International Journal of Clinical Oncology (2019) 24:1549–1557
https://doi.org/10.1007/s10147-019-01525-8

ORIGINAL ARTICLE

Validation of prognostic impact of number of extrathoracic metastases according to the eighth TNM classification: a single-institution retrospective study in Japan

Kosuke Sakai[1,2] · Joji Kuramoto[1] · Akitoshi Kojima[1] · Hiroaki Nishimura[1] · Yoshiki Kuwabara[1] · Maiko Toda[1] · Yumiko Kobayashi[1,2] · Satoshi Kikuchi[1] · Yusuke Hirata[1] · Yuriko Mikami-Saito[1] · Shintaro Mikami[1] · Hiroyuki Kyoyama[1] · Gaku Moriyama[1,2] · Akihiko Gemma[2] · Kazutsugu Uematsu[1]

Received: 15 March 2019 / Accepted: 30 July 2019 / Published online: 26 August 2019

Abstract

Background In the eighth edition of the TNM classification of lung cancer, the M1b and M1c descriptors are newly defined by the number of extrathoracic metastases. To verify the prognostic value of these descriptors in Japan, we reclassified our cases and re-evaluated prognosis in M1b and M1c patients.

Methods All non-small cell lung cancer (NSCLC) patients with extrathoracic metastases who visited Saitama Medical Center from 2010 to 2016 were evaluated, divided according to the eighth edition of the TNM classification criteria into two groups (M1b, patients with single extrathoracic metastasis, and M1c, patients with multiple extrathoracic metastases), and followed up until December 31, 2017. Survival time analysis was performed using the Kaplan–Meier method, and between-group differences in overall survival time (OS) were evaluated by the log-rank test.

Results A total of 231 NSCLC patients were divided into 57 patients with M1b and 174 with M1c. Median OS was 15.2 months (95% confidence interval [CI]: 9.3–19.9) and 7.3 months (95% CI 5.7–10.7) for M1b and M1c, respectively, with no significant between-group difference ($P=0.239$). However, after excluding patients with epidermal growth factor receptor (EGFR) mutation or echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase (EML4–ALK) fusion gene, median OS was 12.9 months (95% CI 7.2–19.9) for M1b and 5.4 months (95% CI 3.8–6.3) for M1c, respectively, showing a significant difference ($P=0.029$).

Conclusions The effect of therapy directed toward EGFR mutation or EML4–ALK fusion gene might obscure the significant prognostic difference between M1b and M1c.

Keywords Eighth edition · TNM classification of lung cancer · M Descriptor · Oligometastasis · EGFR mutation · EML4–ALK fusion gene

Introduction

The eighth edition of the TNM classification of lung cancer has been used for lung cancer treatment since January 1, 2017. It includes new M descriptors defined by the number of extrathoracic metastases and adds a new T descriptor for small nodule with ground-glass attenuation. Although all extrathoracic metastases were reckoned as M1b in the seventh edition, the eighth edition regards a single extrathoracic metastasis as M1b, and multiple extrathoracic metastases as M1c. Lung cancer patients with a limited number of metastases have been treated as if they had oligometastatic disease [1–3], which is still not clearly defined. In the eighth revision, the International Association for the Study of Lung Cancer (IASLC) tries to define oligometastasis and to encourage the development of treatment strategies for oligometastatic lung cancer.

The IASLC was the principal source of data for this revision. There were 2411 non-small cell lung cancer (NSCLC)

✉ Kazutsugu Uematsu
kuematsu@saitama-med.ac.jp

[1] Department of Pulmonary Medicine, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe, Saitama 350-8550, Japan

[2] Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan

cases registered between 1999 and 2012 in their database, and median overall survival time (OS) per M descriptor in the eighth edition was M1a 11.5 months; M1b 11.4 months; and M1c 6.3 months ($P < 0.0001$). The IASLC is trying to clarify oligometastasis prognosis by this new classification, and suggests prospective investigation of prognosis for metastasis of each local organ [4].

This IASLC data used for this latest revision of the TNM classification may not necessarily reflect the current situation in Japan for two reasons. First, the 2411 cases in the database did not include patients from Japan, where adenocarcinoma with epidermal growth factor receptor (EGFR) mutation is more prevalent than in most other parts of world represented in the IASLC database [5]. Second, the data were collected mainly in the 2000s, when standard treatments for lung cancer differed from current standard practices.

To validate the M descriptors of the eighth edition of the TNM classification for lung cancer, M1b disease classified according to the seventh edition at Saitama Medical Center, Saitama Medical University, was reclassified, before prognostic evaluation, as M1b or M1c disease according to the eighth edition. Saitama Medical Center covers 800,000 people and is the only designated regional cancer treatment hospital in the Kawagoe-Hiki healthcare catchment area. Since the number of physicians per 100,000 population in Saitama prefecture was 160.1 in 2016, which was the smallest in Japan, our hospital accepted many patients from other catchment areas in the vicinity; therefore, in fact, our hospital services 1,960,000 people. This investigation was conducted in a physician-depopulated area in Japan.

