



# Predicted outcomes of subdividing M1-stage metastatic lung cancer based on the prognosis and the response to local consolidative therapy

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**Background:** For stage IV non-small cell lung cancer (NSCLC) patients, systemic therapy is the main strategy, and local consolidative therapy tends to be performed for patients with oligometastases. The purpose of this article is to evaluate the prognostic effects of local consolidative therapy for patients with stage IV NSCLC and divide these patients into different subcategories to stratify the prognoses.

**Methods:** A total of 30,583 patients with stage IV NSCLC were identified in the Surveillance, Epidemiology, and End Results (SEER) database. To identify factors related to high cancer-specific mortality (CSM) rates and compare the prognostic effects of different treatment strategies, a competing risk model was developed. Furthermore, independent prognostic factors identified through multivariable analysis were employed to supplement the current M1 subcategory. Cumulative incidence curves were estimated using the Kaplan-Meier method, and the log-rank test was used to compare prognostic differences.

**Results:** The CSM rates of M1a, M1b, and M1c patients were significantly different [M1b versus M1a: subdistribution hazard ratio (SHR), 1.38; 95% confidence interval (CI), 1.31–1.45;  $P < 0.001$ ; M1c *vs.* M1a: SHR, 1.76; 95% CI, 1.67–1.85;  $P < 0.001$ ]. Patients were divided into five groups depending on the M1 subcategory and liver involvement (Group A, M1c NSCLC with liver involvement; Group B, M1c NSCLC without liver involvement; Group C, M1b NSCLC with liver involvement; Group D, M1b NSCLC without liver involvement; and Group E, M1a NSCLC). Univariable analysis showed that liver involvement was associated with increased cancer-specific mortality (CSM) rates in both M1b and M1c patients (A *vs.* B: SHR, 1.36; 95% CI, 1.30–1.43;  $P < 0.001$ ; C *vs.* D: SHR, 1.27; 95% CI, 1.20–1.35;  $P < 0.001$ ). Primary tumor surgery plus chemotherapy may substantially benefit patients, especially M1b patients (surgery alone: SHR, 0.425; 95% CI, 0.361–0.500;  $P < 0.001$  *vs.* chemotherapy alone: SHR, 0.366; 95% CI, 0.352–0.382;  $P < 0.001$  *vs.* chemotherapy plus surgery: SHR, 0.194; 95% CI, 0.165–0.228;  $P < 0.001$ ; no treatment used as reference).

**Conclusions:** Subdivision of M1 disease and awareness of liver involvement may help to inform the prognosis of stage IV NSCLC patients and facilitate treatment planning.

**Keywords:** M1 stage; non-small cell lung cancer (NSCLC); survival; local consolidative therapy

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## Introduction

Lung cancer is the most common cancer worldwide and is also one of the leading causes of cancer-related mortality (1,2). Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer cases (3,4). Appropriate and accurate therapy impacts morbidity and mortality outcomes. Determination of the therapeutic schedule for NSCLC depends on various factors, including but not limited to the period of disease, patient comorbidities or performance scores, and the biological features of carcinoma (3,5). Resection is the standard treatment for patients with an early-stage disease and medically suitable conditions (6,7), whereas multimodality therapy involving chemotherapy, radiotherapy, and surgical resection is recommended for locally advanced tumors (8,9). For patients with stage IV disease, systemic therapy, including chemotherapy, immune therapy, and targeted therapy, is the main strategy, and local consolidative therapy tends to be performed for patients with oligometastases (10-13).

The anatomic extent of malignant carcinoma is presented according to the TNM staging system. Seventy-six types of malignant tumors were described by TNM staging, and approximately 20 types of carcinoma, such as lung and prostate cancers, include further subdivisions of the M1 category (10,14,15). According to the American Joint Committee on Cancer (AJCC) 8th edition, the M1 stage of lung cancer has been divided into three subcategories: M1a, separate tumor nodule(s) in the contralateral lobe, a tumor with pleural or pericardial nodules, malignant pleural nodules, or pericardial effusion; M1b, single extrathoracic metastasis in a single organ; and M1c, multiple extrathoracic metastases in one or several organs (16). However, patients with stage IV NSCLC are thought to have the same prognosis in defiance of histological grade, EGFR mutation, PD-1 expression, and PD-L1 expression (17,18). Therefore, further subdivision of stage IV tumors is clinically important for predicting prognosis and guiding individualized treatment.

By performing a population-based study, we aimed to evaluate the prognostic effects of local consolidative therapy for patients with stage IV NSCLC and divide patients with stage IV NSCLC into different subcategories to stratify the prognoses. We present the following article in accordance with the TRIPOD reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-1383>).

