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Frequent *EGFR* mutations in nonsmall cell lung cancer presenting with miliary intrapulmonary carcinomatosis

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ABSTRACT: Nonsmall cell lung cancer (NSCLC) presenting with miliary intrapulmonary carcinomatosis (MIPC) is rare. We investigated the clinical characteristics and epidermal growth factor receptor (*EGFR*) mutation rate of NSCLC patients with MIPC at initial diagnosis.

From June 2004 to December 2008, we screened newly diagnosed NSCLC patients for MIPC using image-based criteria. We recorded clinical data and analysed *EGFR* mutation status. For comparison, we collected specimens from stage IV NSCLC patients without MIPC tested for *EGFR* mutations from April 2001 to November 2008.

From 3,612 NSCLC patients, 85 patients with MIPC at initial diagnosis were identified; 81 had adenocarcinoma. Of the 85 patients, 60 had specimen sequencing to detect *EGFR* mutation; 42 (70%) were positive. Compared with 673 stage IV patients without MIPC, patients with MIPC had higher *EGFR* mutation rate (p=0.036); even male smokers had a high *EGFR* mutation rate (91%). Multivariate analysis of prognostic factors for overall survival of the 85 patients with MIPC revealed that adenocarcinoma, absence of extrapulmonary metastasis and having *EGFR* mutation were associated with longer overall survival.

NSCLC patients with MIPC at initial diagnosis had higher rates of adenocarcinoma and *EGFR* mutation. EGFR tyrosine kinase inhibition may be the treatment of choice for NSCLC patients with MIPC at initial diagnosis among Asians.

KEYWORDS: Epidermal growth factor receptor mutation, epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib, lung cancer, miliary carcinomatosis

Lung cancer is the leading cause of cancer-related deaths, accounting for 28% of all cancer deaths in the USA and >1 million deaths worldwide annually [1, 2]. Although imaging techniques have advanced, ~70% of nonsmall cell lung cancer (NSCLC) patients are still not diagnosed until the advanced stages of the disease. Their prognoses are also poor [2, 3].

The lung is frequently a metastatic organ of NSCLC, and lung metastasis presents with several different patterns on chest radiography, including multiple pulmonary nodules, pleural effusions and enlarged lymph nodes [4–7]. However, lung cancer with miliary intrapulmonary carcinomatosis (MIPC) is an uncommon phenomenon. A miliary pattern is defined as having diffuse, tiny and discrete pulmonary micronodules of ⩽5 mm on chest radiography [7], indicating haematogenous dissemination [5, 8]. High-resolution computed tomography (CT) provides better and more accurate detection of the widespread micronodules [5, 7].

NSCLC patients who present with MIPC at initial diagnosis have rapidly fatal courses although some case reports have described patients having a good response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy [9, 10]. EGFR controls cell proliferation, differentiation and invasion [11]. It has been found that females, nonsmokers, those with adenocarcinoma and East Asians exhibit increased responses to EGFR-TKI treatment [12, 13], which is associated with increased *EGFR* mutation rates [14–19]. The L858R mutation and deletion in exon-19 (*del-19*) account for 90% of the *EGFR* mutations [15, 17, 18, 20].

LAACK *et al.* [21] reported five never-smokers with miliary pattern lung adenocarcinoma all having

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del-19 EGFR mutations. They had good response to EGFR-TKIs. However, the clinical characteristics and treatment outcomes of NSCLC patients presenting with MIPC were not described.

This study investigates the clinical characteristics, *EGFR* mutation rate and treatment response, and explores prognostic factors for NSCLC patients who presented with MIPC at initial diagnosis.

MATERIALS AND METHODS

Patients

All NSCLC patients diagnosed from June 2004 to December 2008 were identified through the Cancer Registry at the Medical Information Management Office of National Taiwan University Hospital (NTUH) (Taipei, Taiwan). Patients with MIPC at initial diagnosis were enrolled. This study was approved by the NTUH Research Ethics Committee (approval number 9561705036).

For comparison, the *EGFR* mutation status of patients with stage IV lung cancer without MIPC was identified. Patients screened for *EGFR* mutations were: 1) those who underwent fine-needle biopsies (CT/ultrasound-guided) or thoracentesis for pleural effusions after July 2004, when consecutive recruitment for *EGFR* mutations test was started at the hospital [22]; or 2) those who were included for retrospective NSCLC studies [19, 23–25].

