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ORIGINAL RESEARCH

Predictive Value of PERCIST for Locally Advanced Non-Small Cell Lung Cancer Treated with Preoperative Induction Therapy – A Multicenter Study in Japan

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Background: Induction therapy followed by surgery is recommended as an alternative treatment strategy for locally advanced non-small cell lung cancer (NSCLC). Patients who achieve pathologic response after induction therapy have better outcomes than non-responders; therefore, therapeutic response must be evaluated. Recently, new approaches for monitoring therapeutic responses, which are based on ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET), have been developed. In this study, we evaluated the predictive value of Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST), which uses standardized uptake values corrected for lean body mass (SUL) and total lesion glycolysis (TLG).

Methods: A total of 130 patients in the Setouchi Lung Cancer Group who underwent FDG-PET imaging before and after induction therapy prior to a planned surgical resection for NSCLC between 2007 and 2016 were studied retrospectively. The pathologic responses of the primary lung tumors and metastatic lymph nodes were compared with their responses based on evaluation using PERCIST.

Results: Postoperative pathologic studies revealed pathologic complete response (pCR) in 42 (32.3%) patients. PERCIST was significantly correlated with pathologic response ($p < 0.001$). The sensitivity, specificity, and accuracy of PERCIST for predicting pCR were 16.7% (7/42), 88.6% (78/88), and 65.4% (85/130), respectively. Patients with pCR had significantly higher reduction rates in SULpeak for both primary lung tumors and metastatic lymph nodes and TLG for primary tumors than non-responders. In a multivariate Cox regression analysis, tumor site in upper lobes, reduction rate of TLG in primary tumor, and pathologic N0 were independent predictors of favorable recurrence-free survival (RFS).

Conclusion: Our study suggested that PERCIST, especially the rate of TLG reduction rate, are useful to predict the pathological response and prognosis after induction therapy. Although improvement is necessary, PERCIST can be a promising method of the post-induction status in lung cancer. Further research is needed to confirm our findings.

Keywords: non-small cell lung cancer, FDG PET, PERCIST, SUL, TLG

Introduction

Currently, definitive concurrent chemoradiotherapy (CRT) remains the main mode of treatment for stage III non-small cell lung cancer (NSCLC) based on the results of large randomized Phase III trials, which failed to demonstrate a benefit from the addition of surgery.[1] However, for potentially resectable stage III NSCLC, induction therapy followed by surgery is recommended as an alternative treatment strategy.[2–4] Patients who achieve a pathological response after

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induction therapy have a better outcome than non-responders.[5,6] Therefore, evaluation of therapeutic responses after induction treatment remains crucial.

To date, widely used approaches for monitoring therapeutic responses are based on anatomical assessments using computed tomography (CT). The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 is the most commonly used set of criteria for assessing tumor response.[7] However, CT is limited in its ability to distinguish viable residual tumors from reactive changes, such as edema and scar tissue. ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) has advantages over CT in evaluating responses because FDG uptake reflects tumor cell viability. Several studies have demonstrated that FDG-PET is superior to RECIST in evaluating treatment effects in patients with various cancers.[8,9] In 2009, researchers from the United States developed the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST), which uses standardized uptake values corrected for lean body mass (SUL) and total lesion glycolysis (TLG).[10] The usefulness of PERCIST in evaluating treatment effects has been reported for several cancers.[11,12] However, the efficacy of PERCIST in evaluating the responses of induction therapy in NSCLC has not yet been studied.

This study sought to evaluate the predictive value of PERCIST in patients with locally advanced NSCLC who underwent induction treatment followed by pulmonary resection.

Patients and Methods

Patients

The clinical data of 130 patients in the Setouchi Lung Cancer Group (SLCG) who underwent FDG-PET imaging before and after induction therapy prior to a planned surgical resection for NSCLC between April 2007 and December 2016 were analyzed. SLCG is one of the organizations that conducts clinical research and trials for lung cancer in Japan, and has reported several clinical studies to date.[13] Eligible patients were ≥18 years old, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and had histologically or cytologically diagnosed stage IIA-IIIB NSCLC (according to the 7th TNM staging system). Patients with *EGFR*$^+$ or *ALK*$^+$ NSCLC tumors were also enrolled. This study was a retrospective study and data were collected from eight institutions affiliated to the SLCG. All of the institutions are core cancer treatment centers in Japan and each has multiple radiologists and pathologists with expertise in the diagnosis and management of lung cancer. CT imaging conditions, PET scans, and pathological response assessments were performed at each institution. Analysis of the PERCIST data was only performed at Kawasaki Medical School by one radiologist (MI) who was blinded to the clinical information about the patients. Pathological response assessments were also performed at each institution by pathologists who were blinded to the imaging and clinical data of the participating patients. The appropriate review board at each institution approved the study (Representative facility: Kawasaki Medical School, No.3309).

