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Proposing synchronous oligometastatic non–small-cell lung cancer based on progression after first-line systemic therapy

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Abstract

Despite the importance of accurate disease definitions for effective management and treatment decisions, there is currently no consensus on what constitutes oligometastatic non–small-cell lung cancer (NSCLC). Predominant patterns of initial progressive disease (PD) after first-line systemic therapy have been shown to be a substantial basis for local ablative therapy (LAT) for all disease sites in patients with oligometastatic NSCLC, suggesting that these patterns could be helpful in defining synchronous oligometastatic NSCLC. Therefore, this retrospective study aimed to propose a threshold number of metastases for synchronous oligometastatic NSCLC, based on the pattern of initial PD after first-line systemic therapy. The cut-off threshold number of metastases compatible with synchronous oligometastatic NSCLC was determined using receiver operating characteristic (ROC) curve analyses of PD at the initially involved sites alone. ROC analysis of 175 patients revealed that the presence of 1-3 metastases before first-line treatment (sensitivity, 85.9%; specificity, 97.3%; area under the curve, 0.91) was compatible with oligometastatic NSCLC, therefore we divided patients into oligometastatic NSCLC and non-oligometastatic NSCLC groups. Multivariate logistic regression analyses revealed oligometastatic NSCLC to be the only independent predictor of PD at initially involved sites alone (odds ratio 165.7; $P < .001$). The median survival times in patients with oligometastatic or non-oligometastatic NSCLC were 23.0 and 10.9 mo (hazard ratio, 0.51; $P = .002$), respectively. Based on these findings, we propose synchronous oligometastatic NSCLC as 1-3 metastases in accordance with patterns of initial progression. The result of our study might be contributory to provide a common definition of synchronous oligometastatic NSCLC.

1 | INTRODUCTION

Patients with advanced NSCLC treated with platinum-based chemotherapy have poor prognoses, with reported median overall survival (OS) times of 12-13 mo.[1-3]

Synchronous oligometastatic NSCLC is generally recognized as a disease type with limited spreading at the time of diagnosis.[4] Previous studies evaluating patterns of initial PD revealed that almost two-thirds of patients developed PD in the initially involved sites alone after first-line systemic therapy in patients with oligometastatic NSCLC.[5,6] Furthermore, basic science studies have suggested that oligometastatic cancers have metastatic potential that can remain dormant for some time.[7,8] Overall, these findings suggested that oligometastatic NSCLC has distinctive features and that treatment with LAT to all sites may improve survival in this patient group.[9]

Several retrospective and prospective studies have suggested that LAT in patients with few metastases is effective.[10-13] Two randomized phase II trials with patients with oligometastatic NSCLC (defined as 1-3 and 1-5 metastases, respectively) have shown that adding LAT as a treatment delivered to all sites is associated with prolonged progression-free survival (PFS).[14-16] Moreover, one of these trials demonstrated that LAT was associated with prolonged OS.[15] Finally, a meta-analysis has shown that LAT to the primary tumor improved the survival in patients with oligometastatic NSCLC.[17]

Although the number of clinical trials involving patients with oligometastatic NSCLC has increased dramatically over the past decade, the definition of oligometastatic disease remains controversial.[18-21] Accurate disease definition is paramount to effective research and practice. Predominant patterns of initial PD after first-line systemic therapy have shown to be a substantial basis for LAT to all disease sites in patients with oligometastatic NSCLC, suggesting that these patterns could help to define synchronous oligometastatic NSCLC. Therefore, this retrospective study aimed to propose a threshold number of metastases for synchronous oligometastatic NSCLC, based on the pattern of initial PD after first-line systemic therapy.