Patients and methods

Patients

The evaluated patients had (1) visited Saitama Medical Center, Saitama Medical University, from January 1, 2010 to December 31, 2016; (2) received a diagnosis of NSCLC with extrathoracic metastases (M1b according to the seventh edition of the TNM classification of lung cancer criteria); and (3) received inpatient treatment. Extrathoracic metastases had been diagnosed using computed tomography (CT), positron emission tomography-CT, brain magnetic resonance imaging, bone scintigraphy, and abdominal ultrasonography before treatment. This study was approved by the ethics board of Saitama Medical Center, Saitama Medical University (application number: 1730).

Procedures

Patients' pretreatment imaging findings in electronic medical records were used to re-classify M1b based on seventh edition criteria into M1b or M1c based on eighth edition criteria. Accordingly, patients in the M1b group had a single extrathoracic metastasis, and those in the M1c group had multiple extrathoracic metastases. OS was retrospectively measured from the date of treatment initiation to the date of death for any cause, and follow-up was conducted until December 31, 2017. Patients who were lost to follow-up were included in this study because of maintaining continuity in our hospital.

Statistics

The distribution of patients' characteristics (sex, Eastern Cooperative Oncology Group performance status [ECOG-PS], histology, and gene mutation) between the M1b and M1c groups were analyzed by the Fisher accuracy test, and that of age was evaluated by the Mann–Whitney U test. Survival time was estimated by the Kaplan–Meier method, and differences in OS were evaluated by the log-rank test. Statistical analyses were performed using the EZR software program (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [6], with the level of significance set at $P < 0.05$.

Results

In all, 231 NSCLC patients with extrathoracic metastases were enrolled into this single institutional investigation. Among them, 23 patients were alive, 159 patients were dead, and 49 patients were lost to follow-up because of transfer to other hospitals during the observation period. Median OS was 9.5 months (95% confidence interval [CI]: 6.8–13.0).

Among 231 patients, 57 patients (24.7%) with a single metastasis were classified as M1b by the eighth edition of the TNM system, and 174 patients (75.3%) with multiple metastases were classified as M1c. The metastasis in the 57 M1b patients was located in the brain, 15 cases (26.3%); bone, 24 (42.1%); liver, 5 (8.8%); adrenal gland, 4 (7.0%); lymph node, 6 (10.5%) (neck, 4; axillary, 1; abdominal paraaortic, 1); muscle, 2 (3.5%); and meninges, 1 (1.8%).

Patients' characteristics such as sex, age, ECOG-PS, histology, and gene mutations are shown in Table 1. There was no significant difference in sex, age, histology, and gene mutations between the M1b and M1c groups. The patients in the M1b group had significantly better ECOG-PS than those in the M1c group ($P = 0.024$).

Characteristics of NSCLC patients with EGFR mutation or echinoderm microtubule-associated protein-like four and anaplastic lymphoma kinase (EML4–ALK) fusion gene are shown in Table 2. There was no significant difference in sex, ECOG-PS, and histology. The patients in the M1b group had significantly older than those in the M1c group ($P = 0.0213$).

Table 1 Characteristics of patients with extrathoracic metastases

Characteristic	Variable		All ($n=231$)	M1b ($n=57$)	M1c ($n=174$)	P
Sex	Male		158 (68.4%)	39 (68.4%)	119 (68.4%)	1.000
	Female		73 (31.6%)	18 (31.6%)	55 (31.6%)	
Age	Median (range)		67 (32–86)	69 (47–86)	67 (32–83)	0.080
Performance status	0		16 (6.9%)	9 (15.8%)	7 (4.0%)	0.024
	1		99 (42.9%)	27 (47.4%)	72 (41.4%)	
	2		56 (24.2%)	10 (17.5%)	46 (26.4%)	
	3		52 (22.5%)	9 (15.8%)	43 (24.7%)	
	4		8 (3.5%)	2 (3.5%)	6 (3.4%)	
Histology	Adenocarcinoma		153 (66.2%)	38 (66.7%)	115 (66.1%)	0.571
	Squamous-cell carcinoma		42 (18.2%)	13 (22.9%)	29 (16.7%)	
	Non-small cell carcinoma		21 (9.1%)	4 (7.0%)	17 (9.8%)	
	Others		15 (6.5%)	2 (3.5%)	13 (7.5%)	
Gene mutation	EGFR	Ex19 Del	34 (14.7%)	6 (10.5%)	28 (16.1%)	0.369
		L858R	28 (12.1%)	5 (8.8%)	23 (13.2%)	
		G719X	2 (0.9%)	0 (0%)	2 (1.1%)	
	EML4–ALK		3 (1.3%)	2 (3.5%)	1 (0.6%)	

EGFR epidermal growth factor receptor, *Ex19 Del* exon19 deletion, *L858R* point mutation in exon 21 resulting in an amino acid substitution at position 858 from leucine to arginine, *G719X* point mutation in exon 18 resulting in an amino acid substitution at position 719 from glycine to serine, cysteine, or alanine, *EML4–ALK* echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase

Table 2 Characteristics of patients with EGFR mutation or EML4–ALK fusion gene

Characteristic	Variable	All ($n=67$)	M1b ($n=13$)	M1c ($n=54$)	P
Sex	Male	25 (37.3%)	4 (30.8%)	21 (38.9%)	0.753
	Female	42 (62.7%)	9 (69.2%)	33 (61.1%)	
Age	Median (range)	67 (32–83)	71 (47–83)	66 (32–80)	0.0213
Performance status	0	6 (9.0%)	2 (15.4%)	4 (7.4%)	0.478
	1	30 (44.8%)	7 (53.8%)	23 (42.6%)	
	2	15 (22.4%)	1 (7.7%)	14 (25.9%)	
	3	13 (19.4%)	3 (23.1%)	10 (18.5%)	
	4	3 (4.5%)	0 (0)	3 (5.6%)	
Histology	Adenocarcinoma	60 (89.6%)	12 (92.3%)	48 (88.9%)	1
	Squamous-cell carcinoma	0 (0)	0 (0)	0 (0)	
	Non-small cell carcinoma	5 (7.5%)	1 (7.7%)	4 (7.4%)	
	Others	2 (3.0%)	0 (0)	2 (3.7%)	

EGFR epidermal growth factor receptor, *EML4–ALK* echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase

Characteristics of NSCLC patients without EGFR mutation or EML4–ALK fusion gene are shown in Table 3. There was no significant difference in sex, age, and histology. The patients in the M1b group had significantly better ECOG-PS than those in the M1c group ($P=0.0122$).

Treatments for NSCLC patients with EGFR mutation or EML4–ALK fusion gene and those without these mutations are summarized in Tables 4 and 5, respectively. Locoregional therapies were also included in Tables when these therapies were performed for control of intrathoracic or extrathoracic metastases before starting second-line chemotherapy. Most of patients with EGFR mutation or EML4–ALK fusion gene had been treated with tyrosine kinase inhibitors (TKIs) for the first systemic treatment. Locoregional therapies for extrathoracic metastases were performed in 92 (56.1%) of the 164 patients without EGFR mutation or EML4–ALK fusion gene, and in 29 (43.3%) of the 67 patients with these gene mutations ($P=0.0832$). In the patients without EGFR mutation or EML4–ALK fusion gene, 4 (9.1%) of the 44 patients in the M1b group and 2 (1.7%) of the 120 patients in M1c group were concurrently treated by chemotherapy with radiotherapy for local control of thoracic lesion ($P=0.0449$).

Table 3 Characteristics of patients without EGFR mutation or EML4–ALK fusion gene

Characteristic	Variable	All ($n=164$)	M1b ($n=44$)	M1c ($n=120$)	P
Sex	Male	133 (81.1%)	35 (79.5%)	98 (81.7%)	0.823
	Female	31 (18.9%)	9 (20.5%)	22 (18.3%)	
Age	Median (range)	67 (36–86)	68 (51–86)	67 (36–83)	0.556
Performance status	0	10 (6.1%)	7 (15.9%)	3 (2.5%)	0.0122
	1	69 (42.1%)	20 (45.5%)	49 (40.8%)	
	2	41 (25.0%)	9 (20.5%)	32 (26.7%)	
	3	39 (23.8%)	6 (13.6%)	33 (27.5%)	
	4	5 (3.0%)	2 (4.5%)	3 (2.5%)	
Histology	Adenocarcinoma	93 (56.7%)	26 (59.1%)	67 (55.8%)	0.676
	Squamous-cell carcinoma	42 (25.6%)	13 (29.5%)	29 (24.2%)	
	Non-small cell carcinoma	16 (9.8%)	3 (6.8%)	13 (10.8%)	
	Others	13 (7.9%)	2 (4.5%)	11 (9.2%)	

EGFR epidermal growth factor receptor, *EML4–ALK* echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase

Table 4 Summary of treatments for the patients with EGFR mutation or EML4–ALK fusion gene

M descriptor (n)	Treatment	Systemic therapy		Locoregional therapy[a]
		First line	After second line	
1b (13)	*Systemic therapy*			
	Platinum-based chemotherapy	1	4	
	Docetaxel + Ramucirumab		1	
	Single cytotoxic agent		3	
	Gefitinib	9	1	
	Erlotinib	1	5	
	Afatinib	1	1	
	Osimertinib		1	
	Alectinib	1	1	
	Nivolumab		1	
	Locoregional therapy			
	Radiotherapy for thoracic lesion			1
	Resection of brain tumor and WBRT			1
	SRT for brain metastasis			1
	Radiotherapy for bone metastasis			2
1c (54)	*Systemic therapy*			
	Platinum-based chemotherapy		15	
	Docetaxel + Ramucirumab		1	
	Single cytotoxic agent	1	12	
	Gefitinib	34	4	
	Erlotinib	10	21	
	Afatinib	7	7	
	Osimertinib		8	
	Erlotinib + Bevacizumab		1	
	Crizotinib	1		
	Pembrolizumab		1	
	Locoregional therapy			
	WBRT			17
	Radiotherapy for bone metastases			9

EGFR epidermal growth factor receptor, *EML4–ALK* echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase, *WBRT* whole-brain radiotherapy, *SRT* stereotactic radiotherapy