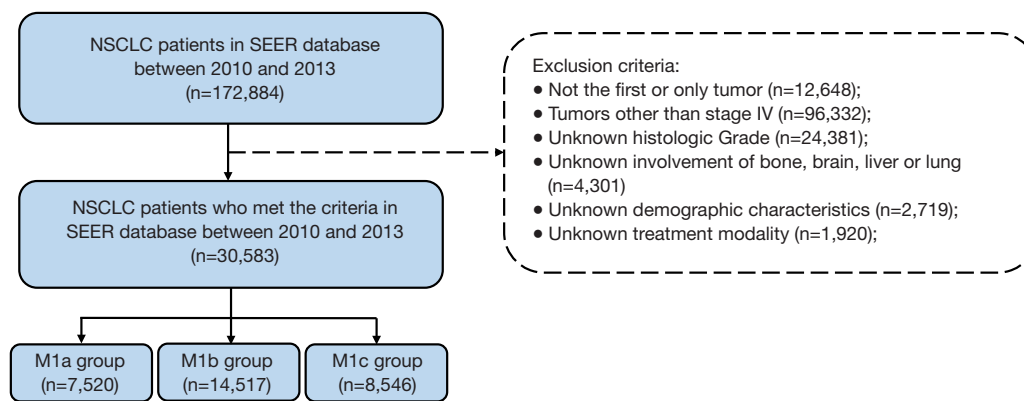
## Methods

### *Patients and methods*

Patients were selected from the SEER database, which includes clinical records for cancer occurrences in 18 areas of the United States corresponding to approximately 27.8% of the population (19). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). SEER\*Stat Database: Incidence, SEER 18 Regs Research Data (with chemotherapy recode), Nov 2015 Sub (2000–2013) software (version 8.3.5; [seer.cancer.gov/seerstat](http://seer.cancer.gov/seerstat)) was used to identify patients with NSCLC diagnosed from 2010 through 2013. Patients with lung cancer were selected using ICD-O-3 codes (C34.0–C34.9). SEER database includes information on patient demographics, the position and morphology of a primary carcinoma, the stage of a tumor at diagnosis, the first treatment modality, and survival status. Only patients who were diagnosed with stage IV NSCLC at the initial diagnosis and had only one malignant primary in lifetime were included. *Figure 1* details the selection process for the inclusion of patients. All patients were at least 18 years old. Patients with tumors that were stage I to III, unknown follow-ups and basic information, or unknown bone involvement, brain involvement, liver involvement, or lung involvement and patients diagnosed by autopsy or death certificate were not included in the study. As a result, we selected a total of 30,583 patients in our cohort for analysis.

### *Distinguishing subgroups*

To supplement the current M1 subdivision, individuals were divided into subgroups according to M1 stage and the presence or absence of liver involvement, which was identified as the most important prognostic factor in multivariable analysis (20). Patients in group A were diagnosed with M1c NSCLC with liver involvement; patients in group B were diagnosed with M1c NSCLC without liver involvement; patients in group C were diagnosed with M1b NSCLC with liver involvement; patients in group D were diagnosed with M1b NSCLC without liver involvement; and patients in group E were diagnosed with M1a NSCLC. And the null hypothesis is that the groups divided by the current M1 subcategory and involvement of liver have no significant difference in prognoses ( $P > 0.05$ ).



**Figure 1** Flow chart of patient screening.

### Statistical analysis

Cancer-specific mortality (CSM) was defined as death due to lung cancer utilizing the specific codes from the SEER database as in prior articles (21,22). Kaplan-Meier and log-rank tests were conducted to evaluate CSM rates. Pearson's  $\chi^2$  test and Fisher's exact test were applied to analyze categorical data, while Student's t-test and the Mann-Whitney U-test were applied to analyze numerical data. SPSS 23.0 software (IBM Corp., Armonk, New York, USA) was used to perform the statistical analysis. A Fine-Gray competing risk model was applied in multivariable analyses by using variables with  $P < 0.05$  in the univariable analysis. All analyses were double-tailed. A  $P$  value  $< 0.05$  was considered statistically significant.

## Results

### Baseline characteristics

Among the 172,884 patients diagnosed with lung cancer, 30,583 with stage IV NSCLC were identified, including 7,520 patients in the M1a group, 14,517 patients in the M1b group and 8,546 patients were in the M1c group (Figure 1). As shown in Table 1, the most common involved organs were the lung, bone, brain, and liver. Totally, 1,328 patients were lost to follow-up and censored. The median follow-up of the whole cohort was calculated to be 23.0 [95% confidence interval (CI), 22.4–23.6] months.

