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Lung Cancer

M1b Disease in the 8th Edition of TNM Staging of Lung Cancer: Pattern of Single Extrathoracic Metastasis and Clinical Outcome

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Abstract

Background. The 8th edition of TNM staging of non-small cell lung cancer (NSCLC) has revised M classification and defined M1b disease with single extrathoracic metastasis, which is distinguished from M1c with multiple extrathoracic metastases. We investigated the prevalence, characteristics, and overall survival (OS) of M1b disease in patients with stage IV NSCLC.

Methods. The study reviewed the medical records and imaging studies of 567 patients with stage IV NSCLC to determine M stage using the 8th edition of TNM staging. Clinical characteristics and OS were compared according to M stages.

Results. Among 567 patients, 57 patients (10%) had M1b disease, whereas 119 patients (21%) had M1a disease and 391 patients (69%) had M1c disease. Squamous histology was more common in M1b (16%) than in M1a (6%) and M1c (6%; $p = .03$). The median OS of patients with M1b disease was 14.8 months, compared with 22.6 months for patients with M1a and 13.4 months for those with M1c disease ($p < .0001$). Significant OS differences of M1b compared with single-organ M1c and multiorgan M1c groups were noted (single-organ M1c vs. M1b: hazard ratio [HR], 1.49; $p = .02$; multiorgan M1c vs. M1b: HR, 1.57; $p = .01$) in multivariable analyses adjusting for smoking and systemic therapy types. Among patients with M1b disease, the brain was the most common site of single metastasis (28/57; 49%), followed by bone (16/57; 28%). Single brain metastasis was more frequently treated with local treatment ($p < .0001$).

Conclusion. M1b disease was noted in 10% of patients with stage IV NSCLC. Squamous histology was more common in M1b group than others. The brain was the most common site of single metastasis and was often treated locally. ***The Oncologist*** 2019;24:e749–e754

Implications for Practice: The newly defined group of M stage consists of a unique subset among patients with stage IV non-small cell lung cancer that can be studied further to optimize treatment approaches.

Introduction

Staging of lung cancer is an essential part of patient management and treatment decisions. Given the advancement of diagnostic tools for detecting metastasis and emerging new possibilities of definite locoregional treatment for low tumor burden, the new 8th edition TNM staging of lung cancer was introduced by International Association for the Study of Lung Cancer in 2017 [1, 2] and has been implemented by the American Joint Committee on Cancer in January 2018 in the U.S. [3]. Of note, the 8th edition updated the M staging, defining M1b disease with single extrathoracic metastasis, which is distinguished from M1c with multiple extrathoracic metastases in one or more organs. This new distinct category of M1b disease consists of patients with a single extrathoracic metastasis and thus consists of a strictly defined "oligometastatic disease." Although oligometastatic non-small cell lung cancer (NSCLC) has been studied previously in the context of locoregional therapy and improved clinical outcome [4–8], nonuniform definitions of oligometastatic disease have been a major limitation. The revised classification of M stage in the new 8th edition of NSCLC staging with a specifically defined M1b group provides a unique opportunity to evaluate the prevalence and characteristics of patients with a single extrathoracic metastasis, which can help further understand oligometastatic NSCLC. There have been only a limited

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number of studies addressing the clinical features and prognosis of new M1b category, and the data in the U.S. population are particularly limited [9–11]. Additionally, it is of great interest to determine if M1b disease with single metastasis has better prognosis compared with M1c disease with more than one metastatic lesion limited to a single organ, which has not been systematically investigated.

The purpose of the present study is to determine the prevalence of M1b disease among patients with stage IV NSCLC and investigate the clinical characteristics and patterns of single extrathoracic metastasis and their relationships with overall survival.

Material and Methods

Study Population and Evaluation of M Staging

The study population included a total of 567 patients with stage IV NSCLC, diagnosed between January 2009 to December 2012 at our institution, who had pretreatment staging imaging studies at diagnosis that were available for review. Patients who were diagnosed with stage I, II, or III disease and progressed to metastatic disease or relapsed were not included. The imaging studies and medical records were retrospectively reviewed with institutional review board approval, and all patients in the study provided written informed consent. Demographics and clinical characteristics, including smoking history, tumor histology, and types of systemic therapy for lung cancer, were obtained by the medial record review.

