学位論文

Clinical impact of cerebral infarction in patients with non-small cell lung cancer
（非小細胞肺癌における脳梗塞合併の予後への臨床的影響）

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ORIGINAL ARTICLE

Clinical impact of cerebral infarction in patients with non-small cell lung cancer

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Abstract

Background Lung cancer patients have a high risk of cerebral infarction, but the clinical significance of cerebral infarction in advanced non-small cell lung cancer (NSCLC) remains unclear. This study aimed to comprehensively investigate the incidence, prognostic impact, and risk factors of cerebral infarction in patients with NSCLC.

Methods We retrospectively examined 710 consecutive patients with advanced or post-operative recurrent NSCLC treated between January 2010 and July 2020 at Kumamoto University Hospital. Cerebral infarction was diagnosed according to the detection of high-intensity lesions on diffusion-weighted magnetic resonance imaging regardless of the presence of neurological symptoms during the entire course from 3 months before NSCLC diagnosis. The prognostic impact and risk factors of cerebral infarction were evaluated based on propensity score matching (PSM) and multivariate logistic regression analysis.

Results Cerebral infarction occurred in 36 patients (5%). Of them, 21 (58%) and 15 (42%) patients developed asymptomatic and symptomatic cerebral infarction, respectively. PSM analysis for survival showed that cerebral infarction was an independent prognostic factor (hazards ratio: 2.45, 95% confidence interval (CI): 1.24–4.85, $P = 0.010$). On multivariate logistic regression analysis, D-dimer (odds ratio [OR]: 1.09, 95% CI 1.05–1.14, $P < 0.001$) and C-reactive protein (OR: 1.10, 95% CI 1.01–1.19, $P = 0.023$) levels were independent risk factors.

Conclusion Cerebral infarction occurred in 5% of NSCLC patients, and asymptomatic cerebral infarction was more frequent. Cerebral infarction was a negative prognostic factor and was associated with hyper-coagulation and inflammation. The high frequency of asymptomatic cerebral infarction and its risk in NSCLC patients with these conditions should be recognized.

Keywords Non-small cell lung cancer · Asymptomatic · Risk factor · D-dimer · C-reactive protein

Introduction

Approximately 15% of cancer patients develop cerebrovascular diseases including cerebral infarctions and hemorrhage regardless of clinical symptoms [1–3]. Cerebral infarction can precede or follow the diagnosis of cancer and develop during antitumor treatment [1]. The risk of cerebral infarction is associated with the cancer stage, with stage 4 patients having the greatest risks [4, 5]. Cerebral infarction in cancer patients is not only life-threatening, but also leads to the deterioration of quality of life due to neurological symptoms. Therefore, it is crucial to identify clinical features indicative of cerebral infarction for appropriate prevention and management in advanced cancer patients.

Lung cancer is a known high-risk factor for cancer-associated cerebral infarction [5, 6]. Approximately 2–3% of lung cancer patients develop cerebral infarction, and this

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incidence rate is higher than that in non-cancer patients [7–9]. Several retrospective studies in lung cancer patients have shown that cerebral infarction is associated with the presence of brain metastasis; elevated plasma D-dimer, cancer antigen (CA) 125, and CA199 levels; and negative prognosis [8, 10]. However, the clinical significance of cerebral infarction in advanced lung cancer patients has not been fully understood.

Magnetic resonance imaging (MRI) is widely used for evaluating disease progression during treatment in advanced non-small cell lung cancer (NSCLC) patients. Diffusion-weighted imaging (DWI) MRI is used as not only tumor assessment, but also a sensitive diagnostic tool for acute cerebral infarction [11–13]. Asymptomatic cerebral infarction is identified by the detection of high-intensity lesions on DWI in patients without neurological symptoms. It is also known as a silent stroke lacking stroke-like symptom and is a high-risk factor for future stroke [14]. In NSCLC patients, asymptomatic cerebral infarction is coincidentally experienced at diagnosis or follow-up; however, its clinical features remain unknown.

Here we performed a retrospective study to clarify the clinical features of NSCLC patients with cerebral infarction, regardless of neurological symptoms, and identify the prognostic impact and risk factors of cerebral infarction in advanced NSCLC patients.