### Association between clinicopathological characteristics of patients and CSM rates

The results of the univariable analysis showed that brain,

liver, and bone involvement, male sex, adenocarcinoma, other marital statuses and advanced histological grade were associated with increased CSM rates. Using a competing risk regression model, advanced histological grade [Grade II *vs.* Grade I: subdistribution hazard ratio (SHR), 1.29; 95% CI, 1.17–1.43,  $P < 0.001$ ; Grade III *vs.* Grade I: SHR, 1.63; 95% CI, 1.48–1.80,  $P < 0.001$ ; Grade IV *vs.* Grade I: SHR, 1.77; 95% CI, 1.52–2.07,  $P < 0.001$ ], male sex (SHR, 1.21; 95% CI, 1.17–1.24;  $P < 0.001$ ), bone involvement (SHR, 1.28; 95% CI, 1.24–1.32;  $P < 0.001$ ), brain involvement (SHR, 1.23; 95% CI, 1.19–1.28;  $P < 0.001$ ), and liver involvement (SHR, 1.47; 95% CI, 1.41–1.53;  $P < 0.001$ ) were independent prognostic factors and other independent prognostic factors were shown in Table 2.

### Subdivision of the M1 category

Patients with stage IV NSCLC were subdivided into three categories: M1a, M1b, and M1c. The CSM rates increased across the M1 subcategories (Figure 2). Compared with bone or brain involved, liver involved was an more important prognostic factor with a higher SHR value of 1.47. To create a concise model that is convenient for clinical practice, all the patients were grouped into five groups considering these two important factors: M1 subcategory and liver involvement: Group A, M1c NSCLC with liver involvement; group B, M1c NSCLC without liver involvement; group C, M1b NSCLC with liver involvement; Group D, M1b NSCLC without liver involvement; and group E, M1a NSCLC. The univariable analysis demonstrated the results that liver involvement was related to increased CSM rates in both M1b and M1c patients [A *vs.* B (B as the reference): SHR, 1.36; 95% CI, 1.30–1.43;  $P < 0.001$ ; C *vs.* D (D as the reference):

**Table 1** Baseline characteristics stratified by M1 subcategory

Variables	Whole cohort	M1a	M1b	M1c	P value
Total	30,583	7,520	14,517	8,546	
Age, mean $\pm$ SD	67.1 $\pm$ 11.2	70.0 $\pm$ 11.3	66.4 $\pm$ 11.0	65.6 $\pm$ 10.9	<0.001
Sex, No (%)					<0.001
Female	13,697 (44.8)	3,537 (47.0)	6,352 (43.8)	3,808 (44.6)	
Male	16,886 (55.2)	3,983 (53.0)	8,165 (56.2)	4,738 (55.4)	
Race, No. (%)					<0.001
Black	4,169 (13.6)	1,094 (14.5)	1,940 (13.4)	1,135 (13.3)	
Other	2,762 (9.0)	709 (9.4)	1,135 (7.8)	918 (10.7)	
White	23,652 (77.3)	5,717 (76.0)	11,442 (78.8)	6,493 (76.0)	
Marital status, No. (%)					
Married	16,153 (52.8)	3,719 (49.5)	7,678 (52.9)	4,756 (55.7)	
Others	14,430 (47.2)	3,801 (50.5)	6,839 (47.1)	3,790 (44.3)	
Histological type, No (%)					<0.001
Squamous cell carcinoma	6,802 (22.2)	2,282 (30.3)	3,152 (21.7)	1,368 (16.0)	
Adenocarcinoma	18,785 (61.4)	4,187 (55.7)	8,814 (60.7)	5,784 (67.7)	
Others	4,996 (16.3)	1,051 (14.0)	2,551 (17.6)	1,394 (16.3)	
Histologic Grade, No. (%)					<0.001
Well differentiated; Grade I	16,69 (5.5)	677 (9.0)	582 (4.0)	410 (4.8)	
Moderately differentiated; Grade II	8,663 (28.3)	2,558 (34.0)	3,848 (26.5)	2,257 (26.4)	
Poorly differentiated; Grade III	19,551 (63.9)	4,163 (55.4)	9,695 (66.8)	5,693 (66.6)	
Undifferentiated; anaplastic; Grade IV	700 (2.3)	122 (1.6)	392 (2.7)	186 (2.2)	
T classification, No. (%)					<0.001
T1a	284 (0.9)	55 (0.7)	187 (1.3)	42 (0.5)	
T1b	1,415 (4.6)	262 (3.5)	902 (6.2)	251 (2.9)	
T1c	2,129 (7.0)	349 (4.6)	1,324 (9.1)	456 (5.3)	
T2a	5,721 (18.7)	1267 (16.8)	3,263 (22.5)	1,191 (13.9)	
T2b	2,689 (8.8)	527 (7)	1,568 (10.8)	594 (7.0)	
T3	8,022 (26.2)	2,086 (27.7)	3,533 (24.3)	2,403 (28.1)	
T4	10,323 (33.8)	2,974 (39.5)	3,740 (25.8)	3,609 (42.2)	
N classification, No. (%)					<0.001
N0	7,535 (24.6)	2,386 (31.7)	3,647 (25.1)	1,502 (17.6)	
N1	2,535 (8.3)	518 (6.9)	1,384 (9.5)	633 (7.4)	
N2	14,366 (47.0)	3,352 (44.6)	6,696 (46.1)	4,318 (50.5)	
N3	6,147 (20.1)	1,264 (16.8)	2,790 (19.2)	2,093 (24.5)	

