


Heterogeneous radiological response to chemotherapy is associated with poor prognosis in advanced non-small-cell lung cancer

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Abstract

Background: A heterogeneous radiological response is frequently observed in cancer patients and could reflect tumor heterogeneity. We investigated the prognostic impact of heterogeneous radiological responses in patients with advanced non-small-cell lung cancer (NSCLC) who received platinum-based chemotherapy.

Methods: The treatment response according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria was evaluated in 212 patients with advanced NSCLC who received platinum-based chemotherapy. Patients with partial response (PR) or stable disease (SD) were classified into “PR homo,” “PR hetero,” “SD homo,” and “SD hetero” by the presence of a heterogeneous radiological response, and survival was compared between groups. We also compared survival based on the presence of metabolic responses in lesions with heterogeneous radiological responses.

Results: Fifty-two patients (24.5%) were classified as PR, 112 patients (52.8%) as SD, and 48 patients (22.7%) as progressive disease (PD). There was no significant difference in progression-free survival (PFS) and overall survival (OS) between the PR homo and PR hetero groups. The SD homo group had a longer PFS and OS than the SD hetero group. In the SD hetero group, patients with increased maximum standardized uptake value (SUVmax) in lesions with heterogeneous radiological responses had a shorter PFS than those with a stable SUVmax.

Conclusions: The presence of lesions with radiological heterogeneity was associated with disease progression and poor prognosis in the SD group. Patients with heterogeneous radiological responses require careful monitoring.

KEYWORDS

metabolic response, non-small-cell lung cancer, radiological heterogeneity, RECIST, survival

INTRODUCTION

Non-small-cell lung cancer (NSCLC) accounts for approximately (~85%) of primary lung cancer and approximately (~60%) of NSCLC patients are diagnosed in the advanced stage.^{1,2} For decades, platinum-based chemotherapy has been used as the standard treatment for advanced NSCLC patients who were not eligible for targeted therapies or immunotherapies.³ However, 5-year survival is only 4% in

the advanced stage.¹ Some lung cancers are initially resistant to chemotherapy, and acquired resistance develops rapidly even in lung cancers that initially respond to chemotherapy.⁴ A comprehensive evaluation of the treatment response is important to determine the treatment regimen when disease progression is suspected.

Response Evaluation Criteria in Solid Tumors (RECIST) criteria have limitations because they do not reflect tumor heterogeneity and do not correlate with survival.⁵ Tumor heterogeneity is associated with tumor progression, treatment failure, and relapse.⁶ Heterogeneous radiological

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responses are frequently observed in cancer patients treated with chemotherapy or radiotherapy.^{7,8} Therefore, it is important to identify heterogeneous radiological responses because they reflect tumor heterogeneity.^{7,9,10} Although a few studies have investigated the association of radiological heterogeneity and prognosis in colorectal cancer and renal cell carcinoma, the prognostic impact on aggressive malignancies, such as lung cancer, have not yet been investigated.^{7,11–13} Positron emission tomography (PET) is expected to provide additional information on metabolic responses for the evaluation of tumor responses, based on anatomic changes evaluated with RECIST.¹⁴ However, further evidence is still needed for the use of PET in the evaluation of tumor responses.¹⁵

The aim of this study was to investigate the prognostic impact of heterogeneous radiological responses to platinum-based chemotherapy. In addition, we investigated the

additional information that PET could provide in the evaluation of treatment responses.

METHODS

Study population

A total of 1242 patients histologically diagnosed with advanced NSCLC and treated with platinum doublet as first-line therapy from July 2006 to June 2014 at Inha University Hospital were initially considered for this study. Among them, patients who did not undergo response evaluation ($n = 431$) or who were not treated with ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) during response evaluation ($n = 458$) were excluded. Patients with brain metastasis at diagnosis ($n = 97$) or who received

TABLE 1 Characteristics of non-small cell lung cancer patients treated with platinum-based chemotherapy