RECIST Evaluation

CT images were retrospectively reviewed by experienced radiologists at each institution. Anatomical changes on CT images were evaluated, as described in RECIST version 1.1 as follows: progressive disease (PD), >20% increase in tumor dimensions or the appearance of metastases; stable disease (SD), <30% shrinkage or <20% increase; partial response (PR), >30% decrease; and complete response (CR), complete disappearance of the primary target tumor. Based on these categories, patients were classified as responders (PR and CR) and non-responders (PD and SD).[7]

Evaluation on PERCIST

Using the commercially available software package, GI-PET (AZE Co., Ltd.) we evaluated FDG-PET images based on PERCIST version 1.0.[14] In using PERCIST for evaluation, SULpeak and total TLG were used as parameters. After the peak standardized uptake value (SUVpeak) was calculated in a 1.2-cm-diameter ROI placed on the hottest point of the tumor, the value was then normalized to the SULpeak (SUVpeak × [lean body mass] / [total body mass]) matched for Japanese individuals. Variations in SUVs among institutions were minimized using an anthropomorphic body phantom. TLG was calculated as SULmean × metabolic tumor value (MTV), where MTV was defined as FDG-avid tumor value, with >1.5 times that of the mean liver SUL value +2 standard deviations.

PERCIST evaluates the percentage change in SULpeak between the pre- and post-treatment scans as follows: progressive metabolic disease (PMD), >30% increase in the SULpeak; stable metabolic disease (SMD), <30% decrease or < 30% increase; partial metabolic response (PMR), >30% decrease; and complete metabolic response (CMR), complete disappearance of the SULpeak.[10] Based on these criteria, patients were considered either responders (PMR and CMR) or non-responders (PMD and SMD). Tumor responses of PERCIST both the primary lung tumor and metastatic lymph nodes were evaluated according to PERCIST. If multiple lesions were present, up to five or the hottest lesions were evaluated, and the worst objective response was chosen for the evaluation of PERCIST.

Pathological Tumor Response

Pathologic tumor response and resection completeness were evaluated according to the General Rule for Clinical and Pathological Record of Lung Cancer (Seventh Edition) developed by the Japan Lung Cancer Society.[15] Pathologic response was defined as follows: Ef.0, no therapeutic effect; Ef.1a, residual viable cancer cells detected in "≥2/3" of resected tumor; Ef.1b, residual viable cancer cells detected in "<2/3 and ≥1/3" of resected tumor; Ef.2, residual viable cancer cells detected in "<1/3" of resected tumor; and Ef.3, no residual viable cancer cells. Ef.3 was considered to be "pathologic complete response (pCR)".

Statistical Analysis

All statistical analyses were performed using IBM SPSS statistics version 22.0 (IBM Japan, Tokyo, Japan). The associations between clinical factors and pathologic response were analyzed using paired *t*-test. The association between RECIST/PERCIST and pathologic response was analyzed using Wilcoxon's signed-rank test. The optimal cut-off values for continuous variables were estimated using receiver operating characteristic (ROC) curve analysis with the area under the curve (AUC). Recurrence-free survival (RFS) and overall survival (OS) were measured from the date of induction therapy initiation to the dates of recurrence and last follow-up, respectively. Variables with *p*-values <0.10 in a univariate analysis were included in a forward, stepwise backward multivariate Cox proportional hazards regression model to identify independent prognostic factors. The inter-rater agreement of the evaluation of treatment response between the two readers was analyzed using the Kappa coefficient. All statistical tests were two-tailed, and *p*-values <0.05 were considered significant.

Results

Patient Characteristics

The clinicopathologic characteristics of all 130 patients are shown in Table 1. The histological tumor types were adenocarcinoma in 70 (53.8%) patients, squamous cell carcinoma in 53 (40.8%) patients, and other specified cancer in seven (5.4%) patients. The tumor stages were T1 in 24 (18.5%) patients, T2 in 41 (31.5%) patients, T3 in 37 (28.5%) patients, and T4 in 28 (21.5%) patients. Regarding staging according to nodal involvement, the stages were N0 in 17 (13.1%) patients, N1 in 28 (21.5%) patients, N2 in 80 (61.5%) patients, and N3 in five (3.9%) patients. All the N3 nodes were located in the supraclavicular area on the affected side. According to the 7th TNM staging system, 11 (8.5%) patients had stage IIA tumors, seven (5.4%) patients had stage IIB tumors, 99 (76.1%) patients had stage IIIA tumors, and 13 (10.0%) patients had stage IIIB tumors. As induction therapy, CRT and chemotherapy only were performed in 102 (78.5%) and 28 (21.5%) patients, respectively. All patients underwent complete R0 resection. Postoperative pathologic studies revealed pathologic responses of Ef.3 in 42 (32.3%) patients, Ef.2 in 48 (36.9%) patients, Ef.1b in 13 (10.0%) patients, and Ef.1a in 27 (20.8%) patients.

Factors Affecting Pathological Complete Response

Table 2 shows the factors affecting pCR. Patients in the CRT group tended to have higher rates of pCR than those in the chemotherapy only group (p=0.065). No significant differences in tumor histology, tumor location, clinical stage, or chemotherapy regimen were observed between the pCR and non-pCR groups.