[a]Regarding locoregional therapies, some patients had a few of therapies

Table 5 Summary of treatments for the patients without EGFR mutation or EML4–ALK fusion gene

M descriptor (*n*)	Treatment	Systemic therapy		Locoregional therapy[a]
		First line	After second line	
1b (44)	*Systemic therapy*			
	Platinum-based chemotherapy	24	3	
	Platinum-based chemotherapy + RT for thoracic lesion	4		
	Single cytotoxic agent	6	14	
	Erlotinib		6	
	Nivolumab		2	
	Locoregional therapy			
	Radiotherapy for thoracic lesion			4
	WBRT			5
	Resection of brain tumor			3
	Resection of brain tumor and WBRT			3
	Radiotherapy for bone metastasis			6
	Laminectomy			1
1c (120)	*Systemic therapy*			
	Platinum-based chemotherapy	59	10	
	Platinum-based chemotherapy + RT for thoracic lesion	1	1	
	Docetaxel + Ramucirumab		1	
	Single cytotoxic agent	14	36	
	Gefitinib	1		
	Erlotinib	3	7	
	Pembrolizumab		1	
	Nivolumab		3	
	Locoregional therapy			
	Radiotherapy for thoracic lesion			19
	WBRT			42
	Resection of brain tumor and WBRT			4
	SRT for brain metastases			3
	Radiotherapy for spinal cord			1
	Radiotherapy for bone metastases			28
	Radiotherapy for lymph nodes			1
	Partial resection of small intestine			1
	Laminectomy			1
	Internal fixation for femur			1

EGFR epidermal growth factor receptor, *EML4–ALK* echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase, *RT* concurrent radiotherapy, *WBRT* whole-brain radiotherapy, *SRT* stereotactic radiotherapy

[a]Regarding locoregional therapies, some patients had a few of therapies

Median OS was not significantly different between the M1b group (15.2 months [95% CI 9.3–19.9]) and M1c group (7.3 months [95% CI 5.7–10.7]) ($P = 0.239$) (Fig. 1a). However, after excluding patients with EGFR mutation or EML4–ALK fusion gene, the between-group difference in median OS was significant (13.0 months [95% CI 7.2–19.9] for the M1b group [44 cases] and 5.4 months [95% CI 3.8–6.3] for the M1c group [120 cases]; $P = 0.029$; Fig. 1b). For ECOG-PS 0–2 patients, who are more likely to be treated with cytotoxic agents, median OS was 17.3 months (95% CI 13.0–26.9) in the M1b group (46 cases) and 11.2 months (95% CI 6.9–14.7) in the M1c group (125 cases), with no significant difference between the groups ($P = 0.334$) (Fig. 2a). By excluding patients with EGFR mutation or EML4–ALK fusion gene from all the ECOG-PS 0–2 patients, the between-group difference in median OS became significant: 15.2 months (95% CI 7.2–23.6) in the M1b group (36

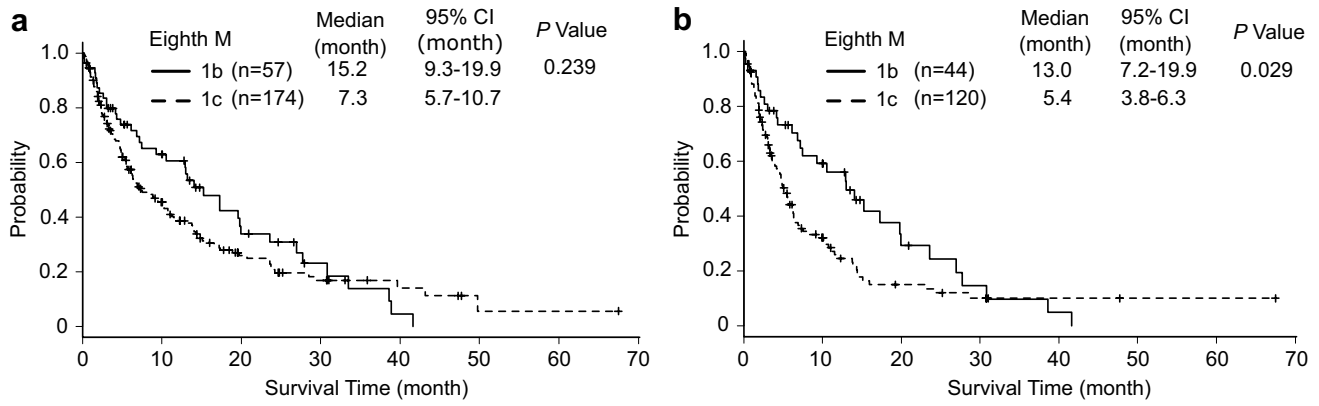

Fig. 1 Kaplan–Meier curves of overall survival by M status (M1b or M1c) in the eighth edition of the TNM system of non-small cell lung cancer classification in patients with extrathoracic metastases (**a**), and in patients with extrathoracic metastases after exclusion of those with epidermal growth factor receptor gene mutation or echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase fusion gene (**b**). *CI* confidence interval