Variables	All patients ($n = 212$)	Treatment response			<i>p</i> value
		PR ($n = 52$)	SD ($n = 112$)	PD ($n = 48$)	
Age, yr					
<66	101 (47.6)	21 (40.4)	61 (54.5)	19 (39.6)	0.109
≥66	111 (52.4)	31 (59.6)	51 (45.5)	29 (60.4)	
Sex					
Male	155 (73.1)	40 (77.0)	85 (75.9)	30 (62.5)	0.167
Female	57 (26.9)	12 (23.0)	27 (24.1)	18 (37.5)	
Smoking habit					
Never	43 (20.3)	8 (15.3)	21 (18.8)	14 (29.2)	0.194
Current + former	169 (79.7)	44 (84.7)	91 (81.2)	34 (70.8)	
ECOG PS					
0–1	161 (75.9)	32 (61.5)	93 (83.0)	36 (75.0)	0.011
≥2	51 (24.1)	20 (38.5)	19 (17.0)	12 (25.0)	
Histology					
SQC	78 (36.8)	23 (44.2)	39 (34.8)	16 (33.3)	0.454
ADC	114 (53.8)	23 (44.2)	65 (58.1)	26 (54.2)	
Others	20 (9.4)	6 (11.6)	8 (7.1)	6 (12.5)	
EGFR mutation					
No	105 (49.5)	20 (38.5)	64 (57.1)	21 (43.8)	0.040
Yes	38 (18)	8 (15.4)	22 (19.7)	8 (16.7)	
Not tested	69 (32.5)	24 (46.1)	26 (23.2)	19 (39.5)	
Stage					
III	65 (30.7)	16 (30.8)	33 (29.5)	16 (33.4)	0.888
IV	147 (69.3)	36 (69.2)	79 (70.5)	32 (66.6)	
Chemotherapy agent					
Irinotecan/cisplatin	129 (60.8)	32 (61.5)	62 (55.3)	35 (72.9)	0.354
Gemcitabine/cisplatin	32 (15.2)	7 (13.5)	19 (17.0)	6 (12.5)	
Pemetrexed/cisplatin	31 (14.6)	6 (11.5)	21 (18.8)	4 (8.3)	
Others	20 (9.4)	7 (13.5)	10 (8.9)	3 (6.3)	

Abbreviations: ADC, adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; PD, progressive disease; PR, partial response; SD, stable disease; SQC, squamous cell carcinoma.

chemoradiation therapy ($n = 44$) were also excluded. In total, 212 patients were included in this study. Information about age, sex, smoking habits, Eastern Cooperative Oncology Group performance status (ECOG PS), histology, epidermal growth factor receptor (EGFR) mutation, staging, and chemotherapeutic agents were analyzed. The stage of all patients was estimated according to the 8th edition of the TNM classification system.¹⁶ All information was collected prospectively from the records of the Lung Cancer Cohort of Inha University Hospital.¹⁷ This study was approved by the Institutional Review Board of Inha University Hospital, and the requirement of obtaining written informed consent from patients was waived.

Response evaluation

Chest CT, PET/CT, and brain magnetic resonance imaging were conducted at the time of diagnosis and every 8–12 weeks using standard protocols. Responses were evaluated using RECIST 1.1.⁵ Radiological heterogeneity was assessed at the first reevaluation in patients who showed a partial response (PR) or stable disease (SD). Heterogeneous radiological response was defined as when the longest diameter of any measurable target lesion or the shortest diameter of any measurable target lymph node changed by more than 20%. Patients with PR or SD were classified as “PR homo,” “PR hetero,” “SD homo,” and “SD hetero” by the presence