**Table 1** (continued)

**Table 1** (continued)

Variables	Whole cohort	M1a	M1b	M1c	P value
Bone involved, No. (%)					<0.001
No	19,037 (62.2)	7,520 (100.0)	9,438 (65.0)	2,079 (24.3)	
Yes	11,546 (37.8)	0 (0.0)	5,079 (35.0)	6,467 (75.7)	
Brain involved, No. (%)					<0.001
No	22,097 (72.3)	7,520 (100.0)	10,387 (71.6)	4,190 (49.0)	
Yes	8,486 (27.7)	0 (0.0)	4,130 (28.4)	4,356 (51.0)	
Liver involved, No. (%)					<0.001
No	25,311 (82.8)	7,520 (100.0)	13,119 (90.4)	4,672 (54.7)	
Yes	5,272 (17.2)	0 (0.0)	1,398 (9.6)	3,874 (45.3)	
Lung involved, No. (%)					<0.001
No	20,974 (68.6)	4,029 (53.6)	13,541 (93.3)	3,404 (39.8)	
Yes	9,609 (31.4)	3,491 (46.4)	976 (6.7)	5,142 (60.2)	
Treatment, No. (%)					<0.001
None	12,977 (42.4)	3,237 (43.0)	6,012 (41.4)	3,728 (43.6)	
Surgery only	531 (1.7)	267 (3.6)	225 (1.5)	39 (0.5)	
Chemo only	16,393 (53.6)	3,750 (49.9)	7,933 (54.6)	4,710 (55.1)	
Chemo + surgery	682 (2.2)	266 (3.5)	347 (2.4)	69 (0.8)	

Chemo, chemotherapy.

**Table 2** Univariable and multivariable analysis of cancer-specific mortality in whole set

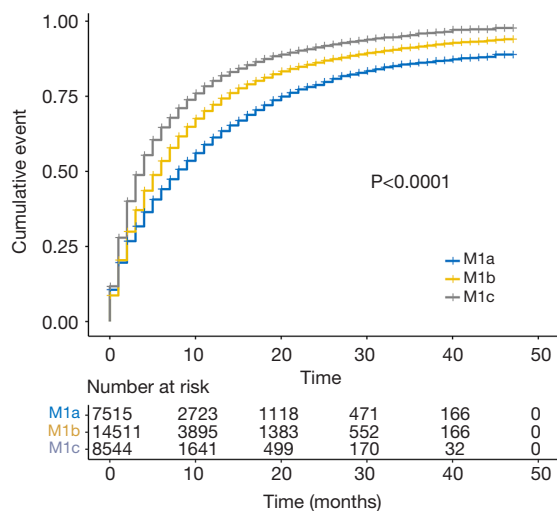
Variables	Univariable analysis		Multivariable analysis	
	SHR (95% CI)	P value	SHR (95% CI)	P value
Age	1.016 (1.015–1.017)	<0.001	1.010 (1.008–1.011)	<0.001
Sex				
Female	Reference		Reference	
Male	1.243 (1.211–1.276)	<0.001	1.206 (1.174–1.239)	<0.001
Race/Ethnicity				
Black	Reference		Reference	
Other	0.677 (0.639–0.718)	<0.001	0.709 (0.668–0.752)	<0.001
White	0.991 (0.955–1.029)	0.644	1.022 (0.984–1.061)	0.268
Marital status				
Married	Reference		Reference	
Others	1.181 (1.151–1.212)	<0.001	1.082 (1.053–1.111)	<0.001
Histological type				
Squamous cell carcinoma	Reference		Reference	
Adenocarcinoma	0.750 (0.727–0.774)	<0.001	0.853 (0.825–0.881)	<0.001
Others	0.968 (0.930–1.008)	0.116	1.004 (0.963–1.046)	0.860