Table 1 Patients Characteristics

Characteristics	Number	Percentage (%)
Age (years)		
Mean (Range)	64.3±7.6 (45–79)	
Sex		
Male/Female	106/24	81.5/18.5
Histology		
Adenocarcinoma/SCC/Others	70/53/7	53.8/40.8/5.4
Tumor location		
Central / Peripheral	51/79	39.2/60.8
RUL/RML/RLL/LUL/LLL	41/2/26/50/11	31.5/1.5/20.0/38.5/8.5
Smoking history		
Smoker/non-smoker	113/17	86.9/13.1
Clinical T status		
T1/T2/T3/T4	24/41/37/28	18.5/31.5/28.5/21.5
Clinical N status		
N0/N1/N2/N3	17/28/80/5	13.1/21.5/61.5/3.9
Clinical Stage		
IIA/IIB/IIIA/IIIB	11/7/99/13	8.5/5.4/76.1/10.0
Induction therapy		
Chemotherapy/Chemoradiation	28/102	21.5/78.5
Chemotherapy regimen		
Cisplatin+Docetaxel	57	43.9
Carboplatin+Paclitaxel	44	33.8
Others*	29	22.3
Type of surgery		
Lobectomy/Pneumonectomy	119/11	91.5/8.5
Pathological response		
Ef.1a/1b/2/3	27/13/48/42	20.8/10.0/36.9/32.3

Notes: *Cisplatin+Vinorelbine:9, Cisplatin+CPT-11:5, Cisplatin+Pemetrexed:3, Cisplatin+S1:3, Cisplatin +Gemcitabine:2, Cisplatin+Pemetrexed+Bevacizumab:2, Carboplatin+Pemetrexed+Bevacizumab:3, Others:2.

Abbreviations: SCC, squamous cell carcinoma; RUL, right upper lobe; RM, right middle lobe, RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

Table 2 Factors Affecting Pathological Complete Response

All	pCR	Non-pCR	p-value
Age, years, Mean	63.4±8.4	64.7±7.2	0.383
Histology			0.139
Non SCC	21	56	
SCC	21	32	
Tumor location			0.841
Central	17	34	
Peripheral	25	54	
Induction therapy			0.065
Chemoradiotherapy	37	65	
Chemotherapy	5	23	
Chemotherapy regimen			0.537
Cisplatin+Docetaxel	19	38	
Carboplatin+Paclitaxel	16	28	
Others	7	22	
Clinical stage			0.898
Stage II	6	12	
Stage III	35	75	

Abbreviations: pCR, pathological complete response; SCC, squamous cell carcinoma.

Metabolic Activities Before and After Induction Therapy

Pre-treatment PET/CT imaging showed that 87 (67.0%) patients had FDG-avid hilar and mediastinal lymph nodes. Table 3 shows changes in SUVmax, SULpeak, and TLG values in primary lung tumors and metastatic lymph nodes before and after induction therapy. SUVmax, SULpeak, and TLG values were significantly decreased after induction therapy in both primary lung tumors and metastatic lymph nodes.

Correlation Between Pathological Response and RECIST / PERCIST

In Table 4, the relation between pathologic response and response assessments based on RESIST and PERCIST have been compared. Unlike RECIST ($p = 0.119$), PERCIST had a correlation with pathologic response ($p < 0.001$).

Regarding pCR (Ef3), 42 patients with pCR were classified as CR (n = 2), PR (n = 33), and SD (n = 7) by RECIST, whereas the same 42 patients were classified as CMR (n = 7) and PMR (n = 35) by PERCIST. The sensitivity, specificity, and accuracy of PERCIST in predicting pCR were 16.7% (7/42), 88.6% (78/88), and 65.4% (85/130), respectively. In contrast, the sensitivity, specificity, and accuracy of RECIST in predicting pCR were 4.8% (2/42), 100% (88/88), and 69.2% (69/130), respectively.

Predictive Value for pCR in Primary Lung Tumors

Among 130 patients, 45 (34.6%) patients were shown to have pCR in primary lung lesions. The reduction rates were calculated using the changes in both SULpeak and TLG before and after induction treatment (Table 5). Patients with pCR had significantly higher reduction rates in both SULpeak and TLG than patients without pCR.

Table 3 Metabolic Activities Before and After Induction Therapy

	Before Induction	After Induction	p-value
Primary lung tumor (n=130)			
SUVmax	11.2±5.5	3.59±2.6	<0.001
SUL peak	9.9±4.8	3.2±2.3	<0.001
TLG	181.2±263.0	14.5±34.9	<0.001
Metastatic lymph node (n=87)			
SUVmax	7.0±4.0	2.4±1.9	<0.001
SUL peak	6.0±3.5	2.0±1.6	<0.001
TLG	35.0±54.7	4.1±9.0	<0.001

Abbreviations: SUV, standardized uptake values; SUL, standardized uptake values corrected for lean body mass; TLG, total lesion glycolysis.