MIPC image-based criteria

The MIPC image-based criteria were: 1) profuse, tiny, discrete and round pulmonary nodules that are generally uniform in size and diffusely distributed throughout both lung fields; 2) number of nodules not easily counted by CT; and 3) most of the pulmonary nodules were $\leqslant$5 mm in diameter (fig. 1a and b) [7, 26, 27]. Patients with unilateral intrapulmonary carcinomatosis, multifocal ground-glass opacities or lymphangitic carcinomatosis were excluded.

Clinical data

The clinical characteristics of eligible patients were recorded. Weight loss was defined as >10% loss of the original body weight in 6 months. We defined patients who smoked <100 cigarettes in their lifetime as nonsmokers, patients who smoked cigarettes within a year of diagnosis as current smokers and the remaining patients as former smokers. Disease stage was determined by the Tumour Node Metastasis system [28].

Lung cancer histology was classified using the World Health Organization criteria [29]. Lung cancer was confirmed by pathological or cytological diagnoses using tissues obtained from biopsy or aspiration.

Response evaluation of NSCLC patients who received first-line systemic treatment

The timing and order of different treatment regimens was at the physicians' discretion after considering the patients clinical situation and a thorough discussion with patients. First-line systemic treatment for NSCLC patients included chemotherapy and EGFR-TKI therapy. The EGFR-TKIs gefitinib 250 mg·day^{-1} (Iressa®; AstraZeneca, Wilmington, DE, USA) or erlotinib 150 mg·day^{-1} (Tarceva®; OSI Pharmaceuticals, Inc., Melville, NY, USA) were prescribed. Patients who received no systemic therapy received best supportive care. To evaluate treatment response, a chest radiograph was obtained every 2–4 weeks and a chest CT every 2–3 months.

All images were reviewed by a pulmonologist (S-G. Wu) and a radiologist (Y-C. Chang) who were blinded to the *EGFR* mutation analysis results and treatment course of the study subjects. Treatment response was evaluated using the Response Evaluation Criteria in Solid Tumour guidelines (version 1.1) [30]. For measurable lesions, the responses were classified into complete response, partial response, stable disease or progressive disease. For patients who had only miliary lesions that were not measurable but evaluable, treatment responses were classified as nonprogressive disease (NPD) or progressive disease. NPD was defined as no new lesions and no unequivocal progression of existing lesions [30]. Disease control rate was calculated from all patients who had complete response, partial response, stable disease or NPD.

Overall survival was defined as the period from the date of NSCLC diagnosis to the date of death. Progression-free survival (PFS) was defined as the period from the date of first-line systemic treatment initiation to the date of the first objective or clinical sign of disease progression or death.

Tissue procurement for EGFR mutation analysis

Tumour specimens from lung tumours, metastatic sites and malignant effusion cell blocks were obtained for mutation analysis. Written informed consent to use tissue for molecular analysis was obtained from patients at the time of specimen collection. Tissue sections were examined for adequacy by microscopy with haematoxylin and eosin staining; tissue