**Table 2** (continued)

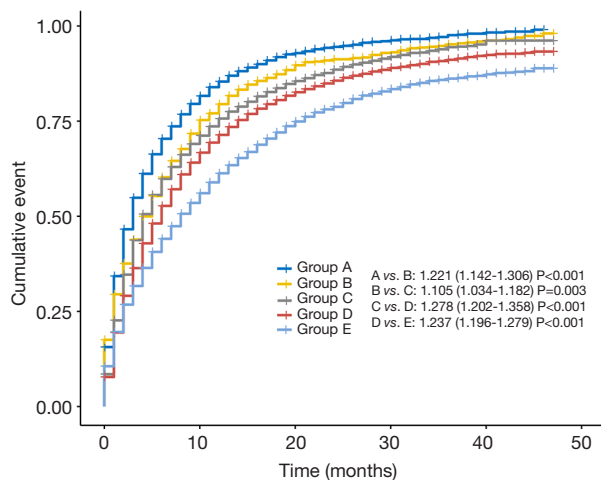
Table 2 (continued)

Variables	Univariable analysis		Multivariable analysis	
	SHR (95% CI)	P value	SHR (95% CI)	P value
<b>Histologic Grade</b>				
Well differentiated; Grade I	Reference		Reference	
Moderately differentiated; Grade II	1.397 (1.263–1.546)	<0.001	1.292 (1.167–1.431)	<0.001
Poorly differentiated; Grade III	1.880 (1.706–2.071)	<0.001	1.630 (1.478–1.798)	<0.001
Undifferentiated; anaplastic; Grade IV	2.041 (1.749–2.380)	<0.001	1.774 (1.520–2.071)	<0.001
<b>T classification</b>				
T1a	Reference		Reference	
T1b	0.986 (0.846–1.149)	0.858	0.922 (0.791–1.075)	0.299
T1c	1.063 (0.916–1.233)	0.420	0.983 (0.847–1.141)	0.824
T2a	1.181 (1.024–1.363)	0.022	1.104 (0.957–1.274)	0.176
T2b	1.401 (1.211–1.621)	<0.001	1.230 (1.063–1.424)	0.006
T3	1.339 (1.161–1.543)	<0.001	1.236 (1.072–1.426)	0.004
T4	1.359 (1.179–1.565)	<0.001	1.252 (1.086–1.444)	0.002
<b>N classification</b>				
N0	Reference		Reference	
N1	1.147 (1.089–1.209)	<0.001	1.190 (1.129–1.255)	<0.001
N2	1.274 (1.233–1.316)	<0.001	1.307 (1.264–1.352)	<0.001
N3	1.258 (1.210–1.309)	<0.001	1.400 (1.344–1.458)	<0.001
<b>M classification</b>				
M1a	Reference		Reference	
M1b	1.261 (1.220–1.304)	<0.001	1.209 (1.162–1.257)	<0.001
M1c	1.625 (1.567–1.685)	<0.001	1.348 (1.274–1.427)	<0.001
<b>Bone involved</b>				
No	Reference		Reference	
Yes	1.266 (1.233–1.300)	<0.001	1.281 (1.240–1.324)	<0.001
<b>Brain involved</b>				
No	Reference		Reference	
Yes	1.114 (1.083–1.147)	<0.001	1.234 (1.193–1.277)	<0.001
<b>Liver involved</b>				
No	Reference		Reference	
Yes	1.536 (1.486–1.587)	<0.001	1.470 (1.414–1.528)	<0.001
<b>Lung involved</b>				
No	Reference			
Yes	0.999 (0.972–1.027)	0.951		
<b>Treatment</b>				
None	Reference		Reference	
Surgery only	0.276 (0.246–0.309)	<0.001	0.383 (0.341–0.430)	<0.001
Chemo only	0.374 (0.364–0.384)	<0.001	0.373 (0.362–0.383)	<0.001
Chemo + surgery	0.183 (0.163–0.803)	<0.001	0.227 (0.203–0.254)	<0.001

Chemo, chemotherapy; CI, confidence interval; SHR, subdistribution hazard ratio.