M stage was determined according to the 8th edition of TNM lung cancer staging, which defines M1a as separate tumor nodules in a contralateral lobe, pleural or pericardial nodule, or effusion; M1b as single extrathoracic metastasis; and M1c as multiple extrathoracic metastases in one or more organs [1], based on the review of initial staging computed tomography (CT) or positron emission tomography (PET)-CT scans. In cases of imaging findings indicative of extrathoracic metastasis, histology results were reviewed to confirm the presence of metastasis. If histology was not available, the lesion was considered to be metastasis if (a) it demonstrated interval size change in keeping with the overall clinical context or (b) it demonstrated 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) uptake on PET-CT and was consistent with metastatic disease, as described previously [12, 13].

In patients with M1b disease, the location of the single metastasis was recorded, and the information of local treatment, such as surgery or radiotherapy, for the single metastasis was obtained from the medical records. Patients with M1c disease were further classified into two subgroups, including those with more than one metastatic lesion limited to a single organ (single-organ M1c) and patients with metastasis in more than one organ (multiorgan M1c)

Statistical Analysis

The prevalence of M1a, M1b, and M1c diseases was obtained. Demographics and clinical characteristics were compared among M1a, M1b, and M1c groups, using the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. Overall survival (OS) was compared according to M stages. In patients with M1b disease, OS was compared according to the organs involved by single metastasis. OS was defined as the time from the date of diagnosis of stage IV NSCLC to the date of death of any cause. Patients who were still alive by the time of analyses were censored at the last known date of follow-up. The log-rank test was used to assess differences in the OS distributions between groups. Cox proportional hazards models were used to estimate hazard ratios (HRs), and multivariable analyses were performed using a stepwise regression. All p values are two-sided, and tests were conducted at the .05 level.

Results

Patient Characteristics

The patient characteristics are summarized in Table 1. Among the total of 567 patients, 57 patients (10%) had M1b disease, whereas 119 patients (21%) had M1a disease, and 391 patients (69%) had M1c disease. Among the 391 patients with M1c disease, 202 patients (51.7%) had single-organ M1c disease, and 189 patients (48.3%) had multiorgan M1c disease. Squamous histology was noted in M1b (9/57; 16%) and was more common in M1b compared with M1a (7/119; 6%) and M1c (22/391; 6%) groups (p = .03). Other demographic data, including age, sex, race, and smoking history, as well as types of systemic therapy (no systemic therapy, chemotherapy, or tyrosine kinase inhibitors [TKIs], including epidermal growth factor receptor inhibitors and anaplastic lymphoma kinase inhibitors) and the staging methods on imaging, had no statistically significant differences among different M stage groups.

Overall Survival Among M Stages

Patients with M1b disease had a median OS of 14.8 months (95% confidence interval [CI], 13.0–27.0 months), compared with 22.6 months (95% CI, 20.0–33.3 months) in patients with M1a disease and 13.4 months (95% CI, 11.8–15.4 months) in those with M1c disease (p < .0001; Fig 1). In multivariable analyses using Cox models, decreased hazards for death are noted in the M1b group (HR, 0.62; p = .005) and the M1a group (HR, 0.52; p < .001) compared with the M1c group, after adjusting for age at diagnosis (HR, 1.01; p = .02), smoking status (never smoker vs. former or current smoker; HR, 0.79; p = .03), and the types of systemic therapy (chemotherapy vs. no therapy, HR, 0.48; p < .001; TKI vs. no therapy, HR, 0.38; p < .001). Other variables, including sex, race, and histology, had no significant impact on OS.

Further comparison of OS among M1b, single-organ M1c, and multiorgan M1c demonstrated that patients with M1b disease had longer OS than those with single-organ M1c or multiorgan M1c (median OS of M1b: 14.8 months; 95% CI, 13.0–27.0 months; median OS of single-organ M1c, 14.4 months; 95% CI, 12.2–16.5; multiorgan M1c, 12.4 months, 10.2–16.5 months, respectively, log-rank p = .03; Fig. 2). In the multivariable Cox models, significant OS differences of the M1b group compared with the single-organ M1c and multiorgan M1c groups were noted (single-organ M1c vs. M1b: HR, 1.49; p = .02; multiorgan M1c vs. M1b: HR, 1.57; p = .01) after adjusting for smoking status (never smoking vs. former