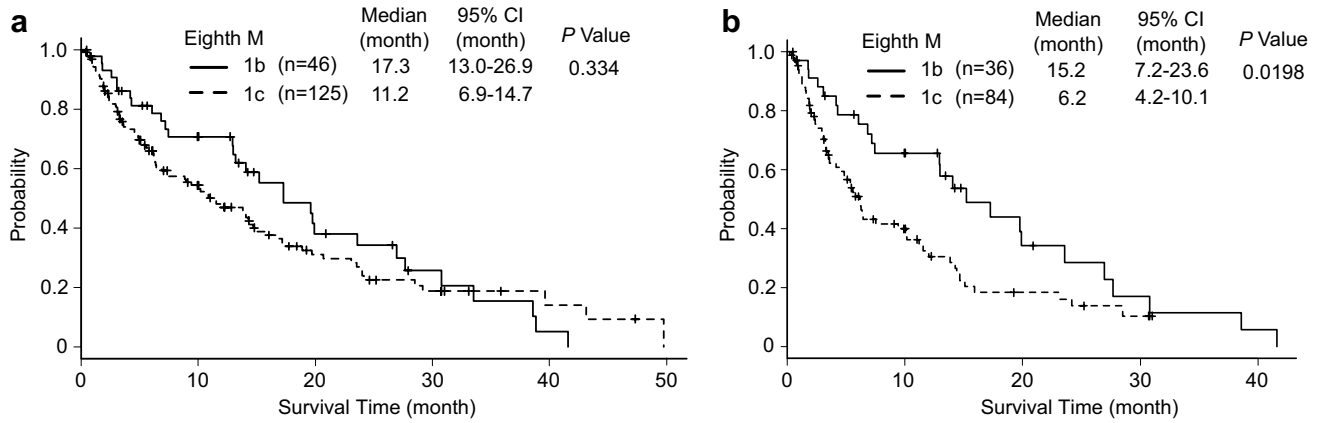

Fig. 2 Kaplan–Meier curves of overall survival by M status (M1b or M1c) in the eighth edition of the TNM system of non-small cell lung cancer classification in patients with ECOG performance status (PS) 0–2 (**a**), and in patients with PS 0–2 after exclusion of those with epidermal growth factor receptor gene mutation or echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase fusion gene (**b**). *CI* confidence interval

cases), as compared with 6.2 months (95% CI 4.2–10.1) in the M1c group (84 cases) ($P=0.0198$) (Fig. 2b). Even after excluding the patients who were lost to follow-up, OS was still significantly different between the M1b and the M1c groups only by excluding the patients with EGFR mutation or EML4–ALK fusion gene.

For patients with ECOG-PS 0–4 and EGFR mutation or EML4–ALK fusion gene, median OS was 19.6 months (95% CI 4.8–not applicable [NA]) in the M1b group (13 cases) and 18.9 months (95% CI 13.3–24.0) in the M1c group (54 cases) ($P=0.952$) (Fig. 3a). On the other hand, for patients with ECOG-PS 0–2 and EGFR mutation or EML4–ALK fusion gene, median OS was 33.5 months (95% CI 3.1–NA) in the M1b group (10 cases) and 20.7 months (95% CI 16.6–39.6) in the M1c group (41 cases) ($P=0.879$) (Fig. 3b). From these results, for ECOG PS 0–4 or 0–2 patients with EGFR mutation or EML4–ALK fusion gene, OS was not significantly different between the M1b and M1c groups.

By metastasis location, ECOG-PS 0–4 patients in the M1b group had the following median OS: adrenal gland (4 cases), 23.4 months (95% CI 0.2–NA); brain (15), 10.5 months (95% CI 3.1–NA); liver (5), 7.2 months (95% CI 0.5–NA); lymph node (6), 13.0 months (95% CI 1.5–NA); meninges (1), 1.6 months (95% CI NA–NA); muscle (2), 4.2 months (95% CI 4.2–NA); and bone (24), 19.6 months (95% CI 7.5–30.8) ($P=0.0884$) (Fig. 4a). After excluding patients with EGFR mutation or EML4–ALK fusion gene, the median OS by metastasis location was as follows in the M1b group: adrenal gland (3 cases), 19.8 months (95% CI 0.2–NA); brain (12), 12.3 months (95% CI 2.1–NA); liver (4), 6.8 months (95% CI 0.5–NA); lymph node (5: neck, 3; axillary, 1; abdominal para-aortic, 1), 13.0 months (95%