2 | MATERIALS AND METHODS

2.1 | Patients

This study protocol was approved by our institutional ethics review board. Medical records of 829 patients with advanced NSCLC who had undergone first-line platinum-based chemotherapy at the Shizuoka Cancer Center between February 2010 and December 2018 were reviewed retrospectively. Patient age, sex, smoking status, ECOG PS, and histology findings at the time of the first dose of platinum-based chemotherapy were recorded. None of the patients in this study was treated with definitive LAT. Patients who had PS scores of 2-4, those with interstitial lung disease, and those with tumors harboring *EGFR/ALK/ROS1* genetic aberrations were excluded from this study. The presence of malignant pleural or pericardial effusion is known to be an independent predictor of poor survival in patients with advanced NSCLC.[22,23] Furthermore, patients with diffuse serosal metastases (pericardial, pleural, meningeal, and mesenteric) were excluded from the present study due to their ineligibility for LAT in accordance with the multidisciplinary consensus statement on the definition of oligometastatic NSCLC.[21] In addition, patients with interstitial lung disease were excluded from this study because they tended to have a poor prognosis due to the limited availability of chemotherapy regimens.[24,25]

2.2 | Treatment and assessments

The tumor stage was assessed using thoracic and abdominal computed tomography (CT) scan, positron emission tomography with fludeoxyglucose F18 integrated with CT (PET-CT), and brain magnetic resonance imaging (MRI). In all eligible patients, metastatic lesions were diagnosed independently by thoracic oncologists and radiologists. Each lesion was counted separately and contributed to the total number of metastatic lesions. Based on a previous study, any metastatic thoracic lymph nodes (N1-N3), including those in the supraclavicular fossae, were collectively considered as a single lesion.[15,26] PD was identified by reviewing follow-up radiological imaging with CT, MRI, or PET-CT after initiation of platinum-based chemotherapy. Eligible patients were required to have at least one available imaging report after initiation of platinum-based chemotherapy. Tumor responses were classified in accordance with RECIST version 1.1.[27] Patients showing PD were included in the analysis to determine the cut-off threshold for the number of metastases, and they were classified in accordance with the pattern of initial PD as follows: PD in the initially involved sites alone without development of new metastatic lesions, PD in new sites, or PD in both initially involved and new sites.

2.3 | Statistical analyses

The cut-off threshold for the number of metastases was determined using ROC curve analyses of the occurrence of PD in the initially involved sites alone, without the development of new metastatic lesions as a function of the number of metastatic lesions.

To determine the optimal cut-off threshold, we determined the number of metastases that produced the maximum sum of sensitivity and specificity. Subsequently, we divided patients into synchronous

oligometastatic NSCLC and non-oligometastatic NSCLC groups. PFS was calculated from the initiation of first-line platinum-based chemotherapy to the first evidence of disease progression or death from any cause. The OS was calculated from the initiation of first-line platinum-based chemotherapy to death from any cause. The end of the follow-up period was February 6, 2020. All categorical variables were analyzed using Fisher exact test, while continuous variables were analyzed using Wilcoxon rank sum test. The median PFS and OS were estimated using the Kaplan-Meier method and compared using log-rank test. Potential predictive factors for PD in the initially involved sites alone were assessed using univariate and multivariate analyses with a logistic regression model. Potential risk factors were assessed using univariate and multivariate analyses with a Cox proportional hazards model for PFS and OS. Covariates in the univariate analysis included age (≥70 vs <70 y), sex, smoking status, ECOG PS, histology findings (non-squamous vs squamous), nodal stage (0-1 vs 2-3), palliative local therapy status, central nervous system (CNS) metastases, number of distant metastatic organs (1 vs 2), and oligometastatic status. Factors with univariate P-values of <.1 were included in multivariate analyses. Differences with P-values <.05 were considered to be statistically significant. All analyses were performed with STATA version 14.0 (Stata Corp., Texas, USA).

3 | RESULTS

### 3.1 | Patient characteristics

From 829 eligible patients, we excluded 253 with *EGFR/ALK/ROS1* gene aberrations, 57 with interstitial lung disease, 96 with postoperative recurrence, 55 with ECOG PS scores of ≥2, and 101 with malignant pleural and pericardial effusion; another 89 patients were excluded for other reasons (Figure 1). Ultimately, 178 patients were included in this study. PET-CT and brain MRI were performed for all of them at diagnosis. The median patient age was 66 y (range 40-80 y). Almost 80% of patients were male, smokers, or had non-squamous NSCLC histology.