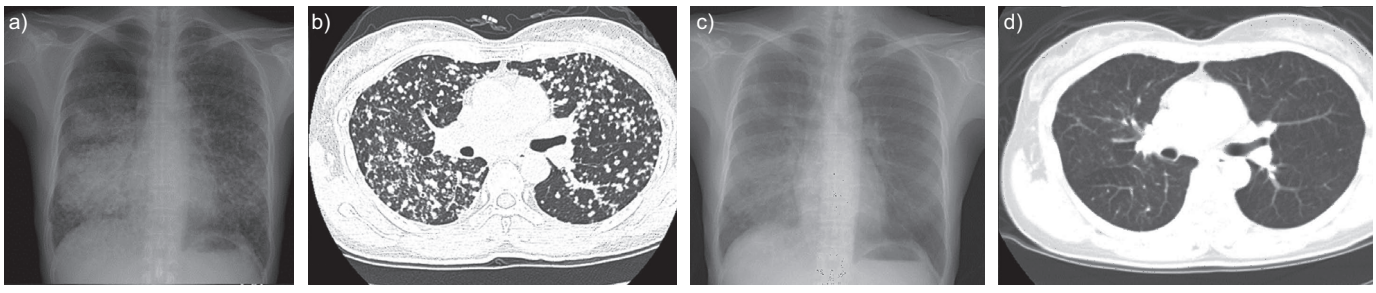

FIGURE 1. a, c) Chest radiography and b, d) computed tomography showing a patient a, b) with miliary intrapulmonary carcinomatosis at initial diagnosis. c, d) After treatment with the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib for 2 months, the images showed an obvious decrease of the miliary lung metastases.

samples that consisted of >80% tumour content were selected for the study.

PCR amplification and direct sequencing

Tumour DNA, obtained from paraffin blocks using a QiAmp DNA Mini kit (Qiagen, Valencia, CA, USA), was used for *EGFR* mutation analysis as described previously [19, 23, 25]. The tyrosine kinase domain of the *EGFR* coding sequence (exons 18–21) was amplified by independent rounds of PCR. The PCR amplicons were purified and sequenced using the BigDye Terminator Sequencing Kit (Applied Biosystems, Foster City, CA, USA).

Statistical analysis

All analyses were performed using the statistical software SPSS 15.0 (SPSS Inc., Chicago, IL, USA) or SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA). Two-sided p-values of <0.05 were considered statistically significant. All categorical variables were analysed by the Chi-squared test, except those with an expected frequency of less than five, which were analysed by Fisher's exact test. Unpaired t-tests were used for mean comparisons of continuous variables between two groups. Survival curves were plotted using the Kaplan–Meier method and compared between groups using the log-rank test.

To account for the patients without *EGFR* sequencing results, a logistic regression analysis was conducted on the predictive factors of the ''missing'' *EGFR* sequencing results *versus* ''nonmissing'' to estimate the probability of ''missing''. Further regression analysis with *EGFR* mutation as a covariate was weighted by the inverse of the predicted probability of ''nonmissing'' from the fitted logistic regression model for ''missing'' to obtain valid result. A weighted Cox's proportional hazards model was used to identify predictive factors of overall survival in the nonmissing patients with MIPC [31, 32].

RESULTS

Clinical characteristics of patients presenting with MIPC at initial diagnosis

From June 2004 to December 2008, there were 3,612 NSCLC patients registered in the Cancer Registry. Among them, 85 (2%) patients presented with MIPC at initial diagnosis. Of the 85 patients, 41 (48%) were male. The mean age was 59.8 yrs (range 28.3–87.7 yrs). There were 63 (74%) nonsmokers. 81 (95%) patients had adenocarcinoma and one had squamous cell carcinoma. The remaining three patients had NSCLC not otherwise specified. The most frequent distant metastasis sites were bone (64%) and brain (37%). Other clinical characteristics are shown in table 1.

The most common respiratory and nonrespiratory symptoms were coughing (66%) and weight loss (45%), respectively. Other symptoms are listed in table S1.

EGFR mutation status of patients presenting with MIPC at initial diagnosis

EGFR mutation testing was performed for 60 (71%) patients with both informed consent and adequate tissue samples. The specimens were obtained from lung tumours (n=23), pleural effusions (n=28), cervical lymph nodes (n=4), metastatic brain lesions (n=3), a metastatic bony lesion (n=1) and ascites (n=1). Patient demographics are shown in table 1.

There were 42 (70%) patients with *EGFR* mutations. The mutation rates did not differ significantly by sex (p=0.052) or smoking status (p=0.194) (table 2). It was noted that mutation rates for males and smokers were 84% (21 out of 25) and 85% (11 out of 13), respectively. The most common mutations were *del-19* (n=21, 35%) and L858R (n=12, 20%) (table S2).

Characteristics and EGFR mutation status of stage IV lung cancer patients without MIPC at initial diagnosis

From April 2001 to November 2009, 673 patients with stage IV lung cancer without MIPC were identified for *EGFR* mutation screening. Compared to patients with MIPC and *EGFR* mutation status, there was no difference in sex, age, smoking history or tumour type between the two groups. The patients with MIPC had higher metastasis rates of bone (p=0.022), brain (p=0.021) and liver (p=0.010) (table 3).

