FFW, LW. Data collection and analysis, synthesis of the findings, and drafting of the manuscript: IS. All authors contributed and approved the final version of the manuscript.

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