Editorial Commentary on Lung Cancer

Imaging procedures in the assessment of response to neoadjuvant treatment in non-small cell lung cancer

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Introduction

Lung cancer is still the most common cause of death among all cancers worldwide (1). At diagnosis, 80% of lung cancers are in non-small cell lung cancer (NSCLC) histology (2). Treatment choice of NSCLC consists of systemic therapy (chemotherapy, targeted therapies, immunotherapies), radiotherapy, and/or surgery or their different combinations. The histopathological type, molecular structure, and stage play a role in the treatment decision. In addition, the individual characteristics of the patient such as performance and comorbidities should be considered (3).

Locally advanced lung cancer is estimated to represent almost 25% of NSCLC cases, with a 5-year survival of 35% (2). Especially, stage III NSCLC (A/B) includes patients with very heterogeneous characteristics, so it can be difficult to make a treatment decision (2,4).

According to TNM 8th staging, different combinations including tumor size up to 7 cm, invasion into local adjacent structures, microscopic or bulky, ipsilateral and/or mediastinal lymph node metastases are in stage III (A/B) (4).

Stage IIIA NSCLC (T1a-T2bN2, T2N1-N2, or T4N0-N1) specifically is amenable to trimodality therapy (neoadjuvant chemotherapy and radiation therapy (sequential), or simultaneous chemoradiotherapy followed by surgery) for patients that are operable candidates and do not show evidence of disease progression (5). In unresectable stage IIIB cases, standard treatment, simultaneous chemoradiotherapy, followed by immunotherapy (durvalumab), and adjuvant treatment are the last National Comprehensive Cancer Network (NCCN) guideline recommendations (3).

Neoadjuvant or induction therapies define the treatment applied before curative treatment in lung cancer, especially in locally advanced diseases (6).

Expected clinical benefit from neoadjuvant therapy: To increase the effectiveness of the curative treatment to be applied (more limited surgery requirement, providing R0 resection, providing nodal downstage, eradication of micrometastasis, etc.) and ultimately prolonging the patient's survival (5,6).

Restaging after neoadjuvant therapy

Staging after neoadjuvant therapy, measuring the change in tumor burden, and determining the response to treatment are among the main criteria in planning the next curative treatment together with clinical evaluation (5).

The determination of "objective change in tumor size" radiologically is one of the most important endpoints used to decide on subsequent oncological treatments. Along with the radiological response, criteria such as overall survival (OS), progression-free survival (PFS), time to progression (TTP), and quality of life (QOL) measurements are the most frequently used parameters in oncological studies (5,6).

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Timing of restaging after neoadjuvant therapy

It has been shown in many studies that mortality is higher in patients undergoing "late surgery" after induction therapy (7,8). In the study of Gao *et al.*, mortality was higher in patients who were operated on for more than 6 weeks after neoadjuvant chemoradiation therapy, compared to other groups (8). Similarly, in a study, mortality was found to be high in surgical applications performed after 3 months after induction (8). Therefore, it is recommended to perform restaging within 4–6 weeks at the end of the treatment in patients with lung cancer who are scheduled for surgery after neoadjuvant therapy (9).

Methods for evaluating radiological response after neoadjuvant therapy

Response assessment after neoadjuvant therapy can be performed with thorax computed tomography (CT) and/or positron emission tomography (PET)-CT (3). Although the method to be chosen varies according to the characteristics of the patient and the center, it is recommended to prefer PET-CT, which is a non-invasive method, especially in N2 cases to demonstrate metabolic response and nodal downstage (8,9).

A one-to-one comparison is recommended in target lesions, preferably by drawing on a device with the same technical specifications and with the same procedure as the method used in the initial staging (9).

Response evaluation in restaging with thorax CT is recommended according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria. RECIST criteria were first defined by the World Health organization (WHO) in 1981 as tumor response criteria for use in studies specifically. The original RECIST criteria were created in February 2000 in collaboration with the European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute (NCI). EORTC also developed different staging methods. The updated version was released in January 2009 as RECIST 1.1 (9,10).