Table 4 Association Between RECIST/PERCIST and Pathological Response

	Ef.3	Ef.2	Ef.1b	Ef.1a	p-value
RECIST					0.119
CR	2	0	0	0	
PR	33	37	7	15	
SD	7	10	5	11	
PD	0	1	1	1	
PERCIST					<0.001
CMR	7	8	1	1	
PMR	35	39	10	15	
SMD	0	1	2	11	
PMD	0	0	0	0	

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors; CMR, complete metabolic response; PMR, partial metabolic response; SMD, stable metabolic disease, PMD, progressive metabolic disease.

Table 5 Reduction Rates of SULpeak and TLG in Primary Lung Tumor and Lymph Nodes

	pCR	Non-pCR	p-value
Primary lung tumor (n=130)	45	85	
SULpeak RR (%) TLG RR (%)	76.0±18.5 95.5±5.8	60.3±25.4 84.1±20.8	<0.001 <0.001
Metastatic lymph nodes (n=87)	46	41	
SULpeak RR (%) TLG RR (%)	68.2±34.6 79.2±41.7	50.1±28.5 72.3±40.6	0.009 0.434

Abbreviations: pCR, pathological complete response; SUL, standardized uptake values corrected for lean body mass; TLG, total lesion glycolysis; RR; reduction rate.

To evaluate the efficacy of predicting pCR in primary lung tumors, the cut-off values for the reduction rates in SULpeak and TLG to pCR were determined using ROC curve analyses. The AUC values were 0.707 for SULpeak and 0.703 for TLG. The optimal cut-off percentages for the reduction rate in primary tumors were 76.0% for SULpeak and 97.0% for TLG. Using the cut-off values of SULpeak reduction rate and TLG, the sensitivity and specificity were 62.2% and 71.8% and 62.2% and 74.1%, respectively (Figure 1a and c).

Predictive Value for Pathological Complete Response in Lymph Nodes

Among 87 patients with possible lymph node metastases, 46 (52.9%) patients were determined to have pCR in lymph nodes. Patients with pCR had a significantly higher reduction rate in SULpeak; however, differences in TLG were not significant between patients in the pCR and non-pCR groups (Table 5).

To evaluate the efficacy of predicting pCR in lymph nodes, the cut-off values for the reduction rates were determined using ROC curve analyses. The AUC values were 0.688 for SULpeak and 0.642 for TLG. The optimal cut-off percentages for the reduction rate in lymph nodes were 75.0% in SULpeak and 97.0% in TLG. Using the cut-off values of SULpeak reduction rate and TLG, the sensitivity and specificity values were 56.5% and 78.0% and 50.0% and 78.0%, respectively (Figure 1b and d).

Comparison of the Reduction Rates According to the Treatment Regimen Used and Histological Tumor Type

We further conducted sub-group analyses according to the induction regimen used (CRT vs chemotherapy) and histological type of the tumor (non-squamous vs squamous cell carcinoma). In regard to the response of the primary lung tumors, a significantly higher reduction rate in the SULpeak and TLG was observed in the patients who received CRT than in those who received chemotherapy (p=0.002 and p=0.007, respectively). However, in the case of the response to treatment of the metastatic lymph node, no significant difference in the reduction rate of the SULpeak and TLG was observed in patients who received CRT than in those who received chemotherapy (p=0.440 and p=0.571, respectively). (Table 6a) In the other sub-analysis, a significantly higher reduction rate in the SULpeak was observed in patients with squamous cell carcinoma histology in the primary tumor than in those with non-squamous cell carcinoma histology, however, no significant differences in the reduction rate of TLG was observed between the two groups (p=0.020 and p=0.130, respectively). In regard to the influence of the tumor histology in the metastatic lymph node, no significant differences in the reduction rate of the SULpeak and TLG was observed in the patients with a significantly higher reduction rate in SULpeak and TLG than patients with squamous cell carcinoma histology than in those with non-squamous cell carcinoma histology (p=0.075 and p=0.101, respectively). (Table 6b)