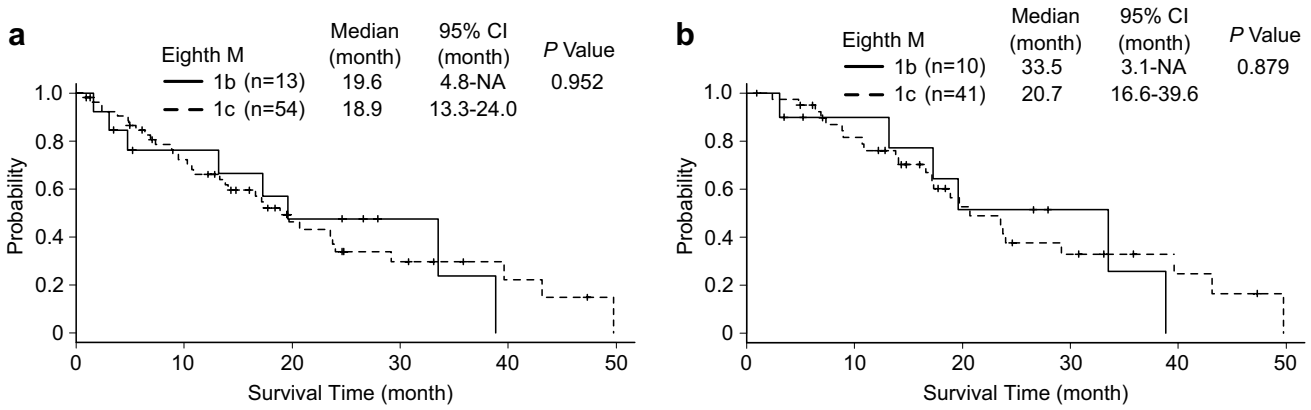

Fig. 3 Kaplan–Meier curves of overall survival by M status (M1b or M1c) in the eighth edition of the TNM system of non-small cell lung cancer classification in patients with epidermal growth factor receptor gene mutation or echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase fusion gene (**a**), and in those with ECOG performance status 0–2 (**b**). *CI* confidence interval, *NA* not applicable

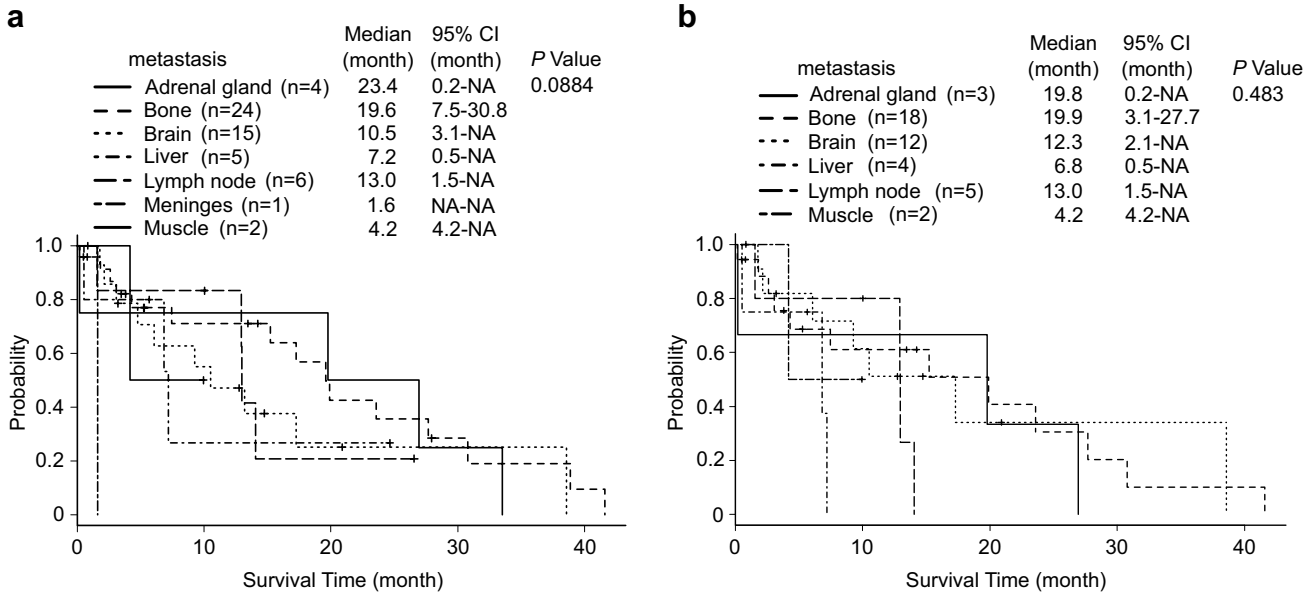

Fig. 4 Kaplan–Meier curves of overall survival by metastatic site of non-small cell lung cancer in patients with a single extrathoracic metastatic lesion (**a**), and in patients with a single extrathoracic metastatic lesion after exclusion of those with epidermal growth factor receptor gene mutation or echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase fusion gene (**b**). *CI* confidence interval, *NA* not applicable

CI 1.5–NA); muscle (2), 4.2 months (95% CI 4.2–NA); and bone (18), 19.9 months (95% CI 3.1–27.7) ($P=0.483$) (Fig. 4b). Therefore, the location of the single metastasis did not significantly affect OS.

There was no significant difference in OS between patients with common EGFR mutations: exon19 deletion vs point mutation in exon 21 resulting in an amino acid substitution at position 858 from leucine to arginine (L858R) (Fig. 5). Median OS was 20.7 months (95% CI 13.8–38.9) in patients with exon19 deletion (34 cases), and 16.6 months (95% CI 6.9–23.6) in those with L858R (28 cases) ($P=0.179$).

Among 67 patients with EGFR mutation or EML4–ALK fusion gene, 64 patients received TKI as the first-line treatment, and 59 patients had progressive disease. Among the 59 patients with progressive disease, 20 patients (33.9%) had no second-line treatment, 15 patients received additional TKI therapy, and one patient received an immune check point inhibitor; 36 patients (61.0%) did not receive cytotoxic agents.