**Figure 2** Kaplan-Meier curves of cancer-specific mortality for different M1 subcategories in whole set.



**Figure 3** Cumulative cancer-specific mortality for five groups constructed based on liver involvement and the current M1 staging. Group A, M1c NSCLC with liver involvement; Group B, M1c NSCLC without liver involvement; Group C, M1b NSCLC with liver involvement; Group D, M1b NSCLC without liver involvement; and Group E, M1a NSCLC. NSCLC, non-small cell lung cancer.

SHR, 1.27; 95% CI, 1.20–1.35;  $P < 0.001$ ] (Figure 3).

#### *Associations between treatment modalities and M1 subcategories with survival status*

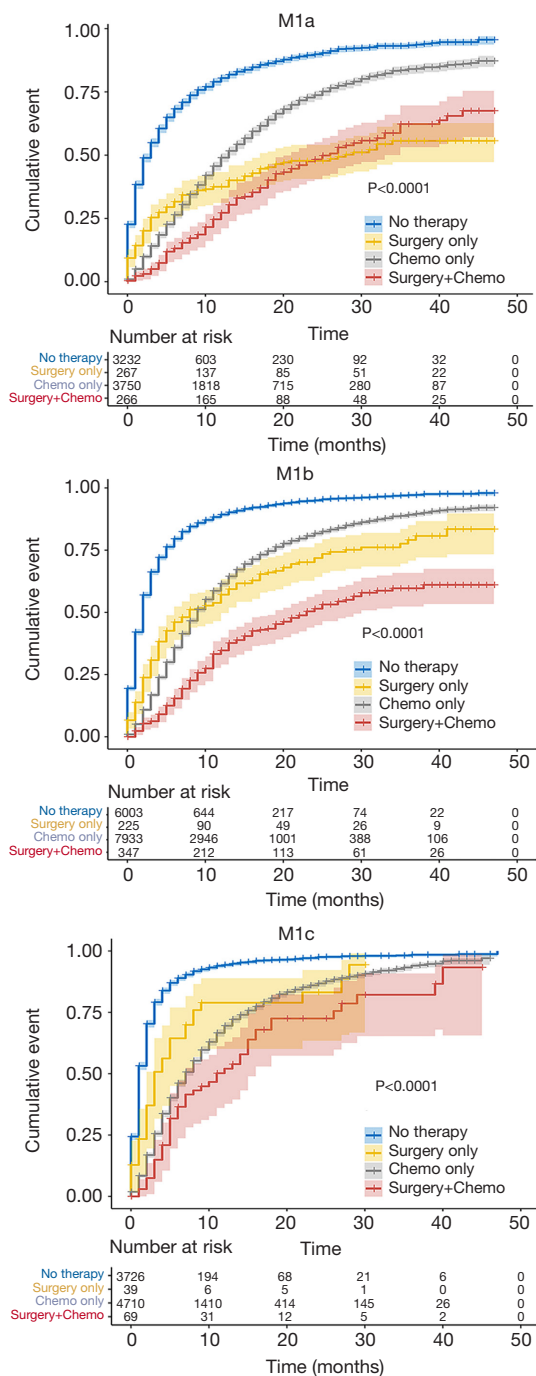
As shown in Figure 4, Kaplan-Meier curves showed reduced

CSM rates after primary tumor surgery, chemotherapy, or combined therapy in patients with M1a, M1b, and M1c diseases. When monotherapy was compared with no therapy, primary tumor surgery was identified as a favorable prognostic factor, particularly for M1a cases (M1a: SHR, 0.35; 95% CI, 0.29–0.42;  $P < 0.001$ ; M1b: SHR, 0.43; 95% CI, 0.36–0.50;  $P < 0.001$ ; M1c: SHR, 0.57; 95% CI, 0.40–0.70;  $P < 0.001$ ) (Table 3). M1a patients benefited less from chemotherapy only than M1b or M1c patients (M1a: SHR, 0.41; 95% CI, 0.39–0.44;  $P < 0.001$ ; M1b: SHR, 0.37; 95% CI, 0.36–0.39;  $P < 0.001$ ; and M1c: SHR, 0.34; 95% CI, 0.32–0.36;  $P < 0.001$ ) (Table 3). Specifically, no significant difference in CSM rates was observed between patients treated with surgery only and those treated with chemotherapy only, with the exception of patients with M1a disease, who showed a worse prognosis when receiving only chemotherapy (SHR, 1.18; 95% CI, 0.98–1.43;  $P = 0.085$ ) (Table 3). Patients receiving combination therapy displayed the lowest SHR in M1a, M1b, and M1c groups (M1a: SHR, 0.27; 95% CI, 0.23–0.33;  $P < 0.001$ ; M1b: SHR, 0.20; 95% CI, 0.17–0.23,  $P < 0.001$ ; M1c: SHR, 0.27; 95% CI, 0.20–0.36;  $P < 0.001$ ) (Table 3).