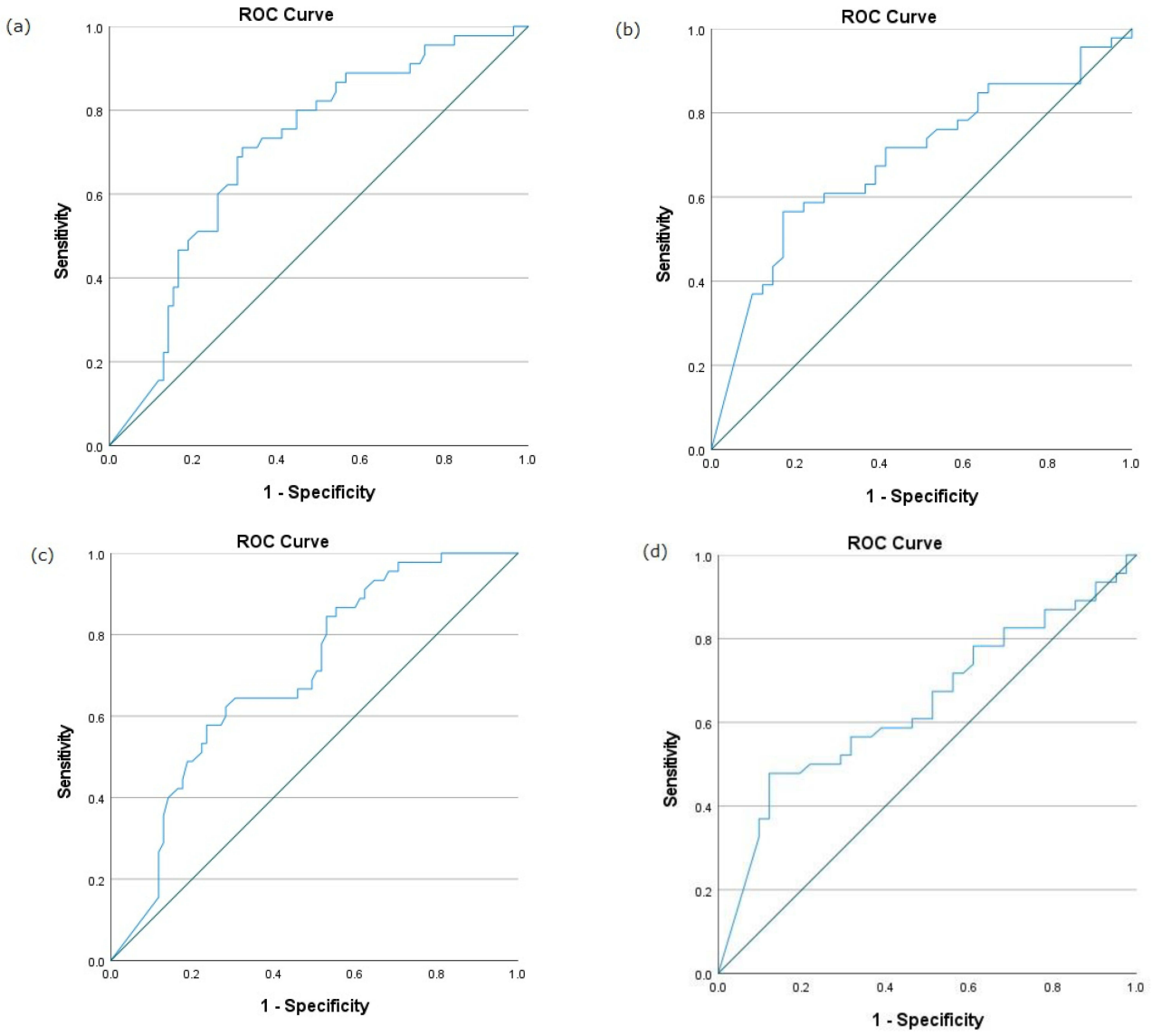

Figure 1 (**a**) Post SULpeak reduction rate ROC curve: AUC; 0.707, 95% CI 0.615–0.798, p<0.001, Sensitivity 62.2%, Specificity 71.8%, best cut off value; 76% to predict complete responder for primary lung tumor. (**b**) Post SULpeak reduction rate ROC curve: AUC; 0.688, 95% CI 0.576–0.800, p=0.003, Sensitivity 56.5%, Specificity 78.0%, best cut off value, 75%; to predict complete responder for metastatic lymph node. (**c**) Post TLG reduction rate ROC curve: AUC; 0.703, 95% CI 0.611–0.792, p<0.001, Sensitivity 62.2%, Specificity 71.8%, best cut off value, 97%; to predict complete responder for primary lung tumor. (**d**) Post TLG reduction rate ROC curve: AUC; 0.642, 95% CI 0.525–0.759, p=0.023, Sensitivity 50.0%, Specificity 78.0%, best cut off value, 97%; to predict complete responder for metastatic lymph node.

Predictive Value for Recurrence-Free Survival

The median follow-up period from the date of induction therapy initiation until recurrence was 59.5 months (range, 3.0–150.0 months). At the time of the analysis, 51 (39.2%) patients had experienced recurrence, and 43 (33.1%) patients had died. The sites of recurrence were the brain (n = 19), intrathoracic lymph node (n = 10), lung (n = 10), bone (n = 4), and other sites (n = 8).

The median OS and RFS were 56.7 and 46.2 months, respectively. The 2-year and 5-year OS rates were 83.8% and 66.7%, respectively, whereas the 2-year and 5-year RFS rates were 65.2% and 58.7%, respectively. In a univariate Cox regression analysis for RFS, the reduction rates of TLG in primary tumor, pCR of primary tumor, and pathologic N0 were significant predictors of a better RFS. In a multivariate Cox regression analysis, tumor site in the upper lobe, reduction rates of TLG, and pathological N0 were independent predictors of RFS (Table 7a).