Patients and methods

Study design and patients

This was a retrospective study of 710 consecutive patients with advanced (stage III or IV) or postoperative recurrence NSCLC who were admitted at Kumamoto University Hospital between January 2010 and July 2020. The following data at the time of diagnosis or postoperative recurrence were collected: age, sex, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status (PS), histological type, clinical stage or postoperative recurrence, use of anticoagulant or antiplatelet treatment, laboratory markers (white blood cell [WBC], C-reactive protein [CRP], D-dimer), comorbidities (hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation), driver oncogene (epidermal growth factor receptor (*EGFR*) mutations/anaplastic lymphoma kinase [*ALK*]), programmed cell death ligand 1 (PD-L1) expression, and treatment.

This study was approved by our institutional review board (IRB number 2198) and was conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was waived because of the retrospective nature of the study.

Definition of cerebral infarction

MR images obtained within 3 months before diagnosis or during the entire disease course were reviewed by two independent physicians (MA and KS) referring to the MRI reports written by radiologists. Cerebral infarction was defined as the detection of high signal intensity in the brain parenchyma on DWI with simultaneous low apparent diffusion coefficient values and no contrast enhancement regardless of neurological symptoms. Symptomatic cerebral infarction was determined as the detection of high-intensity lesions on DWI in patients presenting with neurological symptoms. Meanwhile, asymptomatic cerebral infarction was defined as coincidental findings of high-intensity lesions on routine staging or follow-up MRI with DWI in patients without neurological symptoms. Representative images of high-intensity lesions on DWI are shown in Fig. 1.

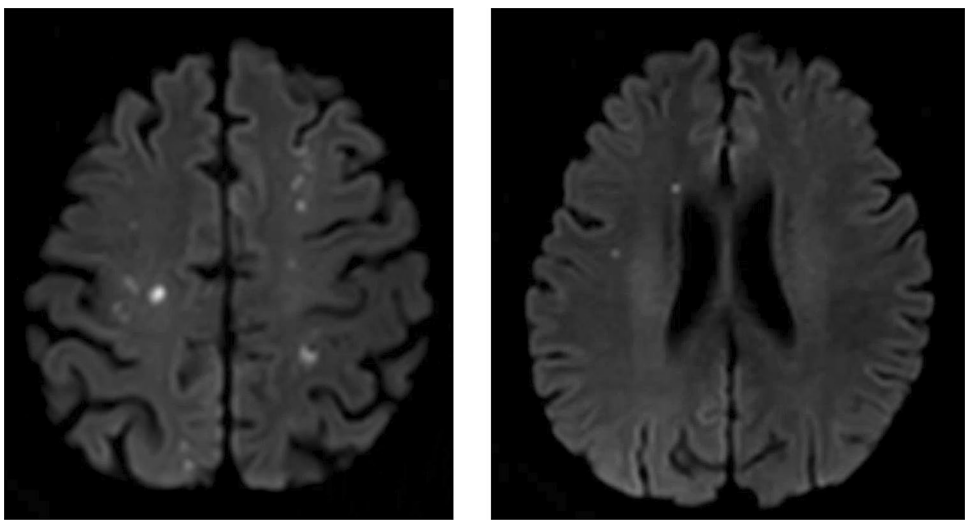

Fig. 1 Representative diffusion-weighted (DW) image of cerebral infarction. A 66-year-old female patient with non-small cell lung cancer (NSCLC) underwent brain magnetic resonance imaging (MRI) for staging. Despite the absence of neurological symptoms, DW imaging (DWI) detected multiple high-intensity lesions, and she was accordingly diagnosed with asymptomatic cerebral infarction

Statistical analysis

Overall survival (OS) was calculated from the date of NSCLC diagnosis or postoperative recurrence to the date of patient's death or last follow-up. Survival after cerebral infarction was defined as the period from the onset of cerebral infarction to the patient's death or last follow-up. The chi-square test, Fisher's exact test, or Mann–Whitney *U* tests was used to investigate the association of clinical factors. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Multivariate analyses were performed using logistic regression to identify the independent risk factors of cerebral infarction. First, covariates of age, sex, histology, *EGFR*, *ALK*, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, smoking history, performance status, stage, brain metastasis, WBC level, D-dimer level, CRP level, anti-platelet use, and anticoagulant use were included in the model. Then, the significant covariates were selected using the backwards stepwise Akaike Information Criteria method.