#### **Discussion**

In 2015, using a database including 94,708 patients diagnosed as lung cancer from 1999 to 2010, the International Association for the Study of Lung Cancer (IASLC) recommended a new TNM classification (23). Totally, 1,059 NSCLC patients were utilized to evaluate prognostic value of distant metastasis and develop a new M classification including M1a, M1b, and M1c (24). Patients with single extra-thoracic metastatic lesion and multiple extra-thoracic metastatic lesions were classified as M1b and M1c, respectively. Nevertheless, this classification was constructed by a univariable analysis and lacked of external validation. Therefore, we conducted a retrospective analysis using SEER database with methods of multivariable adjusted analysis and subgroup analyses. The aim of the current study was to validate the prognostic value of the proposed M classification, evaluate the prognostic effects of local consolidative therapy for stage IV NSCLC patients, and divide these patients into different subcategories to stratify the prognoses.

The current study pay attention to the association between the organs involvement of metastatic disease and the CSM rates in stage IV NSCLC patients. It was found that liver and brain involvement were independently related



**Figure 4** Kaplan-Meier curves of cancer-specific mortality stratified by treatment modality in M1a, M1b, and M1c patients in whole set. Patients receiving no treatment were used as the reference category and data are presented as subdistribution hazard ratio (SHR) (95% CI).

to high CSM rates. In addition, five subcategories were further subdivided and were found to have significantly different cumulative incidence rates of CSM across five groups. Our study indicated that selected patients would obtain benefit from local consolidative therapy and further M1 stage division may help to establish therapies.

Only a small proportion of patients with oligometastatic NSCLC have long-term disease-free intervals. Local treatment, including surgery and radiation, improved the overall survival of these patients in several retrospective studies (25-27). Furthermore, several prospective phase II clinical trials also suggested improved progression-free survival with local consolidative therapy including surgery and stereotactic body radiation therapy (SBRT) for patients with oligometastatic NSCLC (28-30). Recently, a meta-analysis including 943 patients reported that 95% of patients with oligometastatic cancer who received surgery and SBRT had local control at one year (31). The above findings are consistent with the results in the current study. In this article, we also demonstrate that chemotherapy plus surgery can improve the survival of stage IV patients, which strengthens the prognostic impact of local consolidative therapy.

There are several possible mechanisms which may explain the benefit of chemotherapy on the subject of CSM rates. First, chemotherapy may reduce the burden of malignant cells which are difficult to be eliminated by maintenance therapy and may become a source of metastatic spread. Chemotherapy would lessen the burden of malignant cells in that situation. Second, certain chemotherapies have been reported to enhance antitumor immune responses and may improve prognosis of patients (32,33). Third, the growth of distant micro-metastatic disease was promoted by residual tumor after initial systemic therapy through proangiogenic and immunosuppressive effects. In that situation, chemotherapy would slow the growth rate of distant micro-metastasis by reducing the burden of residual tumor. Remarkably, the above mechanisms are not exclusive, and the benefits of chemotherapy may result from more than one of these mechanisms.

Platinum-based chemotherapy used to be first-line therapy for advanced NSCLC lacking targetable mutations. However, immunotherapy has changed the current systemic therapy landscape. For patients with tumor programmed-cell death ligand 1 (PD-L1) expression of 50% or higher, pembrolizumab or