3.2 | Pattern of initial PD

The median follow-up time was 36 mo. PD was observed in 175 patients (98%), the incidences of which in the initially involved sites alone were 2 in all 2 patients with 1 metastasis (100%), 30 in 32 patients with 2 metastases (94%), 23 in 24 patients with 3 metastases (96%), 1 in 11 patients with 4 metastases (9%), 1 in 6 patients with 5 metastases (16%), none in 8 patients with 6 metastases (0%), none in 3 patients with 7 metastases (0%), none in 3 patients with 8 metastases (0%), none in 2 patients with 9 metastases (0%), and 7 in 84 patients with ≥10 metastases (8%) (Figure 2). PD in the initially involved site alone was more frequently observed in patients with 1-3 metastases compared with in patients of other groups. Based on the ROC analysis of PD in the initially involved sites alone per number of metastases, the optimal threshold for the number of metastases was 3, with a sensitivity of 85.9% and specificity of 97.3% (area under the curve, 0.91; 95% CI, 0.86-0.97; Figure 3). Therefore, we defined synchronous oligometastatic and non-oligometastatic NSCLCs as applicable to patients with 1-3 and ≥4 metastases, respectively. These definitions were used to divide patients into the oligometastatic NSCLC and non-oligometastatic NSCLC groups.
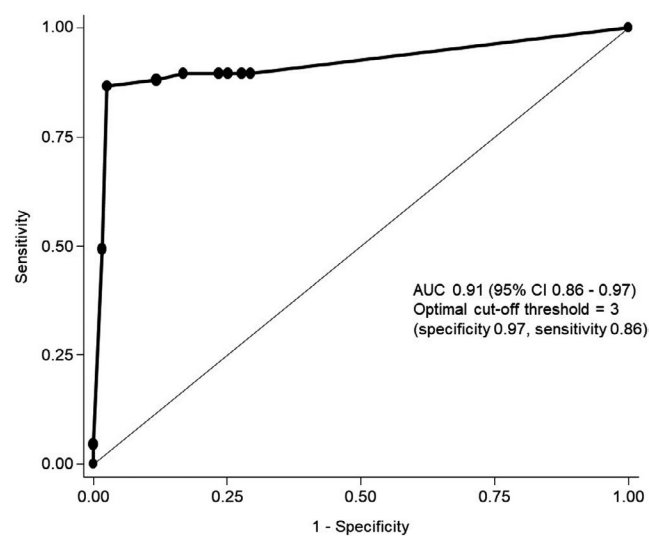
Patient flow diagram
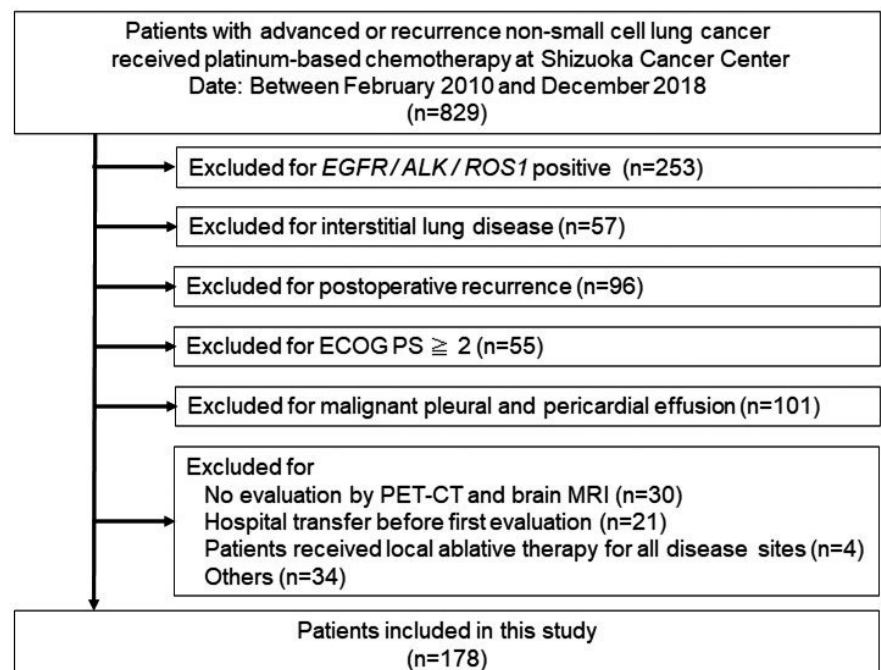
FIGURE 1 Study flowchart. ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; PS, performance status
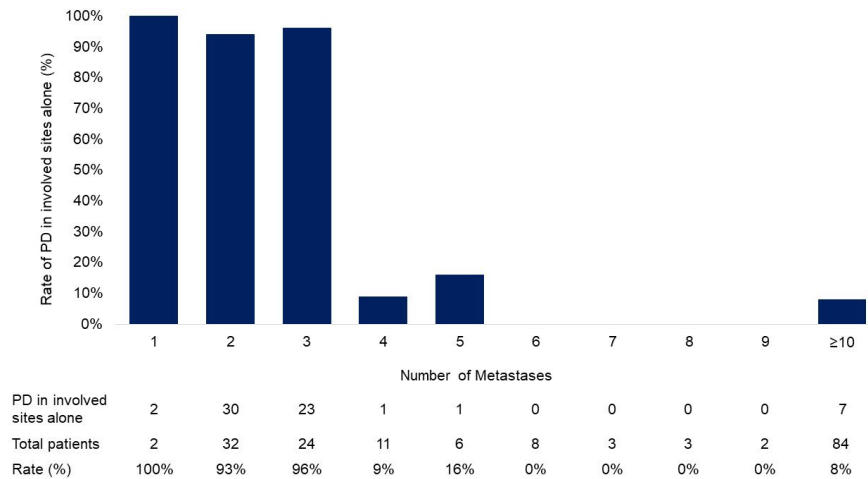
FIGURE 2 Incidence rate of progressive disease at the initially involved sites alone, shown per metastasis site. PD, progressive disease