Variance inflation factors were examined to avoid the influence of multicollinearity. Cox proportional hazards regression models with 1:1 propensity score matching were used to examine prognostic significance. Matching was performed using nearest neighbor matching with a caliper width of 0.20 of the standard deviation of the propensity score logit. The propensity score was calculated using the logistic regression model, in which age, sex, histology, smoking history, *EGFR*, *ALK*, PD-L1 status, performance status, stage, brain metastasis, the use of ant-platelet, and the use of anticoagulant agents were used as background factors.

All statistical analyses were performed using SPSS (version 23.0; IBM, Armonk, NY, USA), and R version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria). $P < 0.05$ was considered significant.

Results

Patient characteristics

The median age at diagnosis was 69 years, and 496 patients (70%) were male; 586 patients (83%) had ECOG PS 0–1, 131 patients (19%) had brain metastases, and 474 patients (67%) had adenocarcinoma. The baseline patient characteristics are summarized in Table 1. The median WBC, CRP, and D-dimer levels were 7100/μl, 0.43 mg/dl, and 1.5 μg/ml, respectively. Regarding comorbidities, 223 patients (31%) had hypertension; 126 patients (18%), diabetes mellitus; 78 patients (11%), hyperlipidemia; and 34 patients (5%), arterial fibrillation. In total, 192 (13%) and 52 patients (7%) were using antiplatelet and anticoagulant agents, respectively.

Incidence and survival analysis

Cerebral infarction occurred in 36 patients (5%) (Fig. 2). Among them, 21 (58%) and 15 (42%) patients had asymptomatic and symptomatic cerebral infarction, respectively.

The median follow-up time from NSCLC diagnosis was 424 days (7–3702 days). The median OS was significantly shorter in the patients with cerebral infarction than in those without cerebral infarction (419 days [95% confidence interval [CI] 173–984 days] vs 851 days [95% CI 745–1063 days], $P = 0.001$], Fig. 3). The 5-year survival rates in the patients without and with cerebral infarction were 35.2% and 16.2%, respectively. The median survival time after cerebral infarction onset was 114 days (95% CI 9.8–208.2) (Supplementary Fig. 1). Cox proportional hazard analysis with propensity score matching for OS revealed that cerebral infarction was an independent negative prognostic factor (hazard ratio: 2.45, 95% CI 1.24–4.85, $P = 0.010$; Table 2).

Risk factors of cerebral infarction

The patients with cerebral infarction showed significantly higher levels of CRP (median: 0.43 mg/dl [0–22.32 mg/dl] vs 1.42 mg/dl [0.01–27.99 mg/dl], $P = 0.004$) and D-dimer (median: 1.5 μg/ml [0–87.7 mg/dl] vs 13.5 μg/ml [0.6–58.7 μg/ml], $P < 0.001$) (Supplementary Table). Multivariate logistic analysis showed that cerebral infarction was significantly associated with elevated levels of CRP (odds ratio [OR]: 1.10, 95% CI 1.01–1.19, $P = 0.023$) and D-dimer (OR: 1.09, 95% CI 1.05–1.14, $P < 0.001$) (Table 3).

Clinical features and comparison between asymptomatic and symptomatic cerebral infarction

The clinical features and outcomes of the NSCLC patients with cerebral infarction are shown in Table 4. As for DWI findings, focal and multifocal cerebral lesions were observed in 7 and 29 patients, respectively. Among the 36 patients with cerebral infarction, 30 patients received antiplatelet therapy or anticoagulant therapy for cerebral infarction. Recurrent cerebral infarction was observed in 11 patients (31%). Among them, six patients were asymptomatic and five were symptomatic at the time of the first cerebral infarction. There was no significant difference in the recurrence of cerebral infarction between the asymptomatic and symptomatic groups.

Comparison of clinical features and outcomes after cerebral infarction between the asymptomatic and symptomatic cerebral infarction patients showed no significant difference in survival and OS (Supplementary Fig. 2a, b).