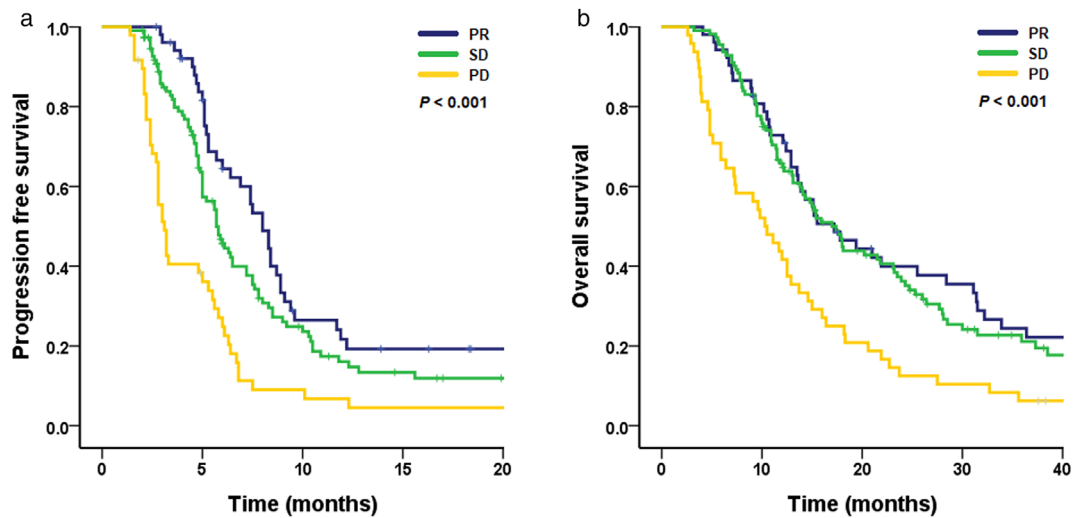


FIGURE 1 Kaplan–Meier curve of (a) progression-free survival and (b) overall survival by treatment response

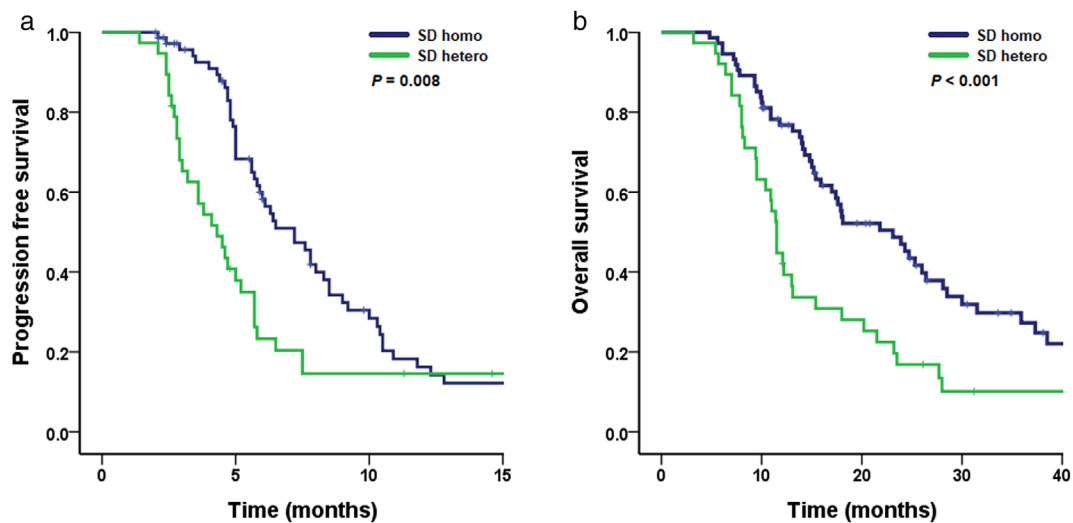


FIGURE 2 Kaplan–Meier curve of (a) progression-free survival and (b) overall survival by radiological heterogeneity in the stable disease group

TABLE 2 Effect of radiological heterogeneity on progression-free survival and overall survival in non-small cell lung cancer patients: univariate and multivariate analyses

