Prognostic significance of sites of extrathoracic metastasis in patients with non-small cell lung cancer

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Contributions: (I) Conception and design: JE Bates, MT Milano; (II) Administrative support: MT Milano; (III) Provision of study materials or patients: JE Bates; (IV) Collection and assembly of data: JE Bates; (V) Data analysis and interpretation: JE Bates, MT Milano; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Metastatic non-small cell lung cancer (NSCLC) continues to have a poor prognosis despite recent advances in both targeted radiotherapy methodologies such as stereotactic body radiotherapy (SBRT) and immunotherapies. The impact of location of metastatic disease in patients with NSCLC has not been investigated; we aimed to investigate this using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: We included 39,910 patients from the SEER database treated for M1b NSCLC from 2010–2013. We identified patients with metastatic disease in the brain, lung, liver, and bone. We used Kaplan-Meier analyses and Cox proportional hazards models to assess the impact of varying sites of metastatic disease on overall survival (OS).

Results: Patients with disease coded as in the brain without other disease in the lung, liver, or bone had improved OS relative to all other comers with M1b disease (HR =0.84, 95% CI, 0.84–0.90, P<0.001). Likewise, patients with disease coded as in the bone without other disease in the lung, liver, or brain had improved OS relative to all other comers with M1b disease (HR =0.89, 95% CI, 0.86–0.92, P<0.001).

Conclusions: This hypothesis-generating analysis suggests that patients with limited metastatic NSCLC to the bone or brain may particularly benefit from aggressive upfront therapies.

Keywords: Non-small cell lung cancer (NSCLC); Surveillance, Epidemiology, and End Results (SEER); oligometastases; extrathoracic metastasis; survival

Introduction

Metastatic disease across tumor histologies remains largely incurable despite significant recent advances in oncologic therapies (1). Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths and represents a prime example of a malignancy for which metastatic disease has markedly worse outcomes as compared to non-metastatic disease (2). The concept of oligometastatic disease was introduced just over two decades ago and

has been expanded to a multitude of cancer histologies including NSCLC (3,4). Notably, oligometastatic NSCLC may represent a disease state with limited disease burden amenable to localized therapy (i.e., resection, radiation, ablation) and improved survival outcomes (3-8) similar to that of locoregionally advanced NSCLC (9).

A recent single-institution retrospective review showed that patients with both synchronous and metachronous oligometastases from NSCLC had excellent overall survival

(OS) (median OS =21.8 months) when the oligometastatic disease was treated radically either with surgery or stereotactic radiation (5). Improved OS was also seen in patients with NSCLC and synchronous limited brain metastases who had both their thoracic and intracranial disease treated (6). Lengthy OS has been shown in patients with oligometastatic lung cancer to a variety of organ sites (7).

However, to date, little comparative information exists to elucidate varying prognosis among patients with different sites of metastatic NSCLC. We aimed to use a large population-based database to investigate if, regardless of treatment paradigm, patients with specific sites of metastatic NSCLC had improved prognosis relative to other patients with M1b NSCLC. We hypothesized that metastatic disease to different organ sites would result in different survival outcomes, and surmised that tails on the survival curves would likely reflect survival of patients with unusually favorable histopathologic variants and/or oligometastatic disease.

Methods

The Surveillance, Epidemiology, and End Results-18 (SEER-18) database was queried for patients who were registered from 2010-2013 and diagnosed with metastatic NSCLC (10). SEER-18 incorporated TNM stage by American Joint Committee on Cancer (AJCC) 7th edition staging criteria in 2010; we chose not to include patients staged by earlier AJCC criteria given the significant changes in NSCLC staging, particularly for metastatic disease, introduced in 7th edition of the AJCC Staging Manual. NSCLC (and subcategory histologies) were defined via the following ICD-O-3 codes: adenocarcinoma (8140/3, 8255/3, 8260/3, 8310/3), bronchoalveolar carcinoma (8250/3–8254/3), adenosquamous carcinoma (8560/3), large cell carcinoma (8012/3), squamous cell carcinoma (8052/3, 8070-76/3, 8078/3, 8082-4/3), and NSCLC, not otherwise specified (NOS) (8046/3). All patients with M1b disease were included in this analysis; patients with unknown survival were excluded. We included patients with M1b disease as this represents patients with extrathoracic metastasis.