	1	2	3	4	5	6	7	8	9	≥10
PD in involved sites alone	2	30	23	1	1	0	0	0	0	7
Total patients	2	32	24	11	6	8	3	3	2	84
Rate (%)	100%	93%	96%	9%	16%	0%	0%	0%	0%	8%

AUC 0.91 (95% CI 0.86 - 0.97)
Optimal cut-off threshold = 3
(specificity 0.97, sensitivity 0.86)

FIGURE 3 Receiver operating characteristic curve analyses for predicting disease progression at the initially involved sites alone per number of metastases. The optimal cut-off threshold for the number of metastases was 3, with a sensitivity of 85.9% and specificity of 97.3% (area under the curve, 0.91; 95% CI, 0.86-0.97)

We investigated several factors present at the time of diagnosis to identify the clinical characteristics predictive of PD in the initially involved sites alone. As shown in Table 1, univariable logistic regression analysis revealed that being a smoker (odds ratio [OR], 4.74; 95% CI, 1.35-16.6; P= 0.015), having one distant metastatic organ (OR, 10.4; 95% CI, 4.87-22.4; P < .001), and having oligometastatic NSCLC (OR, 220.0; 95% CI, 57.2-845.5; P < .001) were significantly associated with PD at the initially involved sites alone. Concurrently, being male (OR, 2.36; 95% CI, 0.96-3.03; P = .061) and having no initial CNS metastasis (OR, 1.96; 95% CI, 0.94-4.05; P = .069) were associated with PD at the initially involved sites alone. Multivariate logistic regression analyses demonstrated that an oligometastatic state (OR, 165.7; 95% CI, 36.7-748.5; P < .001) was the only independent predictor of PD at the initially involved sites alone.

3.3 | Comparisons between oligometastatic and non-oligometastatic NSCLC

The clinical characteristics of patients in both groups are summarized in Table 2. The distribution of smoking status (P = .042) and history of palliative local therapy before chemotherapy (P = .021) differed significantly between the oligometastatic NSCLC and non-oligometastatic NSCLC groups. The predominant distant metastatic organs also differed between the groups because bone, brain, lung, liver, and pleura metastases were more common in the non-oligometastatic compared with in the oligometastatic group. Eighty-nine percent of patients in the oligometastatic NSCLC group had 1 distant metastatic organ, while 69% of patients in the non-oligometastatic NSCLC group had ≥2 distant metastatic organs.