RECIST: basic concepts in response evaluation

It is recommended that the baseline thorax CT be taken 4 weeks before the start of treatment. The ideal time for evaluation of response after treatment is 4–6 weeks. Response assessment should be performed at least 4 weeks after the end of treatment, preferably within 6–8 weeks (9).

The imaging method is chosen to cover all target and non-target lesions detected in initial CT. Whichever effect was evaluated in the initial CT, it should be done with the same method in the same follow-up and reversal. Depending on the nature of the case, additional examinations can be planned [thorax magnetic resonance imaging (MRI), angio thorax CT, etc.] according to the recommendation of the multidisciplinary oncology council (9).

CT and MRI are the most reliable methods in imaging neoadjuvant therapy. Ultrasound is not preferred for routine size measurement and evaluation due to the high individual variability. It is reported in RECIST 1.1 that PET-CT can be used to identify new lesions in staging (9,10).

Thorax CT technical specifications

It is recommended to perform a contrast-enhanced thin-section thorax CT (≤5 mm cross-section) examination. Targetable and non-targetable lesions were identified in radiological examinations (9).

Targetable lesions

By measuring the longest diameter in one plane of the tumoral lesion, lesions ≥10 mm on thin-section spiral thorax CT or lesions ≥20 mm on thorax CT can be considered as targets. Up to 5 targetable lesions were evaluated in RECIST 1.1 (9).

It is defined that the shortest measurable diameter of the targetable lymph node on CT should be ≥15 mm (10,11).

Nontargetable lesions

Lesions with tumor size <10 mm and lymph node size <15 mm smaller, leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitic spread, organomegaly, etc. unmeasurable lesions were identified (9).

Response assessment

At baseline, the long diameters of the target lesions and the short diameters of the pathological lymph nodes are summed, and the sum of the measurements are compared with this initial sum at follow-up. According to response rates, it is classified as complete response, partial response, stable response, and progressive disease (*Table 1*).

Response definitions according to "RECIST 1.1 Criteria" are shown in *Table 1* (9).

Table 1 Response evolution criteria according to RECIST 1.1 (9)

Response level	Response definitions
Complete response	Disappearance of all selected target lesions (short axis of all pathological lymph nodes should fall <10 mm)
Partial response	At least a 30% reduction in the sum of the diameters of the target lesions at baseline
Stable disease	Not as small as a partial response, not as large as progressive disease (<30% less reduction, <20% undergrowth)
Progressive disease	It was defined as an increase of at least 20% in the sum of the diameters of the target lesions at baseline and a net increase of ≥5 mm in total diameter or the formation of a new lesion

RECIST, Response Evaluation Criteria in Solid Tumours.

Table 2 Response evaluation criteria according to PERCIST (13)

Response level	SUL peak change
Complete metabolic response	Disappearance of metabolically active tumor lesions
Partial metabolic response	Decrease of SUL by ≥30% and at least 0.8 SUL units' difference, and no new FDG lesions and no increase in size >30% of target lesion and no increase in SUL or size of non-target lesions
Stable metabolic disease	Increase or decrease of SUL by less than 30%
Progressive metabolic disease	SUL increase by at least 30% and increase by at least 0.8% SUL units of the target lesion or development of at least one new lesion, or increase in target lesion size by 30% or unequivocal progression of non-target lesions

PERCIST, PET Response Criteria in Solid Tumors; PET, positron emission tomography; SUL peak, SUV peak normalized to lean body mass; SUV, standardized uptake value; FDG, fluorodeoxyglucose.

PET Response Criteria in Solid Tumors (PERCIST)

After the widespread use of PET and PET-CT in NSCLC response assessment, evaluation of metabolic activity besides tumor size gained importance (12). First, in 1999, the EORTC PET working group established criteria for revision with PET-CT (12) Widely accepted in the following years, the PERCIST criteria for PET-CT were published in the spring of 2009 (13).

Standardized uptake value (SUV) of the tumor, SUV peak normalized to lean body mass (SUL peak), and lesion are evaluated in 2 measurements in each organ (13).