Patients who presented with MIPC at initial diagnosis had a higher *EGFR* mutation rate than patients without MIPC (70% *versus* 56%, p=0.036) (table 4). The presence of L858R mutation did not differ significantly between the two groups (20% *versus* 22%, p=0.433). However, patients with MIPC had significantly higher rate of *del-19* mutation (35% *versus* 25%, p=0.024) (table 4).

TABLE 1 Clinical characteristics of nonsmall cell lung cancer patients who presented with miliary intrapulmonary carcinomatosis at initial diagnosis

	Patients	*EGFR* tested	p-value[#]
Total n	85	60	
Age yrs	59.8 (28.3–87.7)	61.4 (39.1–87.7)	0.070[+]
Sex			0.060
Females	44 (52)	35 (58)	
Males	41 (48)	25 (42)	
Smoking			0.169
Nonsmokers	63 (74)	47 (78)	
Former/current smokers	22 (26)	13 (22)	
ECOG PS			0.055
0–1	63 (74)	48 (80)	
2–4	22 (26)	12 (20)	
Tumour type			0.577[§]
Nonadenocarcinoma	4 (5)	2 (3)	
Adenocarcinoma	81 (95)	58 (97)	
Distant metastasis			
Bone	54 (64)	37 (62)	0.580
Brain	31 (37)	22 (37)	0.954
Liver	23 (27)	17 (28)	0.682
Adrenal gland	8 (9)	8 (13)	0.098[§]
Others[¶]	12 (14)	7 (12)	0.315

Data are presented as n (%) or mean (range), unless otherwise stated. EGFR: epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group performance status. [#]: comparison between the groups with and without *EGFR* sequencing; [¶]: five spleen, one peritoneal, two cervical lymph nodes, three intra-abdominal lymphoadenopathy and one kidney; [+]: t-test. [§]: Fisher's exact test.

TABLE 2 *EGFR* mutation status of nonsmall cell lung cancer patients who presented with miliary intrapulmonary carcinomatosis at initial diagnosis

	EGFR mutation	Wild type	p-value
Total	42	18	
Age yrs	61.2 (41.3–87.7)	61.7 (39.1–79.6)	0.889[¶]
Sex			0.052[+]
Females	21	14	
Males	21	4	
Smoking			0.308[+]
Nonsmokers	31	16	
Former/current smokers	11	2	
ECOG PS			1.000[+]
0–1	33	15	
2–4	9	3	
Tumour type			0.514[+]
Nonadenocarcinoma	1	1	
Adenocarcinoma	41	17	
Distant metastasis			
Bone	28	9	
Brain	17	5	
Liver	12	5	
Adrenal gland	6	2	
Others[#]	5	2	

Data are presented as n or mean (range), unless otherwise stated. EGFR: epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group performance status. [#]: three spleen, one peritoneal, one cervical lymph node and two intra-abdominal lymphadenopathies; [¶]: t-test; [+]: Fisher's exact test.

Response rate and PFS after first-line systemic treatment

Of the 85 patients with MIPC at initial diagnosis, 80 received systemic treatment. Three patients were grade 4 on the Eastern Cooperative Oncology Group performance status scale at diagnosis, whose clinical conditions worsened rapidly. Two patients refused systemic treatment. The treatment selection depended on the physicians' discretion. The distributions of treatment sequences and their *EGFR* mutation status of patients were shown in table S3.

First-line treatments were EGFR-TKI for 43 patients and chemotherapy for 37 patients. In the EGFR-TKI group, 33 received gefitinib and 10 received erlotinib. Among them, 29 had a partial response (fig. 1c and d), one had NPD and 13 exhibited progressive disease; the disease control rate was 70%. In the chemotherapy group, first-line chemotherapies included platinum-based doublet chemotherapy (n=29), gemcitabine (n=4), vinorelbine (n=3) and paclitaxel (n=1). None received bevacizumab as combination chemotherapy. In this group, 11 patients had a partial response, four patients had NPD and 22 patients had progressive disease; the disease control rate was 41%. Disease control rates between the two groups were different (p=0.009). Furthermore, the EGFR-TKI group had longer median PFS (5.8 *versus* 2.9 months, p=0.001) (fig. 2).