Table 1. Demographic data

Demographic characteristics	M1a (*n* = 119)	M1b (*n* = 57)	M1c (*n* = 391)
Age, mean, years	64.5	63.5	61.6
Sex, *n*			
Male	49	26	161
Female	70	31	230
Smoking history, *n*			
Never smoker	30	8	95
Former smoker	77	39	237
Current smoker	12	10	59
Histopathology, *n*			
Adenocarcinoma	100	39	303
Squamous cell carcinoma	7	9	22
NSCLC NOS	12	9	66
Staging method on imaging, *n*			
PET-CT	104	48	306
CT and bone scintigraphy	4	0	18
CT alone	11	9	67
Types of first-line systemic therapy, *n*			
None	12	4	43
Chemotherapy	82	48	281
EGFR inhibitors	25	5	63
ALK inhibitors	0	0	4

Abbreviations: ALK, anaplastic lymphoma kinase; CT, computed tomography; EGFR, epidermal growth factor receptor; PET, positron emission tomography; NSCLC NOS, non-small cell carcinoma, not otherwise specified.

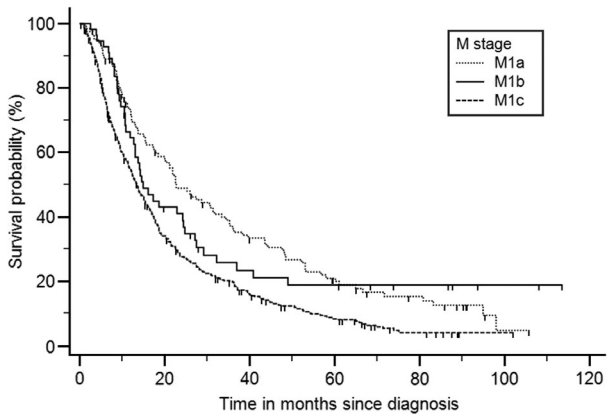

Figure 1. Overall survival among M1 s, M1b, and M1c groups.

or current smoker, HR, 0.77; p = .05) and therapy (chemotherapy vs. no therapy, HR, 0.25; p < .001; TKI vs. no therapy, HR, 0.19; p < .001). Other variables had no significant impact on OS.

Characteristics of M1b Disease

Among the 57 patients with M1b disease, metastatic lesions were confirmed by histology in 35 patients, based on the interval changes on follow-up scans in 12 patients and by FDG

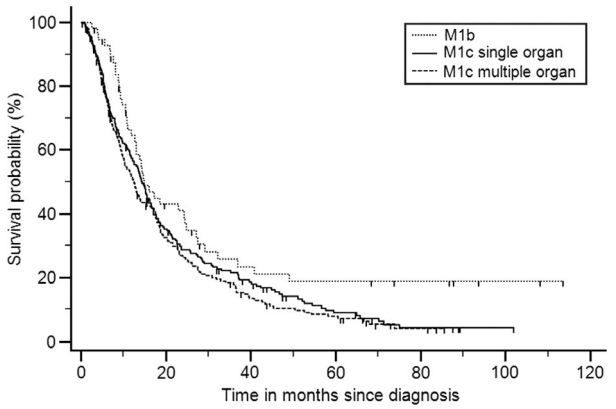

Figure 2. Overall survival among M1b, single-organ M1c, and multiorgan M1c groups.

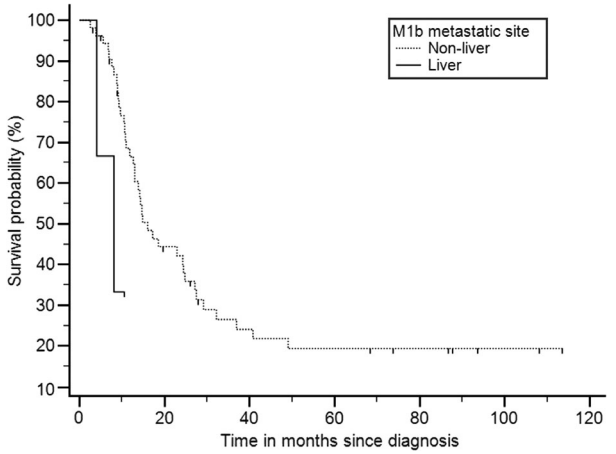

Figure 3. Overall survival of patients with M1b disease with single liver metastasis and others.