Basal SUL peak ≥1.5× SUL + 2 standard deviation (SD) [3-cm region of interest (ROI)] (liver).

With PERCIST criteria, according to metabolic responses in PET-CT, defined complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic response (SMR), and progressive metabolic disease (PMD) are defined (12).

Response definitions according to "PERCIST Criteria" are shown in *Table 2* (13).

PERCIST criteria were defined for PET-CT re-evaluations, in which we measured the metabolic activity of the tumor, after the WHO, EORTS, and RECIST criteria, which were based on thorax CT, which evaluated the anatomical extent (9,12,13).

The different revalidation evaluation criteria are summarized in *Table 3* (9,12,13).

It has been reported that the use of PERCIST criteria in studies is more useful in predicting the survival of patients than RECIST 1.1 criteria based on anatomical measurement (14,15).

In large-scale reviews in recent years, it has been concluded that the concordance of tumor responses between the morphologic criteria and metabolic criteria is not excellent. When adopting the metabolic criteria instead of the RECIST, overall response rates were significantly increased. It has been shown that overall response rates are higher with PERCIST when metabolic criteria are used (15-17).

Neoadjuvant treatment approaches are still an important part of the treatment, especially in locally advanced lung cancer. In the evaluation of response in neoadjuvant therapy, the use of PET-CT and metabolic criteria was found to be more beneficial than morphological criteria in CT alone. By using these criteria, treatment responses can be reported as standardized, and studies worldwide become comparable. It has been shown that PERCIST and EORTC criteria

Table 3 Diagnostic criteria of different methods in re-staging (9,12,13)

Variables	WHO (9)	RECIST 1.1 (9)	EORTC (12)	PERCIST 1.0 (13)
Measurability of baseline lesions	Two-dimensional measurable lesions (longest diameter and vertical dimension are measured)	Lesions >10 mm in the longest dimension, >15 mm in lymph nodes	Lesions with high FDG uptake	Baseline minimal tumor lesions showing SUL peak
Complete response	Complete disappearance of lesions in a new examination performed at least 4 weeks apart	Disappearance of all target lesions (short axis of all pathological lymph nodes should fall <10 mm)	Absence of FDG uptake in the target organ	Disappearance of metabolically active tumor (less a liver SUL mean)
Partial response	>50% reduction in tumor size	At least a 30% reduction in the sum of the diameters of the target lesions at baseline	More than 25% reduction in SUV max	Decrease of greater than or equal to 30% and of at least 0.8 SUL units must be shown between the most intense evaluable lesion at baseline and the most intense lesion at follow-up (not necessarily the same lesion), no new FDG lesions and no increase in size >30% of target lesion and no increase in SUL or size of non-target lesions
Stable disease	More than 25% increase or decrease in tumor size	Not as small as partial response, not as large as progressive disease (<30% less reduction, <20% undergrowth)	More than 25% decrease in SUV max or more than 15% increase below	Increase or decrease of SUL by less than 30%
Progressive disease	More than 50% increase in tumor size	It was defined as an increase of at least 20% in the sum of the diameters of the target lesions at baseline and a net increase of ≥5 mm in total diameter or the formation of a new lesion	More than 25% increase in SUV max or appearance of the new focus	SUL increase by at least 30% and increase by at least 0.8% SUL units of the target lesion or development of at least one new lesion, or increase in target lesion size by % or unequivocal progression of non-target lesions

WHO, World Health organization; RECIST, Response Evaluation Criteria in Solid Tumours; PET, positron emission tomography; EORTC, European Organization for Research and Treatment of Cancer; PERCIST, PET Response Criteria in Solid Tumors; FDG, fluorodeoxyglucose; SUL, SUV normalized to lean body mass; SUV, standardized uptake value.

are more useful than RECIST criteria in determining the prognosis of patients in the evaluation of early or late treatment response of immune checkpoint inhibitors in NSCLC as well as other treatment modalities (15-18).

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Footnote

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