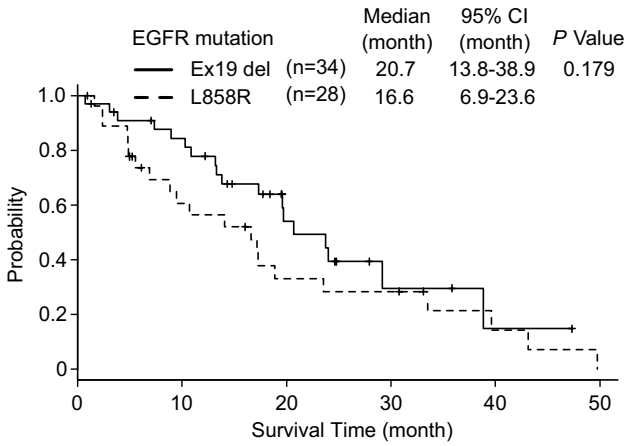

Fig. 5 Kaplan–Meier curves of overall survival by the type of epidermal growth factor receptor gene mutation in non-small cell lung cancer patients with single or multiple extrathoracic metastases. *EGFR* epidermal growth factor receptor, *Ex19 Del* exon19 deletion, *L858R* point mutation in exon 21 resulting in an amino acid substitution at position 858 from leucine to arginine, *CI* confidence interval

Discussion

Data from the IASLC showed that lung cancer patients with a single metastasis had significantly longer survival than those with multiple metastases [4]. In addition, reports from a few countries have indicated the same [7–10]. In the present single-institution (designated regional cancer treatment hospital) study, the OS of patients with a single metastasis tended to be longer than those with multiple metastases; however, the difference in OS was not significant. When patients with EGFR mutation or EML4–ALK fusion gene were excluded, the OS was significantly longer in the single metastasis group than in the multiple metastases group. The difference of OS between the M1b and M1c groups in Fig. 1b might partly be attributed to imbalance of ECOG-PS as shown in Tables 1 and 3. Therefore, we analyzed the patients with ECOG-PS 0–2 in Fig. 2. OS of the M1b group was still significantly longer than M1c group only by excluding the patients with EGFR mutation or EML4–ALK fusion gene (Fig. 2b). We speculated that the difference between our study and the IASLC study was related to the geographic location and timing of data collection.

First, more than half of 2411 patients in the database of the IASLC were Turkish, and only 271 patients were Asians (all from China) [4]. Since NSCLC with EGFR mutation is more prevalent in Asians [5], the study including only 10% Asians might not adequately reflect the effect of EGFR mutation on prognosis.

Second, the database of the IASLC was compiled between 1999 and 2012. During this period in Japan, EGFR-TKI had become the preferred treatment over cytotoxic agents for non-small cell lung cancer with EGFR mutation; and, in 2014, the clinical practice guideline for treating lung cancer eventually recommended EGFR-TKI as a first-line therapy for these patients. Since our investigation included patients who had visited our hospital from 2010 to 2016, a time during which new EGFR-TKIs were being launched and their use became prevalent, EGFR-TKIs were the first-line treatment for 64 (95.5%) of the 67 patients with EGFR mutation in our study. However, it is unclear to what extent EGFR-TKIs were used worldwide for these patients between 1999 and 2012. That is why our results are different from those of the IASLC.

Our results also suggested that in patients with EGFR mutation or EML4–ALK fusion gene, prognosis is unaffected by whether extrathoracic metastasis is single or multiple. On the other hand, in patients without these gene mutations, prognosis differed significantly between patients with extrathoracic single vs multiple metastases, suggesting the importance of defining and treating oligometastasis. Because the therapeutic effects of TKIs may obscure prognostic differences between patients with one extrathoracic metastasis and those with more than one, it is difficult to predict these patients' prognosis from only M descriptors of an anatomy-based TNM system.

There was no significant difference in prognosis based on single metastasis location. Organ-specific treatments for brain or adrenal gland metastasis have improved prognosis in the past [1–3]. However, we had difficulty in showing a prognostic difference depending on metastatic location, because the organ-specific treatment of tumor metastases is determined for individual patients. If we investigate the efficacy of local treatment for oligometastasis in the future, we will need to exclude patients with EGFR mutation or EML4–ALK fusion gene; otherwise, TKI treatment might make a difference in prognosis difficult to detect.

Current treatment includes immuno-checkpoint inhibitors [11–13], third-generation EGFR-TKIs [14], and ALK inhibitors [15–17]. Furthermore, for patients with common EGFR mutations, EGFR-TKIs effectiveness is expected to be enhanced by the addition of cytotoxic agents or a vascular endothelial growth factor (VEGF) antibody [18]; and for patients with EML4–ALK fusion gene, the sequence of use of various ALK inhibitors may be important [19, 20]. Therefore, the first-line treatment will be more complicated in the near future [18, 21]. In these situations, it becomes difficult to evaluate lung cancer outcomes using anatomic (TNM) information.