Table 1 Baseline patient characteristics

		N = 710	%
Age, years	Median (range)	69 (22–92)	
Sex	Male/Female	496/214	70/30
Comorbidity	HT	223	31
	DM	126	18
	HLP	78	11
	Af	34	5
Smoking	Yes/no	540/170	76/24
ECOG PS	0/1/2/3/4	250/336/70/45/9	35/47/10/6/1
Use of antiplatelet agent	Yes/no	92/618	13/87
Use of anticoagulant agent	Yes/no	52/658	7/93
WBC,/μl	Median (range)	7100 (2600–74,300)	
CRP, mg/dl	Median (range)	0.43 (0–27.99)	
D-dimer, μg/ml	Median (range)	1.5 (0–87.7)	
Histology	Ad/Sq/others	474/176/60	67/25/9
Driver oncogene			
EGFR mut	+/-/unknown	171/360/179	24/51/25
ALK	+/-/unknown	21/300/389	3/42/55
PD-L1 expression	< 1%/1–49%/ ≤ 50%/unknown	103/90/68/449	15/13/10/63
Stage	III/IV/postoperative recurrence	193/352/165	27/50/23
Brain metastasis	Yes/no	131/579	18/82
Initial treatment	Yes/no	622/88	88/12
	Surgery	86	12
	Radiotherapy	130	18
	Chemotherapy	512	72
	Angiogenesis inhibitor	66	9
	ICI	63	9

Patients with missing data (3 patients with missing WBC count, 6 patients with no CRP value, and 239 patients with no D-dimer value) were excluded

HT hypertension; *DM* diabetes mellitus; *HLP* hyperlipidemia; *Af* atrial fibrillation; *ECOG PS* Eastern Cooperative Oncology Group performance status; *Ad* adenocarcinoma; *Sq* squamous cell carcinoma; *EGFR* mut, epidermal growth factor receptor mutation; *ALK* anaplastic lymphoma kinase; *PD-L1* programmed death ligand 1; *ICI* immune checkpoint inhibitor

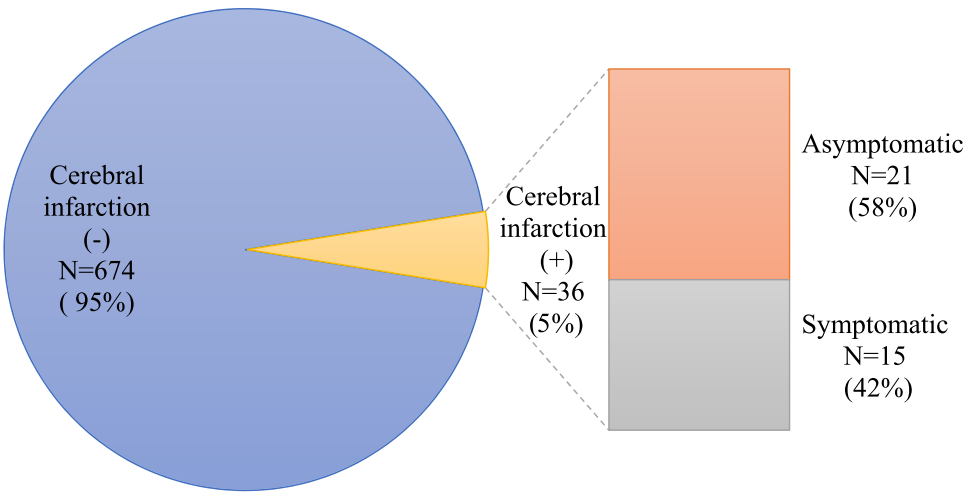

Fig. 2 Incidence of cerebral infarction

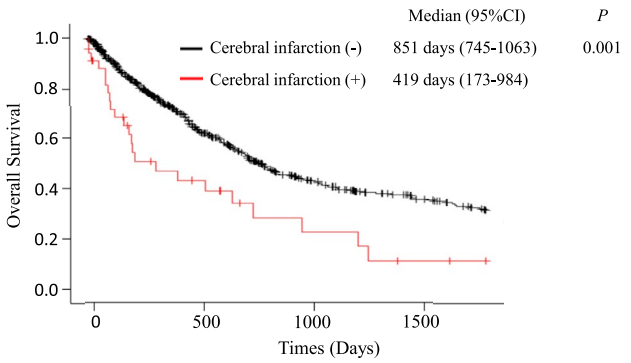

Fig. 3 Overall survival according to cerebral infarction. Abbreviation: *CI* confidence interval

Table 2 Cox proportional hazards models with propensity sore matching for OS

OS (5 years)	HR	95% CI	*P* value
No cerebral infraction (reference)			
Cerebral infraction	2.45	1.24–4.85	0.010

Cox proportional hazards regression models with 1:1 propensity score matching were created to obtain the hazard ratio. The propensity score is calculated using the logistic regression model, in which age, sex, histology, smoking history, *EGFR*, *ALK*, PD-L1 status, performance status, stage, brain metastasis, and ant-platelet and anti-coagulant agents are used as background factors