**Table 3** Association of cancer-specific mortality with treatment modality

Variables	Model 1		Model 2		Model 3	
	SHR (95% CI)	P value	SHR (95% CI)	P value	SHR (95% CI)	P value
Part I: univariable analysis						
M1a						
None	Reference					
Surgery only	0.263 (0.219–0.316)	<0.001	Reference			
Chemo only	0.410 (0.388–0.434)	<0.001	1.559 (1.298–1.874)	<0.001	Reference	
Chemo + surgery	0.222 (0.184–0.268)	<0.001	0.845(0.655–1.092)	0.198	0.542 (0.449–0.654)	<0.001
M1b						
None	Reference					
Surgery only	0.340 (0.289–0.399)	<0.001	Reference			
Chemo only	0.362 (0.348–0.376)	<0.001	1.066 (0.908–1.252)	0.434	Reference	
Chemo + surgery	0.166 (0.141–0.195)	<0.001	0.489 (0.391–0.610)	<0.001	0.458 (0.391–0.537)	<0.001
M1c						
None	Reference					
Surgery only	0.451 (0.319–0.640)	<0.001	Reference			
Chemo only	0.321 (0.306–0.338)	<0.001	0.712 (0.502–1.008)	0.055	Reference	
Chemo + surgery	0.234 (0.176–0.311)	<0.001	0.518 (0.331–0.811)	0.004	0.728 (0.548–0.968)	0.029
Part II: multivariable analysis						
M1a						
None	Reference					
Surgery only	0.347 (0.287–0.418)	<0.001	Reference			
Chemo only	0.409 (0.385–0.435)	<0.001	1.180 (0.977–1.425)	0.085	Reference	
Chemo + surgery	0.274 (0.226–0.332)	<0.001	0.789 (0.610–1.021)	0.072	0.669 (0.553–0.809)	<0.001
M1b						
None	Reference					
Surgery only	0.426 (0.361–0.501)	<0.001	Reference			
Chemo only	0.372 (0.357–0.387)	<0.001	0.874 (0.742–1.029)	0.106	Reference	
Chemo + surgery	0.195 (0.166–0.229)	<0.001	0.458 (0.366–0.573)	<0.001	0.524 (0.447–0.616)	<0.001
M1c						
None	Reference					
Surgery only	0.565 (0.397–0.703)	0.001	Reference			
Chemo only	0.338 (0.321–0.356)	<0.001	0.599 (0.421–0.851)	0.004	Reference	
Chemo + surgery	0.271 (0.203–0.361)	<0.001	0.480 (0.306–0.752)	0.001	0.801 (0.602–1.067)	0.130

Chemo, chemotherapy; SHR, subdistribution hazard ratio; CI, confidence interval. In both the univariable and multivariable analyses, a different treatment modality was selected as the reference category to perform the pairwise comparison (“no treatment” for Model 1, “surgery only” for Model 2, and “chemo only” for Model 3). The risk model was adjusted for age, sex, race/ethnicity, marital status, histological type, histologic grade, AJCC T & N category and treatment modality.

atezolizumab monotherapy improved OS versus doublet chemotherapy (34). In another trial, pembrolizumab plus chemotherapy significantly improved the survival of patients with metastatic nonsquamous NSCLC without EGFR or ALK mutations (35) and patients with previously untreated metastatic squamous NSCLC (36). A survival benefit of atezolizumab plus chemotherapy and bevacizumab was also observed in patients with PD-L1-unselected, advanced, nonsquamous NSCLC (37).

Similar to prior studies (38-40), this study discovered bone, brain, and liver involvement were independently related to an unfavorable prognosis for stage IV NSCLC patients. According to SHR value, the absence or presence of liver involvement was identified as a more important prognostic factor for CSM rates compared with bone and brain involvement. Therefore, we supplemented the current M1 staging and grouped patients with liver involvement metastases into new categories owing to their relatively unfavorable prognoses.

It is of clinical importance to distinguish M1b from M1c disease with the reasons that (I) M1c disease tends to have higher CSM than M1b disease and (II) some patients with M1b NSCLC can benefit from local consolidative therapy. A favorable outcome was observed to be associated with local consolidative therapy in the patients with oligometastatic NSCLC (41-43). Nevertheless, the value of surgery for M1c patients was not confirmed in the current study, which may result from the high heterogeneity of organs with metastases. Given that the prior studies concerning this issue only retrospectively contained a small number of patients (25,44,45), a prospective clinical trial is necessary to be conducted.

Our study has limitations. Data on smoking status, recurrence-free survival, driver gene mutations, the type and cycle number of chemotherapy, targeted therapy, immunotherapy, and performance score are not reported in the SEER database. In addition, our study is a retrospective study, and the nature of a retrospective analysis may lead to limited data and some selection biases; completely accounting for these limitations is impossible outside of a prospective randomized clinical trial. Future prospective and multi-institutional studies are needed to validate our conclusions. Although the SEER database captures most cancer diagnoses, it is not a population-based database, and generalizability may be limited.

In future studies, precisely defining the stage of stage IV NSCLC, its subclassification as metastatic or synchronous, and its differentiation in relation to recurrence and

progression will be important to obtain comparable results based on innovative biomarkers intended to facilitate unbiased treatment allocation. In particular, this process will be important in the evolving field of immunotherapy, which is a substantial pillar in the treatment of stage IV NSCLC.

Disease subdivision within the M1 category and knowledge of liver involvement may help to inform the prognosis of patients with NSCLC and guide treatment modality.

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