The objective response rate (ORR) for all patients was 30%. Patients with oligometastatic NSCLC tended to have better ORR compared with those with non-oligometastatic NSCLC (39% vs 25%, P = .059). The median PFS was 5.5 mo (95% CI, 4.2-6.0) in the oligometastatic NSCLC group vs 3.4 mo (95% CI, 2.9-4.4) in the non-oligometastatic NSCLC group. PFS was significantly longer in patients with oligometastatic NSCLC compared with in those with non-oligometastatic NSCLC (hazard ratio [HR] for disease progression or death, 0.64; 95% CI, 0.46-0.87; P = .005; Figure 4A). In multivariable PFS analyses, the oligometastatic state (HR, 0.65; 95% CI, 0.45-0.94; P = .023) and no initial CNS metastases (HR, 0.70; 95% CI, 0.50-0.99; P = .042) were independent and favorable prognostic factors. Finally, an ECOG PS score of 0 tended to be a favorable prognostic factor (HR, 0.74; 95% CI, 0.53-1.03; P = .070; Table 3).

Median OS was 23.0 mo (95% CI, 16.2-30.8) in the oligometastatic NSCLC group vs 10.9 mo (95% CI, 9.1-13.6) in the non-oligometastatic NSCLC group. OS was significantly longer in patients with oligometastatic NSCLC compared with in those with non-oligometastatic NSCLC (HR for death, 0.51; 95% CI, 0.36-0.73; P < .001; Figure 4B). In multivariable OS analyses, the oligometastatic state was an independent and favorable prognostic factor (HR, 0.51; 95%

TABLE 1 Association between patient characteristics and progression at the initially involved sites alone using a logistic regression model adjusted for patient characteristics (n = 175)

Covariates	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (<70 y vs ≥70 y)	1.15	0.56-2.36	.693			
Sex (male vs female)	2.36	0.96-3.03	.061	2.39	0.33-17.6	.389
ECOG performance status score (0 vs 1)	1.45	0.76-2.77	.257			
Smoking status (ever vs never)	4.74	1.35-16.6	**.015**	3.36	0.31-36.9	.321
Histology (squamous vs non-squamous)	1.10	0.46-2.59	.828			
T stage (1-2 vs 3-4)	1.64	0.88-3.05	.116			
Nodal stage (0-1 vs 2-3)	1.44	0.73-2.84	.283			
LPT before systemic therapy (no vs yes)	1.46	0.72-2.96	.292			
CNS metastases (no vs yes)	1.96	0.94-4.05	.069	1.12	0.28-4.42	.873
Number of metastatic organ (1 vs ≥2)	10.4	4.87-22.4	**<.001**	1.67	0.44-6.27	.447
Oligometastatic vs non-oligometastatic NSCLC	220.0	57.2-845.5	**<.001**	165.7	36.7-748.5	**<.001**

Note: Significant *P*-values are shown in bold type.

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group, LPT, local palliative therapy; OR, odds ratio.

CI, 0.34-0.77; *P* = .001), as was the ECOG PS score of 0 (HR, 0.61; 95% CI, 0.43-0.86; *P* = .005; Table 4).

4 | DISCUSSION

This retrospective study identified a cut-off threshold for the maximum number of metastases, proposing that NSCLC could be defined as a synchronous oligometastatic disease based on PD patterns observed in 175 patients with advanced NSCLC. To the best of our knowledge, this is the first study to propose such a threshold, based on patterns of initial progression after systemic therapy. Our ROC analysis revealed that the cut-off threshold for the maximum number of metastases predicting PD in the initially involved sites alone was 3. Multivariate logistic regression analyses confirmed that no clinical factor except oligometastatic state was an independent predictor of initial PD patterns.