Variables	Progression-free survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age, yr		0.756				0.169		
<66	Reference				Reference			
≥66	0.93 (0.60–1.44)				1.35 (0.88–2.06)			
Sex		0.127				<0.001		0.820
Male	Reference				Reference		Reference	
Female	0.67 (0.40–1.12)				0.33 (0.18–0.58)		0.89 (0.33–2.39)	
Smoking habit		0.038		0.004		<0.001		0.052
Never	Reference		Reference		Reference		Reference	
Ever	1.86 (1.03–3.34)		2.50 (1.34–4.67)		3.92 (1.96–7.85)		2.98 (0.99–8.95)	
ECOG PS		0.211				0.179		
0–1	Reference				Reference			
≥2	1.45 (0.81–2.58)				1.45 (0.84–2.51)			
Histology		0.965				0.006		0.289
SQC	Reference				Reference		Reference	
ADC	0.95 (0.59–1.50)				0.48 (0.31–0.76)		0.74 (0.44–1.25)	
Others	0.91 (0.35–2.37)				0.81 (0.34–1.94)		1.34 (0.54–3.45)	
EGFR mutation		0.704				0.031		0.317
No	Reference				Reference		Reference	
Yes	0.83 (0.46–1.48)				0.49 (0.27–0.89)		0.67 (0.34–1.31)	
Not tested	0.83 (0.49–1.41)				1.15 (0.69–1.91)		0.73 (0.41–1.27)	
Stage		0.095		0.041		0.893		
III	Reference		Reference		Reference			
IV	1.51 (0.93–2.45)		1.76 (1.02–3.01)		1.03 (0.65–1.64)			
Chemotherapy agent		0.054		0.099		0.804		
Irinotecan/cisplatin	Reference		Reference		Reference			
Gemcitabine/cisplatin	1.80 (1.00–3.23)		1.91 (1.06–3.46)		1.15 (0.67–2.00)			
Pemetrexed/cisplatin	2.21 (1.15–4.23)		1.90 (0.96–3.77)		0.95 (0.48–1.91)			
Others	1.22 (0.57–2.58)		1.22 (0.57–2.60)		0.74 (0.34–1.64)			
Radiological heterogeneity		0.010		0.014		0.001		0.001
SD homogeneous	Reference		Reference		Reference		Reference	
SD heterogeneous	1.81 (1.15–2.83)		1.77 (1.12–2.78)		2.17 (1.39–3.38)		2.27 (1.42–3.61)	

Abbreviations: ADC, adenocarcinoma; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; PD, progressive disease; PR, partial response; SD, stable disease; SQC, squamous cell carcinoma.

of lesions with heterogeneous radiological responses. We compared survival by the presence of heterogeneous radiological responses.

In addition, metabolic response was evaluated by changes in the maximum standardized uptake value (SUVmax) using PET/CT. The presence of abnormal fluorodeoxyglucose (FDG) uptake was indicated when accumulation of the radiotracer moderately to markedly increased relative to the expected uptake in normal structures or surrounding tissues, with the exclusion of physiological bowel and urinary activities. We compared survival by the presence of

metabolic responses in lesions with heterogeneous radiological responses.

Statistical analysis

To assess the association between treatment responses and clinical variables, Pearson's χ^2 test was conducted. Progression-free survival (PFS) and overall survival (OS) were calculated according to the Kaplan–Meier method and log-rank test. To assess the effect of radiological

