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ORIGINAL PAPER

Impact of number versus location of metastases on survival in stage IV M1b non-small cell lung cancer

Amanda Jane Williams Gibson[1] · Haocheng Li[1] · Adrijana D'Silva[1] · Roxana A. Tudor[1] · Anifat A. Elegbede[1] · Shannon Mary Otsuka[1] · D. Gwyn Bebb[1,2] · Winson Y. Cheung[1,2]

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Abstract

Background To assess the impact of location versus number of extra-pulmonary metastatic sites (EPMS) on survival in stage IV non-small cell lung cancer (NSCLC).

Methods and materials Retrospective analysis was conducted on patients diagnosed during 1999–2013 with stage IV, M1b (AJCC 7th edition) NSCLC using the large, institutional Glans-Look Database, which contains patient demographic, clinical, pathological, treatment, and outcome information. We assessed the impact of location and number of EPMS and identified correlates of overall survival using the Kaplan–Meier method and Cox regression.

Results We identified a total of 2065 NSCLC patients with EPMS. Median age was 67 (IQR 58–75) years, 52% were men, and 78% were current or former smokers. 60% had one EPMS, and 40% had two or more EPMS. Among those with only one EPMS, most frequent organ involvement included bone (40%), brain (32%), and liver (13%). Median overall survival (mOS) was worst in those with liver metastasis and best in those with adrenal metastasis (2.0 vs. 5.2 months, $p=0.015$). However, outcomes based on site of organ involvement were not significantly different in multivariable analysis. Compared to patients with one EPMS, individuals with two or more EPMS experienced worse outcomes (mOS $\leq$ 2.9 vs. 3.9 months, $p<0.001$), and were associated with worse prognosis in Cox regression analysis (HR 1.5, 95% CI 1.3–1.7, $p<0.001$).

Conclusions Number rather than location of EPMS is a prognostic factor in patients with stage IV M1b NSCLC. This information is relevant for accurate prognostication, stratification of participants in future clinical trials, and timely and appropriate advanced care planning.

Keywords Non-small cell lung cancer · Survival · Distant disease · Extra-pulmonary metastases · Disease burden · Metastatic site · Number of metastases

✉ Winson Y. Cheung
winson.cheung@ahs.ca

Amanda Jane Williams Gibson
ajwgibso@ucalgary.ca

Haocheng Li
haocheng.li@ucalgary.ca

Adrijana D'Silva
asevo@ucalgary.ca

Roxana A. Tudor
roxana.tudor@ucalgary.ca

Anifat A. Elegbede
anifat.elegbede@ahs.ca

Shannon Mary Otsuka
smotsuka@ucalgary.ca

D. Gwyn Bebb
gwyn.bebb@ahs.ca

[1] Department of Oncology, Cumming School of Medicine, University of Calgary, 1331 29th St NW, Calgary, AB T2N 4N2, Canada

[2] Tom Baker Cancer Centre, Alberta Health Services, 1331 29th St NW, Calgary, AB T2N 4N2, Canada

Introduction

Mortality from non-small cell lung cancer (NSCLC) remains high, partly because more than half of newly diagnosed cases present with stage IV [American Joint Committee on Cancer (AJCC), 7th edition, any T, any N, M1a or M1b] disease [1, 2]. Similar to the majority of other cancers, the presence of metastatic disease signifies a terminal condition, which is uniformly associated with a poor prognosis. This is true despite recent advances in systemic therapies, immune modulating treatments, radiation techniques, and surgical interventions [3–6]. The median overall survival among all stage IV NSCLC ranges from 7 to 11 months, with less than 5% of patients surviving beyond 5 years after diagnosis [6, 7]. Compared to patients with M1a disease, those with M1b disease are characterized by distant, extra-pulmonary metastatic involvement. The latter is associated with a median overall survival of 6 months or less [8].

Conducting a real-world, population-based study on the impact of location and number of extra-pulmonary metastatic sites (EPMS) on lung cancer outcomes can be challenging because most registries capture only information on the primary tumor rather than on the metastatic disease [3]. In the few studies that have evaluated the impact of location or number of EPMS, a common limitation has been sample size. In general, the studies did not include an adequate range of patients with different metastatic distributions to permit robust comparisons of location or number of organ involvement. Further, there are inconsistencies in conclusions from prior research where some studies showed that liver or adrenal metastasis is worse, while others demonstrated that bone metastasis is worse [9, 10].

Therefore, the main objective of the current study is to critically evaluate and compare the effect of location versus number of EPMS on survival in a large population-based cohort of NSCLC. Our findings will provide additional insights to existing literature by informing prognostication, future clinical trial design, and advanced care planning in stage IV NSCLC patients.