OS overall survival; *HR* hazard ratio; *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status

Table 3 Multivariate logistic analysis for independent predictors of cerebral infraction

	OR	95% Cl	*P* value
Smoking*	0.46	0.18–1.18	0.11
ECOG PS	0.66	0.40–1.10	0.11
D-dimer	1.09	1.05–1.14	< 0.001
CRP	1.10	1.01–1.19	0.023
Antiplatelet agent*	2.50	0.85–7.34	0.10

Age, sex, histology, *EGFR*, *ALK*, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, smoking history, performance status, stage, brain metastasis, WBC count, D-dimer level, CRP level, use of anti-platelet agents, and use of anti-coagulant agents were used as covariates. Additionally, covariates were selected using the backward stepwise Akaike information criteria method

OR odds ratio; *CI* confidence interval; *ECOG PS* Eastern Cooperative Oncology Group performance status

*Negative (ref) positive

Discussion

Although lung cancer is associated with a high risk of cerebral infarction, the clinical impact of cerebral infarction in lung cancer patients is still unclear. In this study, cerebral infarction occurred in 5% of NSCLC patients. Notably, asymptomatic cerebral infarction was more common. Cerebral infarction was significantly associated with poor prognosis and elevated D-dimer and CRP levels. From this current study, paying particular attention to the appearance of abnormal neurological findings and recognizing the possible presence of asymptomatic cerebral infarction is necessary for patients with coagulation abnormalities or increased inflammatory response at the time of diagnosis of lung cancer or during the clinical course.

The 5% incidence rate of cerebral infarction in the current study is higher than in previous studies on lung cancer (approximately 2–3%) [8, 9]. This difference in incidence might be due to the definition of cerebral infarction. The current study defined cerebral infarction as the detection of high-intensity lesions on DWI regardless of neurological symptoms, thus, asymptomatic cerebral infarction patients who were clinically unsuspected at diagnosis or during the disease course were also included. Notably, more than half of the patients with cerebral infarction in this study were asymptomatic, indicating that advanced NSCLC patients are more likely to develop cerebral infarction without neurological symptoms.

With respect to its prognostic impact, cerebral infarction was found to be an independent negative prognostic factor in NSCLC. This finding is consistent with the report by Kato et al. who showed a significantly shorter OS in advanced/recurrent NSCLC patients with cerebral infarction than in those without cerebral infarction (223 vs. 895 days) [8]. Sorgun et al. retrospectively investigated patients with acute ischemic stroke and found a higher in-hospital mortality rate in these patients than in those without stroke (21.7 vs. 9.9%) [15]. Moreover, deterioration of PS caused by neurological symptoms of cerebral infarction generally leads to disappear indication for chemotherapy and cannot avoid discontinuation of treatment for NSCLC. Thus, the high mortality of cerebral infarction itself and discontinuation of antitumor agents due to deterioration of PS would contribute to worse survival in NSCLC patients with cerebral infarction.

Several previous studies for cerebral infarction patients showed that serum D-dimer, fibrinogen, and CRP could be

Table 4 Characteristics of patients with cerebral infarction

		All		Asymptomatic		Symptomatic		
		N = 36	%	*N* = 21	%	*N* = 15	%	*P* value
Age, years	Median (range)	69 (54–85)		70 (58–84)		69 (54–85)		0.182
Sex	Male	25	69	16	76	9	60	0.250
	Female	11	31	5	24	6	40	
Smoking	Yes	25	69	15	71	10	67	0.521
	No	11	31	6	29	5	33	
Histology	Ad	29	81	18	86	11	73	0.418
	Non-Ad	7	19	3	14	4	27	
CRP	Median (range)	1.51 (0.01–27.99)		1.51 (0.01–27.99)		1.51 (0.2–9.17)		0.594
D-dimer	Median (range)	13.5 (0.6–58.7)		13.3 (0.6–58.7)		13.7 (1.1–18.3)		0.104
Onset of cerebral infarction	At diagnosis	19	53	13	62	6	40	0.169
	During treatment	17	47	8	38	9	60	
MRI findings of cerebral infarction	Focal	7	19	3	14	4	27	0.306
	Multifocal	29	81	18	86	11	73	
Treatment for cerebral infarction	Yes	30	83	17	81	13	87	1.000
	Aspirin	4	11	3	14	1	7	
	Heparin	21	58	10	48	11	73	
	Warfarin	2	5	2	10	0	0	
	DOAC	3	8	2	10	1	7	
	No	6	17	4	19	2	13	
Recurrence of cerebral infarction	Yes	11	31	6	29	5	33	0.521
	No	25	69	15	71	10	67	
Survival after onset of cerebral infarction, days	Median (95% CI)	114 (9.8–208.2)		204 (25.5–383.0)		106 (43.3–166.7)		0.206