avidity on PET-CT in 10 patients. The brain was the most common site of single metastasis (n = 28; 49%), followed by bone (n = 16; 28%), adrenal gland (n = 7; 12%), liver (n = 3; 5%), muscle (n = 2; 4%), and distant lymph node (n = 1; 2%). Single site of metastasis was locally treated in 32 patients (56.1%). Twenty patients had surgery, nine patients had radiation therapy, and three patients had a combination of surgery and radiation therapy as a treatment for metastasis. Among 12 patients who had radiation therapy for single metastasis (9 treated with radiation therapy alone and 3 treated with surgery and radiation therapy), 9 patients had stereotactic radiosurgery and/or stereotactic body radiotherapy, 2 had whole brain radiation therapy, and 1 patient had palliative radiation therapy. Brain metastasis was more frequently treated with local treatment than metastasis in other organs (26/28, 93% vs. 6/29, 21%; p < .0001). Among 32 patients with M1b disease who had local therapy for metastasis, 7 patients (7/32, 22%) also had local therapy for their primary lung cancer (surgery in 4, radiation therapy in 3 patients).

When OS was compared among patients with M1b disease according to the site of single metastasis, patients with liver metastasis had shorter OS than others (median OS: 8.1 vs. 16.0 months, log-rank p = .046; Fig. 3). However, in multivariable Cox models, the liver metastasis did not remain an independent indicator of shorter OS after

adjusting for age at diagnosis (liver metastasis: HR, 2.54; p = .24, age at diagnosis: HR, 1.04; p = .032).

Discussion

The present study demonstrated that M1b disease consists of 10% of stage IV NSCLC and more commonly has squamous cell histology. Overall survival of patients with M1b was significantly longer than that of those with single-organ M1c or multiorgan M1c. The brain was the most common site of single metastasis in M1b disease and more frequently received local treatment. The study characterized the clinical and survival characteristics of this unique category of M stage that is newly defined in the 8th edition of TNM lung cancer staging and represents a subset of patients with NSCLC with strictly defined oligometastatic disease.

In the present study, M1b disease consisted of 10% of the stage IV NSCLC cohort. A few studies have reported the prevalence of M1b disease in stage IV NSCLC using the 8th edition, ranging from 9.7% to 17% [9–11]. The observation in the present study falls into this range and confirms that M1b disease is relatively uncommon among stage IV NSCLC. Prior to the 8th edition of lung cancer staging, the incidence of oligometastasis was reported with a wider range, from 14.8% to 26% [6, 10, 14], likely because of nonuniform definitions of oligometastasis. Most of the previous studies defined oligometastatic disease as a maximum of five extrathoracic metastatic lesions [6, 8, 15], resulting in creating a heterogeneous subgroup of patients. The new M1b category in the 8th edition, defined as a single extrathoracic lesion, clarifies the definition of oligometastatic disease and ensures uniformity of the subset of patients that can be studied for optimal management choices, including locoregional therapy for a single metastatic site.

Among patients' demographic data, squamous cell histology was more common in patients with M1b disease than in those with M1a or M1c disease. Similar observation was also noted in the prior small cohort study of 172 patients with stage IV disease, in which 30 patients (17%) had M1b disease and 29% had squamous cell carcinoma [11]. Although the exact biological mechanisms remain to be clarified, the observations are consistent with the prior knowledge that squamous cell carcinoma of the lung tends to be locally aggressive and less frequently develop metastasis to distant organs compared with adenocarcinoma [16, 17].

The OS of patients with M1b disease was longer than that of patients with M1a disease but shorter than that of patients with M1c disease (median OS: 22.7 months in M1a, 14.8 months in M1b, and 13.4 months in M1c), which supports the modified subdivision of M stage in the 8th staging system. The median OS of each M stage category in the present study was similar to the observations in the prior study by Shin et al., which reported median OS of 22.5 (95% CI, 19.7–29.1) months for M1a, 17.8 (95% CI, 13.8–20.8) months for M1b, and 13.6 (95% CI, 12.5–15.1) months for M1c diseases [10]. In contrast, a study by Eberhardt et al. in 2015 reported a similar OS in patients with M1a and M1b disease, with a median OS of 11.5 (95% CI, 10–13.8) months and 11.4 (95% CI, 9.6–13.7) months, respectively, although they were longer than the median OS of patients with M1c disease (6.3 months, 95% CI, 4.8–7) [2], which provided a basis to classify both M1a and M1b groups as stage IVA in the 8th edition with separate M categories for future data collection and analysis. The similar OS of M1a and M1b in the study by Eberhardt et al. could be explained by the stage migration effect caused by the increasing availability of advanced diagnostic tools over time, including PET-CT and brain MRI. The method and criteria for the confirmation of metastasis may also have affected the results by potential misclassification. Although further data from a larger prospective cohort are needed to determine the prognostic differences of M1a and M1b diseases, the accumulating evidence based on the data from the present study and other previous studies indicates that the M1b category consists of a distinct group of patients with poorer prognosis than patients with M1a disease within stage IVA.