TABLE 3 Clinical characteristics of stage IV nonsmall cell lung cancer patients who presented with and without miliary intrapulmonary carcinomatosis (MIPC) at initial diagnosis

	With MIPC	Without MIPC	p-value
Total	60	673	
Age yrs	61.4 (39.1–87.7)	63.9 (24.8–91.4)	0.130[#]
Sex			0.485
Females	35	361	
Males	25	312	
Smoking			0.091
Nonsmokers	47	456	
Former/current smokers	13	217	
Tumour type			1.000[¶]
Nonadenocarcinoma	2	33	
Adenocarcinoma	58	640	
Distant metastasis			
Bone	37	311	0.022
Brain	22	157	0.021
Liver	17	104	0.010
Malignant pleural effusion	27	331	0.535
Adrenal gland	8	74	0.582
Others	7	71	0.788

Data are presented as n or mean (range), unless otherwise stated. p-values were calculated by the Chi-squared test, unless otherwise stated. [#]: t-test; [¶]: Fisher's exact test.

Overall survival and prognostic factors

Univariate analysis of prognostic factors of the 85 patients with MIPC is shown in table 5. The difference in overall survival between patients with adenocarcinoma and nonadenocarcinoma was statistically significant (p=0.049). Patients without extrapulmonary metastasis had longer overall survival than those with extrapulmonary metastasis (p=0.032) (fig. 3). Patients who received EGFR-TKI sometime during their illness had significantly longer overall survival than those who did not (p<0.001).

TABLE 4 The difference in *EGFR* mutation types between stage IV nonsmall cell lung cancer with and without miliary intrapulmonary carcinomatosis (MIPC) at initial diagnosis

	Wild type	L858R	*del-19*	Other	Total
With MIPC	18 (30)	12 (20)	21 (35)	9 (15)	60
Without MIPC	296 (44)	149 (22)	165 (25)	63 (9)	673

Data are presented as n (%) or n. p=0.036 for MIPC *versus* non-MIPC stage IV nonsmall cell lung cancer specimens for positive and negative of epidermal growth factor receptor (*EGFR*) mutations; p=0.024 for the patient presented with *versus* without MIPC at initial diagnosis with *del-19* mutations. *del-19*: in-frame deletion in exon-19.

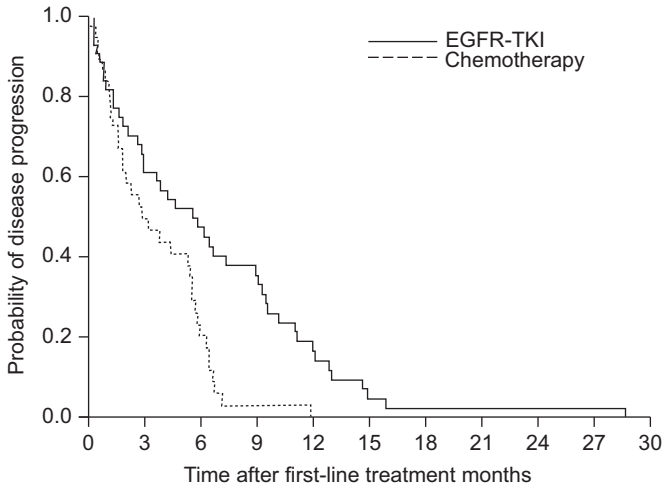

FIGURE 2. Kaplan–Meier curve of progression-free survival (PFS) in nonsmall cell lung cancer patients with miliary intrapulmonary carcinomatosis at initial diagnosis who received epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) (n=43) and systemic chemotherapy (n=37) as first-line treatment. The difference in PFS was statistically significant (median 5.8 *versus* 2.9 months, p=0.001 by the log-rank test).

Among the 60 patients with a known *EGFR* sequence, 55 received EGFR-TKI treatment; among them, 38 (69%) had *EGFR* mutations. Of those treated with EGFR-TKIs, 35 were treated as the first-line treatment and 21 as the second- or subsequent-line treatment. Patients with *EGFR* mutations had longer PFS than those with wild-type *EGFR* (9.2 *versus* 2.7 months, p<0.001) (fig. S1). The difference in overall survival between patients with and without *EGFR* mutations was statistically significant (17.8 *versus* 10.6 months, p=0.008) (fig. 4).