Patients with missing data (1 patient with cerebral infarction had missing CRP value and 8 patients with CI had missing D-dimer value) were excluded

Ad adenocarcinoma; *DOAC* direct oral anticoagulant; *CI* confidence interval

potential biomarkers of occult cancer in cerebral infarction patients [15–17]. In lung cancer patients, the elevation of serum D-dimer, CA125, and CA199 and the presence of brain metastases were reportedly associated with the complication of cerebral infarction [8, 10]. The current study revealed that the elevation of D-dimer and CRP levels was significantly associated with cerebral infarction in NSCLC patients.

Cancer generally leads to thrombosis due to a hypercoagulation state caused by various factors, such as the production of tissue factors and cancer pro-coagulants and the secretion of plasminogen activator inhibitor-1 [18, 19]. In addition, cancer-derived cytokines, such as IL-6 and TNF-α, also promote a hyper-coagulative state and the development of cancer-associated thrombosis [20, 21]. D-dimer and CRP levels clinically represent hypercoagulability and an inflammatory condition, respectively. As such, NSCLC patients with elevated D-dimer and CRP levels could have a high risk of cerebral infarction, highlighting their need for more active interventions against cerebral infarction.

NSCLC patients with cerebral infarction had a poorer prognosis and a higher recurrence rate of cerebral infarction; thus, cerebral infarction prevention is crucial for improving survival in this population. Considering that a hyper-coagulative state causes cancer-associated cerebral infarction, anticoagulants such as heparin and direct oral anticoagulant in cancer patients with cerebral infarction could be theoretically useful for the treatment and prevention of cerebral infarction, considering the hyper-coagulation state as the cause of cancer-associated cerebral infarction [1, 22–24]. However, recurrence of cerebral infarction in NSCLC patients with cerebral infarction was observed in approximately 30% in spite of the high rate of treatment of anti-platelet or anti-coagulant agents after the onset of cerebral infarction and had no significant difference between asymptomatic and symptomatic groups. Further research is required to examine how to prevent subsequent cerebral infarction in NSCLC patients with cerebral infarction and prophylactic therapy in the high-risk group of cerebral infarction, such as aberrant coagulation and inflammatory reactions.

Our study has several limitations. First, this study was a retrospective design and performed only single institution, thus might involve various selection biases. Second, risk factors for cerebral infarction include various comorbidities (e.g., hypertension, hypercholesterolemia, and atrial fibrillation) and lifestyles (e.g., alcohol, cigarette smoking, and obesity) [25–27]. We performed multivariate analysis including several factors among them; however, other comorbidity and lifestyle factors might influence our results. Third, treatments factors, such as platinum-based chemotherapy, molecular target therapy to vascular endothelial growth factor and immunotherapy for NSCLC, reportedly contribute to cancer-associated thrombosis and might have possibly affected our results [28–31]. Fourth, laboratory data in this study were collected at NSCLC diagnosis or postoperative recurrence regardless of the presence of complications, such as infectious diseases, which might have affected our results. Finally, MRI scans, including the DWI images, were routinely performed at the staging of NSCLC or follow-up of brain metastasis in our institution, but brain CT was only performed for specific cases, such as patients with metal implants in the body and history of claustrophobia. Moreover, the interval of follow-up brain MRI scans was decided by each physician. Thus, these factors might have affected the detection of cerebral infarction, especially in asymptomatic cases.

Cerebral infarction occurred in 5% of NSCLC patients and was accompanied by a relatively frequent occurrence of asymptomatic cerebral infarction during the clinical course. NSCLC patients with cerebral infarction had poor prognosis and were significantly associated with elevate levels of D-dimer and CRP. The latently frequent occurrence of asymptomatic cerebral infarction and risk of cerebral infarction in NSCLC patients with hyper-coagulations and inflammatory reactions should be recognized.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10147-022-02132-w.

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Data availability All data in this study were obtained from the electronic medical records of Kumamoto University Hospital.

Declarations

Conflict of interest The authors declare no conflicts of interest.

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