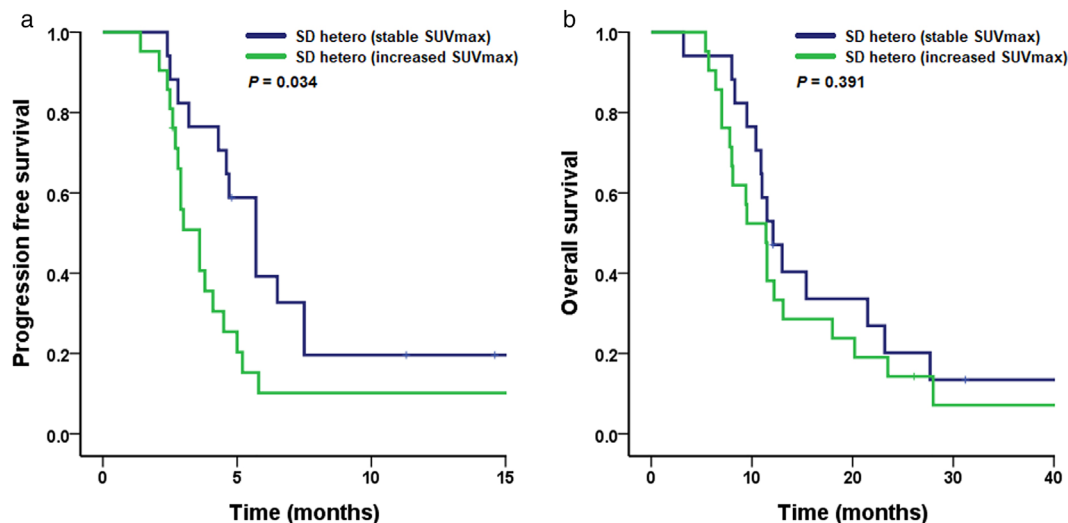


FIGURE 3 Kaplan–Meier curve of (a) progression-free survival and (b) overall survival by metabolic response in the stable disease hetero group

heterogeneity, we performed univariate and multivariate analyses using the Cox proportional hazards model. Variables that were found to have a value of $p \leq 0.1$ in univariate analysis were included in a multivariate Cox proportional hazards model. Statistical significance was considered as two-sided p values of < 0.05 . All statistical analyses were performed by using a statistical software package (SPSS, version 19.0).

RESULTS

Patient characteristics

According to RECIST 1.1, 52 patients (24.5%) were classified as PR, 112 patients (52.8%) as SD, and 48 patients (22.7%) as progressive disease (PD). Table 1 summarizes the baseline characteristics of the study population. The median age of the patients was 66 years (range, 37–84 years), and 155 (73.1%) patients were male. No statistically significant differences were found in the baseline variables between the three groups, except for the ECOG PS and EGFR mutation status. All patients received a combination of platinum-based chemotherapy, and more than half received irinotecan/cisplatin (60.8%).

Survival by treatment response

The median PFS and OS times were 5.7 months (95% confidence interval [CI] = 5.2–6.3 months) and 15 months (95% CI = 13.1–16.9 months), respectively. The PD group had shorter PFS than the SD and PR groups (median PFS [95% CI]; 3.1 months [2.7–3.6 months] in the PD group, 5.7 months [4.9–6.5 months] in the SD group, and 8.0 months [6.8–9.2 months] in the PR group, $p < 0.001$, Figure 1(a)). However, there was no significant difference in

PFS between the SD and PR groups. The PD group had a shorter OS than the SD and PR groups (median OS [95% CI]; 10.3 months [7.4–13.2 months] in the PD group, 17.0 [14.3–19.8 months] in the SD group, and 17.2 [11.5–22.9 months] in the PR group, $p < 0.001$, Figure 1(b)). However, there was no significant difference in the OS between the SD and PR groups.

The effect of radiological heterogeneity on survival

Of the 52 patients in the PR group, 46 patients (88.5%) had a homogeneous response (PR homo group) and 6 patients (11.5%) had a heterogeneous response (PR hetero group). There was no significant difference in PFS (median PFS [95% CI]; 8.3 months [7.2–9.4 months] in the PR homo group and 5.2 months [5.0–5.4 months] in the PR hetero group, $p = 0.271$) and OS (median OS [95% CI]; 17.2 months [11.7–22.7 months] in the PR homo group and 13.9 months [0.0–34.9 months] in the PR hetero group, $p = 0.530$) between the PR homo and PR hetero groups. Of the 112 patients in the SD group, there were 74 patients (66.1%) in the SD homo group and 38 patients (33.9%) in the SD hetero group. The SD homo group had a longer PFS (median PFS [95% CI]; 7.2 months [5.7–8.7 months] vs. 4.3 [3.1–5.5 months], $p = 0.008$) and OS (23.1 months [16.2–30.0 months] vs. 11.5 [10.7–12.3 months], $p < 0.001$) than the SD hetero group (Figure 2). Two representative examples of how the size of the lesion showing radiological heterogeneity increased, resulting PD in the patients of SD hetero group were highlighted in Figure S1.