The extent and location of metastatic disease was determined through several fields in the Collaborative Stage Data Set used by the SEER-18 database. The "CS Mets at DX" code provides detailed information regarding location of metastatic disease (11). Specifically, code 40 indicates patients who have distant metastatic disease including those with metastasis to abdominal organs or other distant metastasis, and excluding those with distant lymph node disease, pericardial or pleural effusion, pleural disease, extension to the skeletal muscle, sternum, or chest skin, and intrapulmonary metastasis. It does include patients with carcinomatosis, distant metastasis not otherwise specific, and patients with a separate lesion in the chest wall or diaphragm. Additional codes for CS Mets at Dx-Brain, -Liver, and -Bone were used to further elucidate the location of distant metastatic disease. There is an additional code for CS Mets at Dx-Lung; however, given that we were assessing patients with primary lung malignancies and the inclusion of intrapulmonary metastasis within the AJCC 7th edition T and M staging for lung cancer, we chose to use this field only to verify that patients did not have intrapulmonary metastatic disease, thus all patients in this analysis had a value of 0 for this field. Any patient who did not have complete information for these four fields was excluded from further analysis. We separately grouped patients with brain metastases and without lung, liver, or bone metastases (brain-group); likewise we separately grouped those with liver and without lung, bone, or brain metastases (liver-group), and separately grouped those with bone and without lung, liver, or brain metastases (bone-group). Different combinations (i.e., brain-bone, brain-liver, liver-bone, and brain-liver-bone groups) were also categorized. Survival was compared to all other patients with M1b disease regardless of T or N stage.

Counts and percentages were used to describe categorical variables. Medians and interquartile ranges (IQRs) were used to describe continuous variables. Survival statistics were determined using Kaplan-Meier survival analyses. Both univariate and multivariate Cox proportional hazards models were used to determine the implications of various demographic and tumor characteristics on survival. All statistical analysis was performed using Stata 13 (College Station, TX, USA).

Results

Patient characteristics and impact on prognosis

A total of 39,910 patients from the SEER-18 database met inclusion criteria. Details regarding patient demographics are shown in *Table 1*. Of note, the cohort was male (56.7%), Caucasian descent (79.0%), and had adenocarcinoma

Table 1 Demographic and tumor characteristics and their prognostic significant in patients with M1b non-small cell lung cancer (n=39,910)

Variable	n (%)	Median OS (months)	12 month OS (%)	24 month OS (%)	Univariate analysis			Multivariate analysis		
					HR	95% CI	P value	HR	95% CI	P value
Gender										
Male	22,621 (56.7)	5	23.3	9.8	1.21	1.19–1.24	<0.001	1.19	1.16–1.22	<0.001
Female	17,289 (42.3)	6	30.3	15.1	–	–	–	–	–	–
Race										
White	31,544 (79.0)	5	25.1	11.3	–	–	–	–	–	–
Black	5,109 (12.8)	5	25.0	10.7	1.01	0.98–1.05	0.43	1.00	0.96–1.04	0.97
Other	3,257 (8.2)	8	40.0	22.7	0.71	0.67–0.74	<0.001	0.70	0.67–0.73	<0.001
Histology										
Adenocarcinoma	24,701 (61.9)	6	30.1	14.7	–	–	–	–	–	–
Bronchoalveolar Carcinoma	199 (0.5)	12	45.0	24.5	0.68	0.57–0.81	<0.001	0.71	0.59–0.85	<0.001
Adenosquamous Carcinoma	643 (1.6)	5	23.8	12.0	1.17	1.06–1.29	0.001	1.14	1.03–1.25	0.008
Large Cell Carcinoma	597 (1.5)	4	16.1	6.9	1.42	1.29–1.56	<0.001	1.36	1.23–1.49	<0.001
NSCLC, NOS	5,659 (14.2)	4	19.9	8.2	1.30	1.26–1.35	<0.001	1.29	1.24–1.33	<0.001
Squamous Cell Carcinoma	8,111 (20.3)	5	19.8	6.9	1.33	1.29–1.38	<0.001	1.28	1.24–1.33	<0.001
T Stage										
0	5,541 (13.9)	5	23.5	9.7	1.39	1.33–1.47	<0.001	1.34	1.27–1.41	<0.001
1	4,148 (10.4)	8	36.9	18.7	–	–	–	–	–	–
2	9,696 (24.3)	6	28.3	13.1	1.24	1.19–1.30	<0.001	1.20	1.15–1.26	<0.001
3	9,178 (23.0)	5	24.1	11.3	1.28	1.31–1.44	<0.001	1.30	1.24–1.36	<0.001
4	11,347 (28.4)	5	23.8	10.7	1.40	1.34–1.46	<0.001	1.33	1.27–1.40	<0.001
N Stage (n=37,648)										
0	8,692 (23.1)	7	30.7	15.6	–	–	–	–	–	–
1	3,173 (8.4)	6	27.8	12.7	1.10	1.05–1.16	<0.001	1.07	1.02–1.13	0.005
2	17,712 (47.1)	5	24.4	10.7	1.22	1.18–1.26	<0.001	1.16	1.12–1.20	<0.001
3	8,071 (21.4)	6	26.3	11.7	1.16	1.12–1.20	<0.001	1.10	1.06–1.14	<0.001
Sites of disease										
Brain-group	5,781 (14.5)	6	30.9	14.7	0.87	0.84–0.90	<0.001	0.91	0.87–0.94	<0.001
Bone-group	7,299 (18.3)	6	29.5	13.7	0.89	0.86–0.92	<0.001	0.90	0.87–0.94	<0.001
Liver-group	2,070 (5.2)	6	22.9	8.1	1.00	0.95–1.06	0.98	0.95	0.89–1.01	0.10
Brain + Bone group	1,971 (4.9)	4	24.8	11.7	1.05	0.99–1.11	0.08	1.11	1.05–1.17	<0.001