We recognize the following limitations in our study. First, it is a retrospective and single-institution study. However, especially in single institutions, evaluation of M descriptors in the TNM classification might reflect practical circumstances. Second, the risk of serious complications such as cardiovascular events or interstitial pneumonia (IP) was not assessed. Third, we did not assess the contribution of

programmed death-ligand 1 (PD-L1) status to lung cancer prognosis since examination of PD-L1 status had not been available in routine clinical practice during most of the period of this research. PD-L1 status and the use of PD-1/PD-L1 antibodies may also alter the impact of M descriptors. To overcome these limitations, we suggest conducting clinical studies that include several regional cancer treatment hospitals, similar to our hospital which covers a relatively diverse population, to estimate the impact of M descriptors on lung cancer outcomes and whether comorbidities (such as cardiovascular disease and IP) and other factors (including PD-L1 status) affect this impact.

The OS of patients with a single metastasis tended to be longer than those with multiple metastases in our research, but the difference was not significant. When patients with EGFR mutation or EML4–ALK fusion gene were excluded, OS in the single metastasis group was significantly longer than in the multiple metastases group, which suggests that treatment with drugs targeting EGFR mutation or EML4–ALK fusion gene obscured this prognostic difference between the groups. This finding has not been previously reported. Through this retrospective study in Japan, we provide two proposals. First, estimating the prognosis of lung cancer patients in Japan using only the anatomy-based TNM classification is difficult and thus requires taking into account gene mutation status. Second, to investigate the clinical significance of oligometastasis, patients with either EGFR mutation or EML4–ALK fusion gene should be excluded before examining patients' outcomes, and these patients should be dealt with as a separate group.

Acknowledgements This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest Kosuke Sakai received research funding from Eli-Lilly. Akihiko Gemma received honoraria from Nippon Boehringer Ingelheim, Pfizer, Ono Pharmaceutical, Taiho Phamaceutical, MSD, AstraZeneca, Chugai Pharmaceutical and Nippon Kayaku.

References

1. Bonnette P, Puyo P, Gabriel C et al (2001) Surgical management of non-small cell lung cancer with synchronous brain metastases. Chest 119:1469–1475
2. Nieder C, Hintz M, Oehlke O et al (2017) The TNM 8 M1b and M1c classification for non-small cell lung cancer in a cohort of patients with brain metastases. Clin Transl Oncol 19:1141–1146
3. Gao XL, Zhang KW, Tang MB et al (2017) Pooled analysis for surgical treatment for isolated adrenal metastasis and non-small cell lung cancer. Interact Cardiovasc Thorac Surg 24:1–7
4. Eberhardt WE, Mitchell A, Crowley J et al (2015) The IASLC lung cancer staging project: proposals for the revision of the M descriptors in the forthcoming eighth edition of the TNM classification of lung cancer. J Thorac Oncol 10:1515–1522
5. Midha A, Dearden S, McCormack R (2015) EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). Am J Cancer Res 5:2892–2911
6. Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48:452–458
7. Shin J, Keam B, Kim M et al (2017) Prognostic impact of newly proposed M descriptors in TNM classification of non-small cell lung cancer. J Thorac Oncol 12:520–528
8. Tufman A, Kahnert K, Kauffmann-Guerrero D et al (2017) Clinical relevance of the M1b and M1c descriptors from the proposed TNM 8 classification of lung cancer. Strahlenther Onkol 193:392–401
9. Dias M, Antunes A, Campainha S et al (2017) Prognostic impact of M descriptors of the 8th edition of TNM classification of lung cancer. J Thorac Dis 9:685–691
10. Yang L, Wang S, Zhou Y et al (2017) Evaluation of the 7(th) and 8(th) editions of the AJCC/UICC TNM staging systems for lung cancer in a large North American cohort. Oncotarget 8:66784–66795
11. Borghaei H, Paz-Ares L, Horn L et al (2015) Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373:1627–1639
12. Reck M, Rodriguez-Abreu D, Robinson AG et al (2016) Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375:1823–1833
13. Rittmeyer A, Barlesi F, Waterkamp D et al (2017) Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 389:255–265
14. Mok TS, Wu YL, Ahn MJ et al (2017) Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 376:629–640
15. Solomon BJ, Kim DW, Wu YL et al (2018) Final overall survival analysis from a study comparing first-line crizotinib versus chemotherapy in ALK-mutation-positive non-small-cell lung cancer. J Clin Oncol 36:2251–2258
16. Hida T, Nokihara H, Kondo M et al (2017) Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet 90:29–39
17. Peters S, Camidge DR, Shaw AT et al (2017) Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med 377:829–838
18. Rosell R, Dafni U, Felip E et al (2017) Erlotinib and bevacizumab in patients with advanced non-small-cell lung cancer and activating EGFR mutations (BELIEF): an international, multicentre, single-arm, phase 2 trial. Lancet Respir Med 5:435–444
19. Gainor JF, Dardaei L, Yoda S et al (2016) Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. Cancer Discov 6:1118–1133
20. Shaw AT, Kim TM, Crino L et al (2017) Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 18:874–886
21. Paz-Ares L, Luft A, Vicente D et al (2018) Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 379:2040–2051