Table 6 Reduction Rates of the SULpeak and TLG Depending on the Treatment Regimen and Tumor Histological Type

(a) Comparison according to the induction regimen used			
	Chemoradiotherapy	**Chemotherapy**	**p-value**
Primary lung tumor (n=130)			
SUL RR	69.9±21.6	50.7±28.0	0.002
TLG RR	90.7±15.1	78.4±23.8	0.007
Metastatic lymph node (n=87)			
SUL RR	61.3±32.1	54.1±36.2	0.44
TLG RR	74.9±44.4	79.6±26.8	0.571
(b) Comparison according to the histological type of the tumor			
	Non-Squamous	**Squamous**	**p-value**
Primary lung tumor (n=130)			
SUL RR	61.7±24.8	71.6±22.6	0.02
TLG RR	86.2±19.4	90.8±15.5	0.13
Metastatic lymph node (n=87)			
SUL RR	63.3±24.7	73.2±25.1	0.075
TLG RR	85.1±20.4	91.7±17.1	0.101

Table 7 Factors Associated with Recurrence-Free Survival

	Univariate		**Multivariate**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
(**a**) all cases (n=130)				
Age (years) >70 vs <70	1.36 (0.75–2.46)	0.313		
Sex Male vs Female	0.54 (0.29–1.08)	0.053	0.76 (0.40–1.45)	0.411
Histology SCC vs non-SCC	0.68 (0.38–1.22)	0.600		
Tumor Location Lower vs Upper lobe	1.62 (0.91–2.87)	0.099	1.95 (1.06–3.59)	0.031
Clinical Stage III vs II	1.57 (0.62–3.95)	0.341		
Induction therapy Chemotherapy vs CRT	0.89 (0.46–1.69)	0.715		
PERCIST NonCMR vs CMR	1.50 (0.54–4.15)	0.440		
SULpeak RR in primary tumor <76 vs >76	1.57 (0.88–2.82)	0.128		
TLG RR in primary tumor <97 vs >97	2.46 (1.31–4.62)	0.005	2.14 (1.06–4.34)	0.035

(*Continued*)

Table 7 (Continued).

	Univariate		Multivariate	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Pathological T factor T0 vs T1-4	2.40 (1.23–4.68)	0.010	1.31 (0.59–2.92)	0.513
Pathological N factor N0 vs N1-2	2.81 (1.61–4.92)	<0.001	2.09 (1.12–3.92)	0.021
(**b**) cases with possible metastatic lymph nodes (n=87)				
Age (years) >70 vs <70	1.09 (0.56–2.10)	0.805		
Sex Male vs Female	0.74 (0.36–1.51)	0.402		
Histology SCC vs non-SCC	0.67 (0.35–1.27)	0.219		
Tumor Location Lower vs Upper lobe	1.35 (0.72–2.51)	0.349		
Clinical Stage III vs II	1.09 (0.34–3.53)	0.888		
Induction therapy Chemotherapy vs CRT	1.12 (0.53–2.35)	0.762		
PERCIST NonCMR vs CMR	1.80 (0.64–5.07)	0.263		
SULpeak RR in lymph node <75 vs >75	1.71 (0.87–3.35)	0.120		
TLG RR in lymph node <97 vs >97	2.23 (1.07–4.69)	0.033	1.53 (0.69–3.42)	0.298
Pathological T factor T0 vs T1-4	3.09 (1.42–6.70)	0.004	2.29 (0.95–5.51)	0.064
Pathological N factor N0 vs N1-2	2.33 (1.24–4.37)	0.009	1.38 (0.66–2.89)	0.393

Abbreviations: SCC, squamous cell carcinoma; CRT, chemoradiotherapy; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors CMR, complete metabolic response; SUL, standardized uptake values corrected for lean body mass; TLG, total lesion glycolysis; RR; reduction rate.

In cases with possible metastatic lymph nodes, a multivariate Cox regression analysis showed that the reduction rates of TLG in lymph nodes, pCR of primary tumor, and pathologic N0 were significant predictors of better RFS. However, in a multivariate Cox regression analysis, reduction rate of TLG in lymph nodes was not an independent predictor of RFS (Table 7b).

Discussion

PERCIST is a relatively new method for assessing tumor viability. In assessments using FDG-PET, SUV value is a widely used metric for assessing tissue accumulation of tracers. However, SUV is influenced by several variables, such as blood glucose level, body weight, reconstruction method, matrix size, and partial volume effect. Additionally, SUVmax is determined based on only one pixel representing the most intense FDG uptake in the tumor, and it may

not be representative of the total uptake by the whole tumor mass. In assessments using PERCIST, glucose uptake in adipose tissues was found to be relatively low and was not overestimated in patients with obesity.[16,17] Additionally, the potential noise at a single pixel could be reduced by assessments based on the SULpeak.[18] TLG, as a volume-based parameter, can be used to evaluate total tumor burden and metabolic activity. Recent studies have demonstrated the possible efficacy of TLG rather than SUVmax in predicting response to therapy.[17] Therefore, PERCIST is expected to gather more accurate data on tumor viability.