Table 1 (*continued*)

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Variable	n (%)	Median OS (months)	12 month OS (%)	24 month OS (%)	Univariate analysis			Multivariate analysis		
					HR	95% CI	P value	HR	95% CI	P value
Brain + Liver group	544 (1.4)	3	15.7	7.0	1.41	1.27–1.55	<0.001	1.40	1.26–1.55	<0.001
Bone + Liver group	1,948 (4.9)	4	16.8	6.2	1.27	1.20–1.34	<0.001	1.27	1.19–1.34	<0.001
Brain + Bone + Liver group	762 (1.9)	3	16.6	7.4	1.35	1.25–1.48	<0.001	1.44	1.32–1.58	<0.001
Non-lung, liver, bone, or brain group[a]	3,092 (7.8)	8	32.5	15.3	0.79	0.75–0.83	<0.001	0.78	0.74–0.82	<0.001
M1b disease, NOS	16,443 (41.2)	5	24.6	11.5	–	–	–	–	–	–

a, this group includes patients who were coded as having metastasis to "abdominal organs or other distant (sites)" who did not have disease in the brain, bone, lung, or liver and additionally were not coded as having malignant effusions or distant nodal, pleural, chest wall or sternal metastases
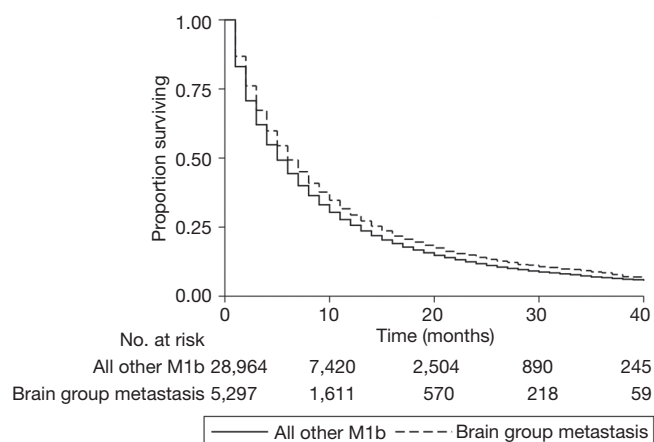

Figure 1 Kaplan-Meier survival curve of patients with M1b non-small cell lung cancer in the brain-group (i.e., without lung, bone or liver metastases) compared to all other M1b patients.

histology (61.9%). There was a spread of patients across various T and N stages (*Table 1*). The median follow-up period was 3 months (IQR 1–9 months). The median OS was 5 months (IQR 2–13 months).