Synchronous oligometastatic NSCLC has been defined differently in previous trials or guidelines; such definitions included 1 metastasis in 1 organ,[20] 1-3 metastases,[12,14,15,19,28,29] and 1-5 metastases.[11,16,21] The standardized definition for synchronous oligometastatic NSCLC has not been formulated.[18] An ongoing phase III trial defines patients with synchronous oligometastatic NSCLC as those with 1-3 metastases.[28] Furthermore, a survey by the European Organization for Research and Treatment of Cancer has shown that the maximum number of metastases considered indicative of a synchronous oligometastatic state in NSCLC varies; 19%, 42%, 4%, and 17% of the respondents

claimed that the maximum number of metastatic lesions was ≤2, 3, 4, and ≥5, respectively.[29] Our findings showed that 1-3 metastases appeared to be an acceptable criterion for synchronous oligometastatic NSCLC.

Our study findings are consistent with those of previous studies that have shown the dominant pattern of PD in patients with synchronous oligometastatic NSCLC after systemic chemotherapy was PD at the initially involved sites alone.[5,6] The oligometastatic state was described as an intermediate state of cancer spread between localized disease and widespread metastases.[4] PD in the initially involved sites alone indicated that the oligometastatic state remained confined to localized disease. Therefore, we considered it appropriate to use the patterns of initial PD to determine the criteria for defining a synchronous oligometastatic NSCLC.

Our study also revealed that patients with oligometastatic NSCLC had a better prognosis compared with those with non-oligometastatic NSCLC. Likewise, a previous retrospective study showed that patients with oligometastatic NSCLC had a better OS compared with those with multiple metastases.[12] This survival difference was consistent with data from previous trials by the Southwest Oncology Group, in which multivariate analyses revealed that an oligometastatic state was strongly associated with significantly prolonged OS.[30] The ECOG PS has also been found to be a significant prognostic factor in several previous studies that performed multivariable analyses.[31] A synchronous oligometastatic NSCLC may reflect a more indolent phenotype than does widespread metastatic disease.[12,30,32]

TABLE 2 Characteristics of patients with oligometastatic NSCLC and non-oligometastatic NSCLC patients at baseline (n = 178)

Characteristics		Oligometastatic NSCLC (n = 61)	Non-oligometastatic NSCLC (n = 117)	P
Age (range)		65 (40-77)	66 (41-80)	.507
Gender	Male	53 (87%)	92 (79%)	.224
	Female	8 (13%)	25 (21%)	
ECOG PS	0	26 (43%)	35 (30%)	.099
	1	35 (57%)	82 (70%)	
Smoking status	Ever	57 (93%)	96 (82%)	**.042**
	Never	4 (7%)	21 (18%)	
Histology	Non-squamous	48 (79%)	101 (85%)	.205
	Squamous	13 (21%)	16 (14%)	
Palliative local therapy before systemic therapy	Yes	10 (16%)	39 (33%)	**.021**
	No	51 (84%)	78 (67%)	
T	T1	16 (26%)	20 (17%)	.118
	T2	18 (30%)	31 (27%)	
	T3	16 (26%)	25 (21%)	
	T4	11 (18%)	40 (34%)	
	TX	0 (0%)	1 (1%)	
N	N0	10 (16%)	19 (16%)	.569
	N1	9 (15%)	11 (10%)	
	N2	19 (31%)	32 (27%)	
	N3	23 (38%)	55 (47%)	
Distant metastatic organ				
Bone		14 (23%)	56 (48%)	**.001**
Adrenal grand		16 (26%)	30 (26%)	1.000
Extra-thoracic lymph node		12 (20%)	20 (17%)	.685
Brain		12 (20%)	39 (33%)	.080
Pulmonary		5 (8%)	54 (46%)	**<.001**
Liver		4 (7%)	23 (20%)	**.026**
Pleura		0	14 (12%)	**.003**
Others		3 (5%)	25 (21%)	**.004**
Number of distant metastatic organs				
1		54 (89%)	36 (31%)	
2		7 (11%)	40 (34%)	
3		0	25 (21%)	
4		0	10 (9%)	
5		0	5 (4%)	
6		0	0	
7		0	1 (1%)	
Number of metastases				
1		2 (3%)	0	
2		34 (56%)	0	
3		25 (41%)	0	
4		0	11 (9%)	
5		0	6 (5%)	
6		0	8 (7%)	
7		0	3 (3%)	

(Continues)

TABLE 2 (Continued)