Overall survival analysis based on the order of treatment received showed that patients who received EGFR-TKI therapy as first-line treatment and chemotherapy as second-line treatment had the longest overall survival (median 20.9 months). This is followed sequentially by patients who received chemotherapy as both first- and second-line treatments, chemotherapy with subsequent EGFR-TKI, EGFR-TKI only, chemotherapy only and, lastly, supportive care alone (p<0.001) (table 5).

Logistic regression of the 25 patients with no *EGFR* sequencing showed that they were primarily male (p=0.052), had poorer performance status (p=0.035) and received chemotherapy as the first-line treatment (p=0.006). Their *EGFR* status was weighted according to these factors. Multivariate analysis of overall survival was then performed using the Cox proportional hazard model for potential prognostic factors, including sex, age, smoking status, tumour type, extrapulmonary metastasis, *EGFR* mutation status, EGFR-TKI use and treatment order.

Longer overall survival was associated with having adenocarcinoma (hazard ratio (HR) 0.16, p=0.0448), absence of extrapulmonary metastasis (HR 0.45, p=0.0514) and *EGFR* mutation (HR 0.19, p=0.0001). Factors with a significantly negative effect on overall survival were best supportive care (HR 106.19, p<0.0001) and the use of first-line EGFR-TKI therapy as the only treatment (HR 4.46, p=0.0003) (table 5). The measured goodness-of-fit values and the results of the goodness-of-fit test indicated that the Cox proportional hazards model fitted the observed binary data well.

DISCUSSION

NSCLC patients with *EGFR* mutations are known to have better response to EGFR-TKI treatment [14, 16]. The present study showed that NSCLC patients presented with MIPC at initial diagnosis had a higher *EGFR* mutation rate than those without MIPC. We enrolled more patients than the five cases originally reported by LAACK *et al.* [21]; therefore, we are able to present the complete clinical characteristics, metastatic sites and *EGFR* mutation types in this subgroup of patients. Currently known clinical characteristics associated with *EGFR* mutation include female sex, adenocarcinoma, never having smoked and being Asian [17, 33]. Our finding of a high *EGFR* mutation rate among patients presenting with the special image pattern of MIPC at initial diagnosis provide physicians an additional characteristic in selecting patients who may have better response to EGFR-TKIs.

The Iressa Pan-Asia Study (IPASS), conducted on East Asian nonsmokers and former light smokers with lung adenocarcinoma, showed that initial gefitinib treatment resulted in a better response rate and longer PFS than carboplatin–paclitaxel treatment [16]. The *EGFR* mutation rate of IPASS was 60%, which is lower than the 70% found in the present study. Furthermore, contrary to the general concept regarding high *EGFR* mutation subgroups [12, 13], we also found that the subgroups of NSCLC patients with MIPC, males and smokers, have high *EGFR* mutation rates. The high *EGFR* mutation rate was consistent with a better treatment response and longer PFS among patients treated with EGFR-TKI as first-line treatment.

MIPC at initial diagnosis is a more invasive disease state. Most NSCLC patients with MIPC at initial diagnosis often have poor performance status and rapidly fatal courses [34], and chemotherapy is not usually recommended [35]. The present study showed a high *EGFR* mutation rate in this subgroup of NSCLC patients. In addition, best supportive care had a very short overall survival. EGFR-TKIs may be the treatment of choice for NSCLC patients with MIPC, especially for patients with poor performance status.

The mutation rate of *del-19* was higher in patients with MIPC than those without MIPC (35% *versus* 25%). The high *del-19* mutation rate resulted in a higher *EGFR* mutation rate in patients with MIPC than those without MIPC at initial diagnosis. Further studies are necessary to investigate the relationship between *del-19* mutation and miliary pulmonary metastasis in NSCLC.