Univariate and multivariate Cox proportional hazards analyses were performed using a variety of patient and tumor characteristics (*Table 1*). Male patients had a significantly worse prognosis than female patients on both univariate (HR =1.21, P<0.001) and multivariate (HR =1.19, P<0.001) analyses. Patients who had an ethnicity other than Caucasian or African-American had improved survival relative to those with Caucasian ethnicity on

both univariate (HR =0.71, P<0.001) and multivariate (HR =0.70, P<0.001) analyses. As described in *Table 1*, patients with bronchoalveolar carcinoma had increased OS relative to those with adenocarcinoma; patients with all other histologies had decreased OS relative to those with adenocarcinoma on both univariate and multivariate analyses. Patients with a T stage other than T1 disease had decreased OS relative to those with T1 disease. Patients with any nodal disease had decreased OS relative to those with N0 disease.

Impact of sites of metastatic disease

The distribution of sites of metastatic disease is shown in *Table 1*. A plurality of patients (41.2%) had M1b disease without documented evidence of distant metastasis to the brain, bone, liver, or lung. Of particular note to this analysis, 7.8% of patients had a CS Mets at DX code of 40 (see Methods for description) but did not have any documented brain, bone, liver, or lung metastases. This suggests that 7.8% of patients with a CS Mets at DX code of 40 have distant metastatic disease elsewhere in the body, and one could thus extrapolate that a similar percentage of patients in each anatomic grouping have an additional metastatic burden beyond the organs specified. Patients in the brain-group had improved survival relative to those with disease elsewhere on both univariate (HR =0.87, P<0.001, *Figure 1*) and multivariate (HR =0.91, P<0.001) analyses. Likewise, patients in the bone-group had improved survival relative to those with disease elsewhere on both univariate (HR =0.89,
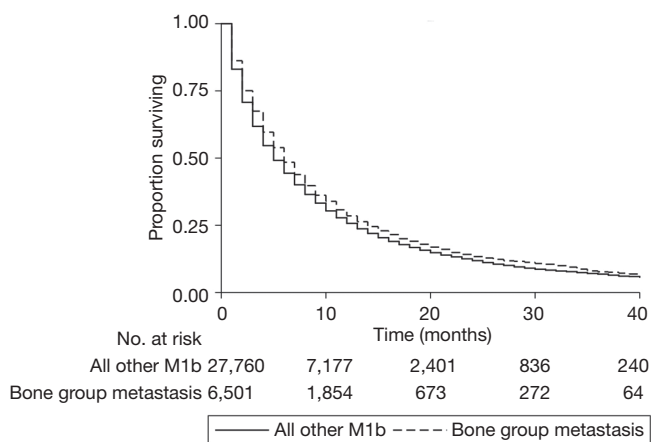
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Figure 2 Kaplan-Meier survival curve of patients with M1b non-small cell lung cancer in the bone-group (i.e., without lung, brain or liver metastases) compared to all other M1b patients.

P<0.001, *Figure 2*) and multivariate (HR =0.90, P<0.001) analyses. Patients who had metastatic disease at organs not specified by the organ-specific codes also had improved OS relative to all others (*Table 1*). No other combination of organ metastases had improved OS relative to all other with M1b disease (*Table 1*).

Conclusions

We present this hypothesis-generating large population-based analysis of the prognostic significance of varying sites of synchronous oligometastatic disease in patients with NSCLC. This represents the largest study that we are able to identify to date that investigates this. We show that patients in the brain- and bone-groups represent populations that have improved OS relative to other patients with M1b disease. While the absolute increase in OS for both groups is only one month (median OS =6 months for brain-group and bone-group patients, median OS =5 months for patients with M1b disease, NOS), this represents a 20% increase in OS. Most significantly, this identifies a subset of patients with metastatic disease who have improved outcomes relative to other patients with metastatic NSCLC. Given the significant recent advances in the treatment of NSCLC using PD-1 inhibitors and the repeated studies showing their successes in treating metastatic NSCLC, especially to the brain, this offers further evidence that these patients represent a subset that may benefit from aggressive upfront therapy (12-16). We

additionally show that patients who have diffusely metastatic disease to multiple organs have decreased OS relative to others with M1b disease, reinforcing the great strides still left to be made in the treatment of metastatic NSCLC. This is consistent with a prior report showing that patients with NSCLC metastatic to a single organ have improved OS relative to those with a more extensive disease burden (17). Further analysis of combining metastatic burden with genetic abnormalities present may further subcategorize patients with metastatic NSCLC (18).