In this study, we evaluated the predictive value of PERCIST for predicting pathologic response in patients with locally advanced NSCLC who underwent induction chemotherapy or CRT followed by surgery. The results demonstrated that PERCIST was significantly correlated with pathologic response, whereas the correlation between RECIST and pathological response was not significant. Regarding primary lung tumors, patients with pCR had significantly higher reduction rates in both SULpeak and TLG than those without pCR. Regarding metastatic lymph nodes, SULpeak was significantly decreased in patients with pCR. Recently, perioperative treatment of lung cancer, especially treatment with immune checkpoint inhibitors, has shifted in the direction of neoadjuvant therapy, and the post-neoadjuvant status is extremely important to determine the surgical indication.[19] Our study suggested that PERCIST, especially the rate of TLG reduction rate, are useful to predict the pathological response and prognosis after induction therapy. The sensitivity of PERCIST in predicting pCR was superior to that of RECIST (16.7% vs 4.8%). However, the sensitivity value of 16.7% was unsatisfactory for use in clinical practice. If pCR can be predicted at a high sensitivity, it would be possible to avoid unnecessary surgery and would be of great benefit to the patients. However, our data show that in many cases, pCR could not be confirmed without surgery in this study.

The possible reason for the low sensitivity would be the influence of radiation therapy. In this study, 102 (78.5%) patients underwent CRT. Persistent local inflammation or granulation caused by radiation therapy could induce false-positive FDG accumulation. Therefore, FDG-PET should be performed no sooner than about 2 months after the completion of radiation therapy. However, in the treatment for lung cancer, the optimal interval between the completion of induction therapy and pulmonary resection is thought to be 4–6 weeks. Therefore, the shorter interval between the completion of induction CRT and surgery might have affected the sensitivity in this retrospective study. On the other hand, the specificity of PERCIST in predicting pCR was inferior to that of RECIST (88.6% vs 100%). Among 10 patients with false-negative results after evaluation with PERCIST, four and six patients had residual tumor cells in primary tumors and both primary tumors and lymph nodes, respectively. Since the current study was retrospective, detailed pathologic findings of those patients could not be evaluated.

As a predictive value for prognosis, multivariate analysis demonstrated that the reduction rate of >97% in TLG was one of the independent predictors of RFS. However, in cases with metastatic lymph nodes, neither SULpeak reduction rates nor TLG reduction rates were correlated with RFS. Previous studies have already reported the predictive value of PERCIST in several malignancies. In cases of breast cancer, Kitajima et al reported that cases with CMR had a significantly longer RFS than those without CMR.[11] In cases of esophageal cancer, Nakajo et al reported that patients with CMR or PMR had significantly longer survival than those with SMD or PMD.[12] Additionally, in cases of pancreatic cancer, Yokose et al reported that the MTV reduction rates were independent predictors of RFS.[20] These studies demonstrated the predictive value of PERCIST in determining prognosis, whereas the variables used in predicting prognosis were different in each study. In our study, TLG RR was one of the independent predictors of RFS; however, CMR was not correlated with RFS. The differences in cancer type and treatment regimens could have affected the results; therefore, further studies on these malignancies are needed.

In addition to RESIST and PERCIST, several investigators have proposed a method called radiomics. Radiomics is the extraction of quantitative data from medical imaging, with the potential to characterize the tumor phenotype. Chang et al, who proposed identification of predictive imaging biomarkers from pre-treatment CT images and constructed a radiomics model, reported a high accuracy of the radiomics model to predict the response to chemotherapy in patients with NSCLC. On the other hand, Chetan MR who published a review article on radiomics, described that radiomics research is not yet ready to be translated into clinical use. Further studies adopting a standardized approach are needed.[21,22]

Our study had some limitations. First, it was a retrospective study among a selected patient group with a relatively small sample size, thus limiting the generalizability of the study findings and possibly introducing statistical errors. Second, the chemotherapy regimen and radiation dose in this retrospective multicenter study were heterogeneous. Further prospective investigations with large numbers of patients with scheduled chemotherapy regimens and RT doses are needed.

In conclusion, our study suggested that PERCIST, especially the rate of TLG reduction rate, are useful to predict the pathological response and prognosis after induction therapy. Although improvement is necessary, PERCIST can be a promising method of the post-induction status in lung cancer. Further research is needed to confirm our findings.

Data Sharing Statement

The data is not publicly available to protect patient privacy. Further details and other data supporting our study's findings are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

All procedures were performed in accordance with the Helsinki Declaration and were reviewed and approved by the Ethics Committee of the Kawasaki medical school. This study was conducted retrospectively, and some patients were deceased at the commencement of the study. Our data did not contain any personally identifiable patient information and underwent confidentiality measures during the data collection process. Due to these aforementioned factors, the need for written informed consent was waived by the ethics committee of the Kawasaki medical school.

Consent for Publication

All authors agreed to publish the paper in any form.

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Disclosure

The authors declare no conflicts of interest in this work.