Characteristics	Oligometastatic NSCLC (n = 61)	Non-oligometastatic NSCLC (n = 117)	P
8	0	3 (3%)	
9	0	2 (2%)	
≥10	0	84 (71%)	

Note: Significant *P*-values are shown in bold type. 'Oligometastatic' refers to synchronous oligometastatic disease.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; N, regional lymph node involvement; PS, performance status; T, primary tumor.
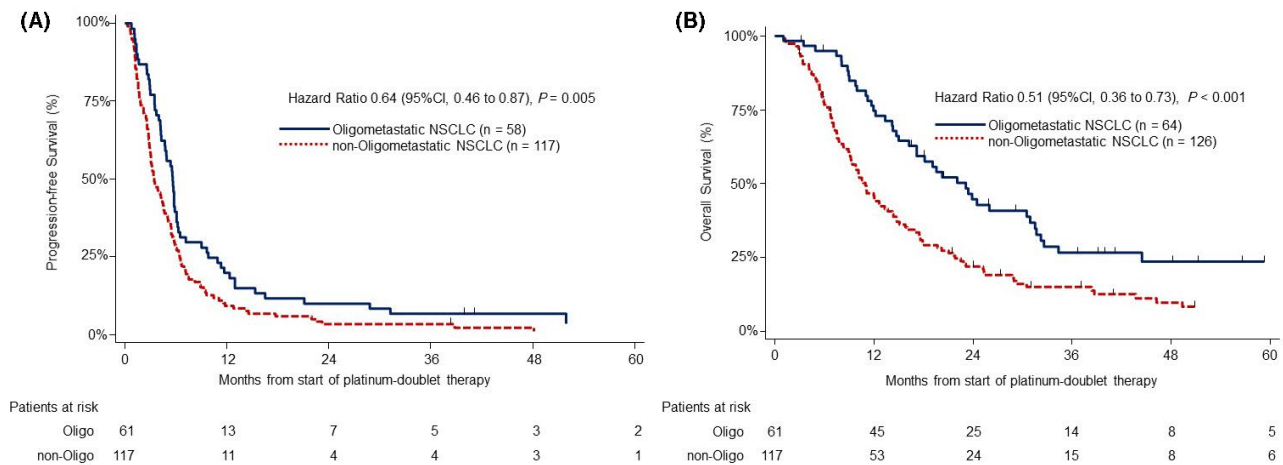
FIGURE 4 Kaplan-Meier curves for progression-free survival (A) and overall survival (B), in accordance with oligometastatic state. *P*-values were calculated using the log-rank test. CI, confidence interval; Oligo, oligometastatic. Small vertical lines on the curve indicate patients who were censored

TABLE 3 Univariable and multivariable analyses of covariates for progression-free survival (n = 178)

	Univariate analysis			Multivariate analysis		
Covariates	HR	95% CI	P-value	HR	95% CI	P-value
Age (<70 y vs ≥70 y)	0.76	0.54-1.07	.127			
Gender (female vs male)	0.60	0.41-0.89	**.013**	0.68	0.43-1.06	.087
ECOG performance status score (0 vs 1)	0.63	0.45-0.87	**.005**	0.74	0.53-1.03	.070
Smoking status (never vs ever)	0.57	0.37-0.89	**.032**	0.70	0.42-1.17	.142
Histology (non-squamous vs squamous)	1.21	0.79-1.84	.365			
T stage (1-2 vs 3-4)	0.73	0.54-1.00	.054	0.87	0.63-1.20	.418
Nodal stage (0-1 vs 2-3)	0.84	0.60-1.17	.311			
LPT before systemic therapy (no vs yes)	0.79	0.75-1.11	.186			
CNS metastases (no vs yes)	0.64	0.45-0.88	**.008**	0.70	0.50-0.99	**.042**
Number of metastatic organ (1 vs ≥2)	0.63	0.46-0.86	**.004**	0.87	0.60-1.25	.460
Oligometastatic vs non-oligometastatic NSCLC	0.64	0.46-0.87	**.006**	0.65	0.45-0.94	**.023**

Note: Significant *P*-values are shown in bold type.

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LPT, local palliative therapy.