Tumour cell metastasis *via* the haematogenous route can result in diffuse miliary seeding [36]. UMEKI *et al.* [34] showed that MIPC of lung cancer was associated with bone metastasis because all five of his patients had bone metastases. They proposed that bone metastasis occurred from the lung *via* the haematogenous route, whereas MIPC arises from multiple tumour emboli from secondary bone metastatic foci [34]. KOLSUZ *et al.* [37] described a lung adenocarcinoma patient with MIPC and bone marrow involvement, which was thought to be caused by tumour cell spread *via* the haematogenous

TABLE 5 Prognostic factors for overall survival (OS) of nonsmall cell lung cancer patients who presented with miliary intrapulmonary carcinomatosis at initial diagnosis

Factor	Patients n	OS months	Univariate analysis	Multivariate analysis#	
			p-value	HR (95% CI)	p-value
Sex					
Female	44	12.3			
Male	41	12.4	0.770		
Age yrs					
<65	54	11.5			
⩾65	31	13.4	0.893		
Smoking					
Nonsmokers	63	14.6			
Current/former smokers	22	8.3	0.226		
ECOG PS					
0–1	63	14.1			
2–4	22	6.8	0.165		
Tumour type					
Nonadenocarcinoma	4	3.5		1	
Adenocarcinoma	81	13.1	0.049	0.16 (0.03–0.96)	0.0448
Extrapulmonary metastasis					
Yes	70	10.4		1	
No	15	23.5	0.032	0.45 (0.20–1.01)	0.0514
EGFR					
Wild type	18	10.6		1	
Mutation	42	17.8	0.008	0.19 (0.08–0.44)	0.0001
TKI use					
No	14	4.8			
Yes	71	16.2	<0.001		
Treatment sequence¶					
Best supportive care	5	0.3		106.19 (18.24–618.11)	<0.0001
TKI only+	18	6.9		4.46 (2.00–9.95)	0.0003
Chemotherapy only+	5	6.3			
TKI then chemotherapy	25	20.9			
Chemotherapy then TKI	15	16.2			
Chemotherapy then chemotherapy	17	19.7			

HR: hazard ratio; ECOG PS: Eastern Cooperative Oncology Group performance status; EGFR: epidermal growth factor receptor, TKI: tyrosine kinase inhibitor. #: before performing multivariate analysis, we performed logistic regression to identify potential factors associated with the 25 patients lacking *EGFR* sequencing data. Potential factors mainly included male sex, poor performance status and chemotherapy as the first-line treatment. After weighting the missing data of the 25 patients lacking *EGFR* sequencing data by logistic regression, we used the Cox proportional hazard method for multivariate analysis of OS. ¶: the sequence of patient treatment courses was classified according to the first- and second-line medications. +: TKI-only and chemotherapy-only patients received only first-line systemic treatment without second-line treatment.

route. The present study also showed that 63.5% of NSCLC patients with MIPC at initial diagnosis had synchronous bone metastasis (table 1). In comparison with the stage IV NSCLC patients presented without MIPC at initial diagnosis, patients with MIPC had higher rates of metastasis to the liver, bone and brain, all sites of haematogenous spread. This result supports that haematogenous spread plays an important role in both MIPC and bone metastases of NSCLC.

The present study showed that the majority of NSCLC patients with MIPC at initial diagnosis had adenocarcinoma. The patients with MIPC in the previous reports all had adenocarcinoma [21, 34]. The probable pathophysiology is that miliary presentation is a manifestation of haematogenous spread, which is associated with angiogenesis of cancer [5]. In comparison with lung squamous cell carcinoma, lung adenocarcinoma has more tumour angiogenic potential, which may contribute to the high haematogenous spread [38]. In addition, lung adenocarcinoma may develop early metastasis *via* haematogenous spread [5, 8, 39]. Therefore, adenocarcinoma is the dominant histopathology type of MIPC at initial diagnosis.