References

1. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomized controlled trial. *Lancet*. 2009;374(9687):379–386. doi:10.1016/S0140-6736(09)60737-6
2. Toyooka S, Kiura K, Takemoto M, et al. Long-term outcome of induction chemoradiotherapy with docetaxel and cisplatin followed by surgery for non-small-cell lung cancer with mediastinal lymph node metastasis. *Interact Cardiovasc Thorac Surg*. 2012;14(5):565–569. doi:10.1093/icvts/ivs028
3. Nagai K, Tsuchiya R, Mori T, et al.; Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group. A randomized trial comparing induction chemotherapy followed by surgery with surgery alone for patients with stage IIIA N2 non-small cell lung cancer (JCOG 9209). *J Thorac Cardiovasc Surg*. 2003;125(2):254–260. doi:10.1067/mtc.2003.15
4. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst*. 2007;99(6):442–450. doi:10.1093/jnci/djk093
5. Yokomise H, Gotoh M, Okamoto T, et al. Induction chemoradiotherapy (carboplatin-taxane and concurrent 50-Gy radiation) for bulky cN2, N3 non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2007;133(5):1179–1185. doi:10.1016/j.jtcvs.2006.12.039
6. Kayawake H, Okumura N, Yamanashi K, et al. Non-small cell lung cancer with pathological complete response: predictive factors and surgical outcomes. *Gen Thorac Cardiovasc Surg*. 2019;67(9):773–781. doi:10.1007/s11748-019-01076-9
7. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247. doi:10.1016/j.ejca.2008.10.026
8. de Geus-Oei LF, van der Heijden HF, Corstens FH, Oyen WJ. Predictive and prognostic value of FDG-PET in nonsmall-cell lung cancer: a systematic review. *Cancer*. 2007;110(8):1654–1664. doi:10.1002/cncr.22979
9. Tamandl D, Gore RM, Fueger B, et al. Change in volume parameters induced by neoadjuvant chemotherapy provide accurate prediction of overall survival after resection in patients with oesophageal cancer. *Eur Radiol*. 2016;26(2):311–321. doi:10.1007/s00330-015-3860-7
10. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving Considerations for PET response criteria in solid tumors. *J Nucl Med*. 2009;50(Suppl 1):122S–50S. doi:10.2967/jnumed.108.057307

11. Kitajima K, Nakatani K, Yamaguchi K, et al. Response to neoadjuvant chemotherapy for breast cancer judged by PERCIST: multicenter study in Japan. *Eur J Nucl Med Mol Imaging*. 2018;45(10):1661–1671. doi:10.1007/s00259-018-4008-1
12. Nakajo M, Kitajima K, Kaida H, et al. The clinical value of PERCIST to predict tumour response and prognosis of patients with oesophageal cancer treated by neoadjuvant chemoradiotherapy. *Clin Radiol*. 2020;75(1):79.e9–79.e18. doi:10.1016/j.crad.2019.09.132
13. Toyooka S, Okumura M, Nakamura H, et al. A multicenter randomized controlled study of paclitaxel plus carboplatin versus oral uracil-tegafur as the adjuvant chemotherapy in resected non-small cell lung cancer. *J Thorac Oncol*. 2018;13(5):699–706. doi:10.1016/j.jtho.2018.02.015
14. Ding Q, Cheng X, Yang L, et al. PET/CT evaluation of response to chemotherapy in non-small cell lung cancer: PET response criteria in solid tumors (PERCIST) versus response evaluation criteria in solid tumors (RECIST). *J Thorac Dis*. 2014;6(6):677–683. doi:10.3978/j.issn.2072-1439.2014.05.10
15. Japan Lung Cancer Society. *General Rule for Clinical and Pathological Record of Lung Cancer*. 7th ed. Tokyo, Japan: Kanehara & Co;2010.
16. Nahmias C, Wahl LM. Reproducibility of standardized uptake value measurements determined by ^{18}F-FDG PET in malignant tumours. *J Nucl Med*. 2008;49(11):1804–1808. doi:10.2967/jnumed.108.054239
17. Tahari AK, Chien D, Azadi JR, Wahl RL. Optimum lean body formulation for correction of standardized uptake value in PET imaging. *J Nucl Med*. 2014;55(9):1481–1484. doi:10.2967/jnumed.113.136986
18. Boellaard R. Standards for PET image acquisition and quantitative data analysis. *J Nucl Med*. 2009;50(Suppl 1):11S–20S. doi:10.2967/jnumed.108.057182
19. Forde PM, Spicer J, Lu S, et al.; CheckMate 816 Investigators. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N Engl J Med*. 2022;386(21):1973–1985. doi:10.1056/NEJMoa2202170
20. Yokose T, Kitago M, Matsusaka Y, et al. Usefulness of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography for predicting the prognosis and treatment response of neoadjuvant therapy for pancreatic ductal adenocarcinoma. *Cancer Med*. 2020;9(12):4059–4068. doi:10.1002/cam4.3044
21. Chang R, Qi S, Yue Y, Zhang X, Song J, Qian W. Predictive radiomic models for the chemotherapy response in non-small-cell lung cancer based on computerized-tomography images. *Front Oncol*. 2021;11:646190. eCollection 2021. doi:10.3389/fonc.2021.646190
22. Chetan MR, Gleeson FV. Radiomics in predicting treatment response in non-small-cell lung cancer: current status, challenges and future perspectives. *Eur Radiol*. 2021;31(2):1049–1058. doi:10.1007/s00330-020-07141-9