We did not analyze the impact of various treatment modalities in this study given the limited information in the SEER database regarding treatment. Specifically, it would be impossible for us to ascertain using SEER information alone if a patient received radiation or surgery to the primary NSCLC, the site(s) of metastatic disease, or both. Further, we could not investigate the use of chemotherapy, as that is not recorded in the SEER database. The safety and efficacy of aggressive management of limited metastatic disease, especially among patients with metastases to brain and bone has been well-documented. Retrospective review of patients with a solitary synchronous brain metastasis showed that they could undergo cranial metastatectomy along with local treatment of their NSCLC without additional risk of complication or mortality. One-year OS in that cohort was 62% (19). Stereotactic radiosurgery (SRS) has also been shown to be safe and effective in control of intracranial disease when combined with local treatment of primary tumor (20-22). A small five-person prospective study in China of patients with synchronous solitary bone metastasis and primary NSCLC showed that simultaneous bone metastatectomy and lung cancer resection followed by chemotherapy was safe; no post-operative complications were seen. Median progression-free survival in this cohort was 13.2 months (23). Stereotactic body radiotherapy (SBRT) has been shown to be safe and efficacious in patients with oligometastatic lung cancer in a variety of additional anatomic locations (8,24-26). Further, a previous study of the SEER database showed that patients refusing palliative RT for metastatic NSCLC had diminished OS relative to those not refusing RT (27).

Our results also produced several other insights that are in agreement with previous literature. The majority of patients are male and the most frequent histology is adenocarcinoma (28). These results are also in concordance in broader studies of patients with any stage NSCLC in that male patients have decreased OS relative to female

patients and Caucasian and African-American patients have decreased OS relative to those with other ethnicities (29). Of note, previous analysis of the SEER database has shown that among the "Other Ethnicity" category, there are disparities; patients with Asian heritage have improved survival relative to those with Native American heritage (30). We have reaffirmed that T stage remains a prognostic factor even in those with metastatic disease (31). Additionally, we have shown that patients with advanced nodal involvement have worse outcomes than those without nodal involvement, in concordance with previous reports in patients with metastatic NSCLC (18).

This analysis is limited by many factors that consistently limit others that use the SEER database. There is a limited amount of information that one can ascertain from the SEER database and there is likely some level of error in coding in individual patients; however the large number of patients that we have in the study will mitigate that somewhat. Specific to this study, we attempt to isolate patients with metastasis to specific organs. Presumably, most patients in a specific group (bone, brain, liver) had metastases confined to that organ, although patients may have harbored other sites of metastases not specifically recorded by the SEER program (most common site not recorded is likely adrenal). We do show that only 7.8% of patients who were coded as not having brain, bone, or liver metastasis were also coded as having distant metastatic disease in the absence of nodal disease, malignant effusions, or chest wall extension, suggesting that approximately 8% of patients in each grouping of organ-site metastasis had macroscopic disease elsewhere in the body.

Our methodology has been used previous to analyze the patterns of metastatic disease in patients with colorectal cancer (32). This study is also limited by a relatively small median follow-up time of only three months, though this is not surprising as we only assessed patients with M1b disease who have a very poor prognosis at diagnosis. We also could not assess the impact of metachronous metastasis as within the SEER database we can only investigate disease at time of diagnosis. Likewise, we could not analyze time to disease progression or the anatomic spread of disease progression as that information is not in the SEER database. Further, we could not assess the disease burden, either number of metastases or volume of disease, within each organ identified.

In this large population-based hypothesis-generating analysis of patients with M1b NSCLC using the SEER database, we have shown that patients with disease of the brain or bone alone in the absence of malignant effusions or liver, lung, chest wall, or distant nodal metastases have improved survival relative to those patients with metastatic disease elsewhere in the body. Given the incredible recent advances in both local and systemic treatment of metastatic disease, these patients may represent a population who could potentially benefit greatly from aggressive treatment of their upfront disease; further prospective study should investigate the ideal treatment options for these patients.

Acknowledgements

Footnote

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