The present study further classified M1c disease into two categories, single-organ M1c (more than one metastatic lesion in a single organ) and multiorgan M1c (metastases in multiple organs), and demonstrated that patients with M1b disease had longer OS compared with single-organ M1c or multiorgan M1c, which remained significant after adjusting for other significant clinical variables, including the types of systemic therapy, in the multivariate model. Longer OS of patients with M1b disease compared with that of patients with single-organ M1c disease further emphasizes the unique prognostic characteristics of M1b disease, in that single metastatic focus demonstrates better prognosis compared with more than one metastatic focus even if the metastatic sites are confined to a single organ. This result also emphasizes the importance of precise classification of M1b disease in the 8th staging by clinical providers and diagnostic physicians, so that the cases of single extrathoracic metastasis (M1b) can be accurately differentiated from the cases of more than one metastatic lesion that are limited to a single organ (single-organ M1c).

According to the location of the single metastasis in M1b disease, the brain was the most common site (49%), followed by bone (28%). The results are consistent with the prior studies that reported bone and brain as the top two sites of metastasis in M1b disease [9, 10]. Local treatment was provided for 56% of the patients, and the patients with single brain metastasis received local treatment more frequently than those with single metastasis in other organs. Local therapy for limited metastatic disease can be beneficial in that it can decrease overall tumor burden. In lung cancer, several retrospective and a few prospective studies have suggested a potential benefit of using locoregional therapy for metastasis [7, 18–20]. Furthermore, prior studies focusing on a single extrathoracic metastasis, especially brain metastasis, have demonstrated better prognostic outcome with local therapy using surgery or stereotactic radiation therapy [4, 5, 15, 18, 21–24]. Given these data in the local therapy for oligometastatic disease, the newly defined M1b category with frequent involvement of brain consists of a unique subset of patients who can be considered as potential candidates for further studies to optimize locoregional treatment approaches.

In the present study, patients with single liver metastasis appeared to have a shorter OS than others with the M1b disease; however, this observation did not remain significant after adjusting for other factors in the multivariable

models. Likewise, the data from a prior study by Eberhardt et al. suggested an association between adrenal metastasis and poorer prognosis among M1b disease; however, the observation was not consistent depending on the data source and not validated [2]. Further studies with a larger number of patients and a consistent data source are needed to validate the findings of association between the site of single metastasis in M1b and survival.

The limitations of the present study include a retrospective design with patients treated at a single institution. Not all single metastasis in M1b disease was confirmed histologically; however, we used the predefined criteria to determine the presence of metastasis, according to methods in prior publications [12, 25]. The relatively low prevalence of M1b disease by nature resulted in a relatively small number of patients for subcohort analyses focusing on the prognostic implications of the site of metastasis among M1b disease. The results need to be validated in a larger cohort with prospective evaluation and follow-up. The presence of targetable oncogenic driver mutations may affect the clinical outcome of the patients; however, the systematic collection of tumor genotype data was beyond the scope of this retrospective study focusing on M1b disease in the 8th TNM staging system. Additionally, the patients in the present study were diagnosed from 2009 to 2012, before immune-checkpoint inhibitor therapy had become widely available for treatment of advanced NSCLC. The impact of immune-checkpoint inhibitor therapy in the survival of patients with M1b disease remains to be investigated. It should also be noted that the patients with previously treated stage I–III NSCLC experiencing recurrent disease with a single-site metastasis are not included in the study, which could be another important focus of the future investigations.

Conclusion

M1b disease was noted in 10% of patients with stage IV NSCLC and more commonly had squamous histology. The brain was the most common site of single metastasis and more frequently received locoregional treatment. OS of M1b disease was distinct from M1a, single-organ M1c, and multiorgan M1c disease, indicating that this newly defined group of M stage consists of a unique subset among patients with stage IV NSCLC that can be studied further to optimize treatment approaches.

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Disclosures

Suzanne E. Dahlberg: AstraZeneca (C/A); **Bruce E. Johnson:** Toshiba, Novartis (RF); **Mizuki Nishino:** Bristol-Myers Squibb, Toshiba Medical Systems, WorldCare Clinical, Daiichi Sankyo (C/A), Merck Investigator Studies Program, Toshiba Medical Systems, AstraZeneca (RF), Bayer, Roche (H). The other authors indicated no financial relationships.

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