Using multivariate analysis, smoking history (hazard ratio [HR] = 2.50 and 95% CI = 1.34–4.67, $p = 0.004$), stage (HR = 1.76 and 95% CI = 1.02–3.01, $p = 0.041$), and radiological heterogeneity (HR = 1.77 and 95% CI = 1.12–2.78, $p = 0.014$) were associated with PFS, whereas only

radiological heterogeneity (HR = 2.27 and 95% CI = 1.42–3.61, $p = 0.001$) was associated with OS (Table 2).

Association between metabolic response and survival in the SD hetero group

Among the SD hetero group ($n = 38$), lesions with heterogeneous radiological responses in 21 patients (55.3%) showed an increased SUVmax. In addition, lesions with heterogeneous radiological responses in 17 patients (44.7%) showed a stable SUVmax. Patients with an increased SUVmax in lesions with heterogeneous radiological responses had a shorter PFS than patients with a stable SUVmax (3.6 months vs. 5.7 months, $p = 0.034$) (Figure 3(a)). However, there was no significant difference in OS between patients with increased SUVmax and those with stable SUVmax (11.4 months vs. 12.1 months, $p = 0.391$) (Figure 3(b)).

DISCUSSION

In this study, patients with heterogeneous radiological responses in the SD group had shorter PFS and OS. This result suggested that radiological heterogeneity was associated with poor prognosis in NSCLC patients who received platinum-based chemotherapy. The presence of tumor cell variants with varying sensitivities to chemotherapy leads to the emergence of drug resistance.^{18,19} In addition, differences in blood supply within tumors are associated with poor delivery of chemotherapeutic agents to areas of low vascularity, resulting in impaired treatment response.²⁰ Therefore, we speculate that radiological heterogeneity represents tumor heterogeneity and the presence of treatment-resistant clones.

In this study, 11.5% of patients in the PR group and 44.7% of patients in the SD group showed radiological heterogeneity. This incidence is comparable to those of radiological heterogeneity in other kinds of cancer in previous studies.^{12,13} We defined radiological heterogeneity as more than 20% increase in the size of particular lesion in patients with PR or SD, considering the criteria in RECIST. Various criteria have been applied to the definition of radiological heterogeneity in previous studies, but it is necessary to establish clear definition. In addition, whereas previous studies limited the study subjects to patients with specific metastatic organs or mutations, we showed that the prognostic impact of radiological heterogeneity is applicable even in the broad patient population.

This study also showed that metabolic response was a predictive factor for disease progression in the SD hetero group. A PET/CT parameter, such as SUVmax, can reflect glucose metabolism of the tumor.^{21–23} Increased FDG uptake is associated with tumor cell proliferation because of enhanced glycolysis and overexpression of glucose transport in malignant cells.^{24–26} This potential mechanism could explain why patients with increased SUVmax in lesions with

heterogeneous radiological responses had a significantly shorter PFS.

There were several limitations in this study. First, this study was conducted at a single center, so external confirmatory studies should be conducted in the future. However, all clinical information was obtained prospectively from the Inha Lung Cancer Cohort. Second, this study population included patients with EGFR mutations who received platinum-based chemotherapy as a first-line treatment. This was because some patients were included before EGFR tyrosine kinase inhibitors were officially approved as a first-line therapy for metastatic NSCLC in the Republic of Korea. However, we adjusted for the effect of EGFR mutations on survival by using multivariate analyses. Third, in the PR group, radiological heterogeneity did not show a prognostic impact on survival, which could result from the small number of patients in the PR hetero group, so further research is needed.

In conclusion, the presence of lesions with radiological heterogeneity is associated with disease progression and poor prognosis in the SD group. We suggest that patients with heterogeneous radiological responses should be carefully monitored with frequent imaging tests. In particular, we suggest that clinicians can predict disease progression by the presence of metabolic responses in lesions with heterogeneous radiological responses.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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