TABLE 4 Univariable and multivariable analyses of covariates for survival outcomes

Covariates	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (<70 y vs ≥70 y)	0.87	0.59-1.27	.491			
Gender (female vs male)	0.71	0.46-1.09	.126			
ECOG performance status score (0 vs 1)	0.61	0.43-0.86	**.005**	0.61	0.43-0.86	**.005**
Smoking status (never vs ever)	0.60	0.35-1.02	.122			
Histology (non-squamous vs squamous)	1.19	0.74-1.91	.470			
T stage (1-2 vs 3-4)	0.82	0.59-1.14	.260			
Nodal stage (0-1 vs 2-3)	0.71	0.49-1.03	.074	0.74	0.51-1.09	.138
LPT before systemic therapy (no vs yes)	1.04	0.72-1.48	.758			
Brain metastases (no vs yes)	0.90	0.65-1.25	.528			
Number of metastatic organ (1 vs ≥2)	0.66	0.48-0.92	**.015**	1.02	0.70-1.50	.881
Oligometastatic vs non-oligometastatic NSCLC	0.51	0.36-0.73	**<.001**	0.51	0.34-0.77	**.001**

Note: Significant P-values are shown in bold type.

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LPT, local palliative therapy.

TABLE 5 Trials of PD-1/PD-L1 inhibitors for oligometastatic NSCLC

Trial	Eligibility criteria	Study design	Primary outcome	Treatment
NCT03275597	≤6 metastatic lesions	Phase I	Safety	Durvalumab/Tremelimumab with SBRT (30-50 Gy in 5 fractions) to all sites
NCT03965468	≤3 metastatic lesions	Phase II	OS	Durvalumab + Carboplatin + Paclitaxel followed by SBRT to all sites
NCT03774732	≤6 metastatic lesions	Phase III	OS	PD-1/PD-L1 Inhibitors with concurrent irradiation to all sites

Abbreviations: NSCLC, non–small-cell lung cancer; OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; SBRT, stereotactic body radiotherapy.

There were some limitations to our study. First, our analysis was limited by its retrospective nature and our inability to account for unknown confounders. Our study results were based on only 21.5% (n = 178) of patients with advanced NSCLC who received first-line platinum-based chemotherapy. Although not all patients had undergone comprehensive imaging at the time of disease progression, the patients were categorized based on all available imaging findings. Moreover, the cut-off threshold was determined from a cohort derived from a single institution and was not validated independently. Further multicenter studies with larger samples are required to validate our findings. Because previously there have been no specific criteria with which to define synchronous oligometastatic NSCLC, the approach shown in this study might be helpful in future investigations of synchronous oligometastatic NSCLC.

Although the present study proposed to define oligometastatic NSCLC as that with 1-3 metastases, the number of metastases might be a crude marker of compartmentalizing oligometastatic NSCLC. Further translational research into the definition of oligometastatic NSCLC is required.

Previous trials have suggested a benefit of LAT to all disease sites in patients with oligometastatic NSCLC with EGFR mutation.[17] Patients with EGFR mutated NSCLC had prolonged PFS and OS compared with those without EGFR mutation.[33] Concurrently, a separate report has shown no significant association between the number of metastases and patterns of initial PD in patients with EGFR-mutant NSCLC,[34] suggesting that a different approach might be required to explore the pattern of initial PD in EGFR tyrosine kinase inhibitors.

Recently, anti-programmed death 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors have transformed the treatment for patients with advanced NSCLC.[35,36] Various studies have revealed that LAT to multiple sites of disease could enhance the efficacy of PD-1/PD-L1 inhibitors.[37-40] Several trials are currently ongoing that are

investigating the feasibility and efficacy of radiotherapy combined with PD-1/PD-L1 inhibitors for patients with oligometastatic NSCLC (Table 5). Subsequent studies should aim to elucidate the pattern of initial PD in patients treated with PD-1/PD-L1 inhibitors.

In conclusion, our study has proposed that patients with synchronous oligometastatic NSCLC are those with 1-3 metastases, based on initial progression patterns. Patients with synchronous oligometastatic disease may experience a more indolent disease course compared with patients with non-oligometastatic NSCLC. The result of our study might be contributory to provide a common definition of synchronous oligometastatic NSCLC.

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