Despite multiple pulmonary metastases, patients may still respond to EGFR-TKIs. CHANG *et al.* [10] reported successful treatment of multifocal bronchioloalveolar cell carcinoma with gefitinib in two patients. GOTO *et al.* [40] showed that NSCLC patients who had more than six metastatic pulmonary nodules (particularly diffuse miliary metastases) were significantly

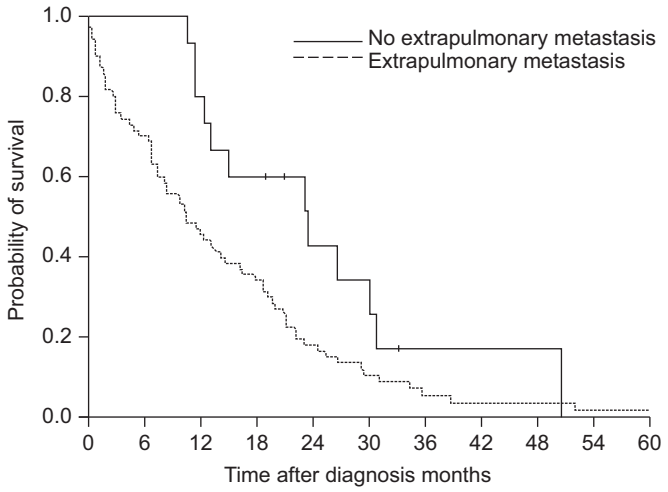

FIGURE 3. Kaplan–Meier curve of overall survival in nonsmall cell lung cancer patients with miliary intrapulmonary carcinomatosis at initial diagnosis. The difference in overall survival between patients without extrapulmonary metastasis (n=15) and those with extrapulmonary metastasis (n=70) was statistically significant (median 23.5 *versus* 10.4 months, p=0.032 by the log-rank test).

associated with a positive response to gefitinib. However, *EGFR* mutation status, the most important factor in determining response to EGFR-TKI treatment, was not known at that time. In 2006, KOBAYASHI *et al.* [9] linked *EGFR* mutation with a good gefitinib response among two diffuse micronodular pulmonary metastasis patients. In our study, we also showed that patients presenting with MIPC responded well to EGFR-TKIs, which may be associated with the high *EGFR* mutation rate among our patients.

The present study has some limitations. First, the patient number was small because MIPC is a rare presentation of lung cancer at diagnosis. Secondly, this was a retrospective observational study, and inherent biases cannot be completely excluded. Thirdly, differentiating intrapulmonary metastasis from independent multiple primary tumours is difficult in miliary pulmonary nodules of NSCLC. Comprehensive histological assessment and molecular analysis of different nodules are powerful tools [41], but obtaining specimens from multiple micronodules is difficult because the lesions are too small. Lastly, all enrolled patients in this study were Asian, known to have higher *EGFR* mutation rate. The results may not be generalisable to all patients presenting with MIPC.

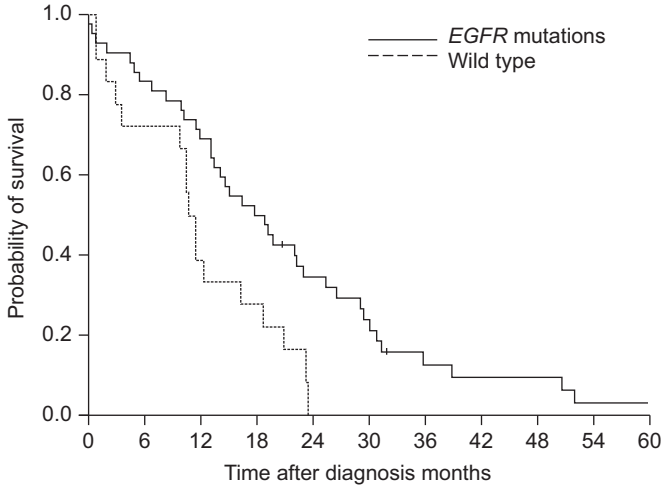

FIGURE 4. Kaplan–Meier curve of overall survival after first-line treatment in non-small cell lung cancer patients with miliary intrapulmonary carcinomatosis at initial diagnosis. The difference in overall survival between the patients with epidermal growth factor receptor (*EGFR*) mutations (n=42) and those with wild-type *EGFR* (n=18) was statistically significant (median 17.8 *versus* 10.6 months, p=0.008 by the log-rank test).

In conclusion, NSCLC patients presenting with MIPC at initial diagnosis have high rates of adenocarcinoma and *EGFR* mutation rate even among males and smokers. MIPC pattern helps to identify patients who have a high likelihood of having *EGFR* mutation. EGFR-TKI may be the treatment of choice for NSCLC patients with MIPC at initial diagnosis among Asians regardless of sex or smoking status.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

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