Methods and materials

Description of patient population

The institutional Glans-Look Database (GLD) captures demographic, clinical, pathological, treatment, and outcome data for all individuals who were identified in the Alberta Cancer Registry (ACR) as having been diagnosed with NSCLC and who were seen at the Tom Baker Cancer Center (TBCC) in Southern Alberta, Canada for at least part of their disease management. The catchment area of TBCC is over 1 million residents. For this study, we included adult patients aged 18 years or older with a new diagnosis of NSCLC between January 1999 and December 2013. This study timeframe was selected in order to allow for reliable ascertainment of follow-up and outcomes; follow-up to death or last contact is complete for 100% of the cohort. Patients must have also presented at diagnosis with Stage IV, M1b extra-pulmonary metastatic disease as per the AJCC 7th edition staging criteria. Patients with pulmonary metastases only, individuals who had incomplete staging or second primary malignancies, and those who were lost to follow-up were excluded from the analysis. Of note, the Glans-Look Database is a privately housed database. Therefore, approval from the Health Research Ethics Board of Alberta (HREBA) was obtained prior to the conduct of this study.

Covariates and outcomes

Additional variables were extracted from the GLD and considered in our analyses, including age at diagnosis, sex, histology, smoking history, year of diagnosis, location of EPMS, number of EPMS, and types of treatments that were received (systemic therapy, radiation therapy, and/or surgical resection). Patients were subsequently assigned into different year groupings (e.g., 1999–2004, 2005–2009, and 2010–2013) based on the calendar year of their NSCLC diagnosis so that we could detect changes over time periods that could be attributed to advances in screening, diagnosis, and/or treatment. The main outcome measure was overall survival, which was defined as the interval from date of stage IV M1b NSCLC diagnosis and date for death from any cause, and censored at last follow-up.

Statistical analysis

Baseline demographics, clinical characteristics, and treatment details were summarized with descriptive statistics. Distributions of these features were compared across different patient subgroups using Chi-square and Wilcoxon tests for categorical and continuous factors, respectively. Survival outcomes were analyzed using the Kaplan–Meier method and compared among groups using the log-rank test. Multivariate Cox regression models were constructed to determine the independent impact of both location and number of EPMS on survival, while adjusting for multiple measured cofounders. A p value of <0.05 was considered a priori as statistically significant. All analyses were conducted using the R statistical package v3.3.0 [11].

Results

In total, we identified 7329 patients with a new diagnosis of NSCLC between January 1999 and December 2013 of whom 3039 (41%) patients were classified as having metastatic disease. In this subset of stage IV cases, 2065 (68%) were determined to be M1b, which is characterized by the presence of one or more EPMS. Among them, 1241 (60%) had one EPMS, and the remaining 824 (40%) had 2 or more EPMS (range 1–5). Figure 1 outlines distribution, by locations of EPMS in our study cohort.

In the subgroup with one EPMS, differences in baseline characteristics are summarized in Table 1. The most common sites of involvement included bone (40%), brain (32%), and liver (13%). Briefly, patients with liver metastasis were more likely to be older (median age 72 [IQR 66–79] years vs. 67 [IQR 59–75] years, $p < 0.001$) and never smokers (31% vs. 21%, $p < 0.001$) when compared to patients with other sites of metastasis. Table 2 compares the baseline characteristics of patients with two or more EPMS. In general, patients with multiple EPMS were younger than those with only a single EPMS (median age 65 [IQR 57–74] years versus 68 [IQR 59–76] years, $p = 0.02$). Diagnostic year, grouped by 5 year cohorts demonstrated different patterns of number and location of EPMS, but this association did not persist in multivariate analysis. Otherwise, there were no major differences in baseline features based on site or number of metastases.

At the time of analysis, 2052 (99%) of patients were deceased and the median overall survival (mOS) for the entire study cohort was 3.0 months. In the subgroup with single EPMS, the mOS for each of brain and liver metastasis was 3.6 and 2.0 months when compared to adrenal and bone metastasis of 5.2 and 4.5 months, respectively ($p < 0.001$) (Fig. 2a). In a multivariate model, older age (HR 0.86, 95% CI 0.75–0.98, $p = 0.022$) and those who received surgical resection of metastatic disease (HR 0.3, 95% CI 0.23–0.4, $p < 0.001$), systemic anti-cancer therapy (HR 0.3, 95% CI 0.26–0.37, $p < 0.001$), and radiation therapy (HR 0.56, 95% CI 0.49–0.64, $p < 0.001$) also experienced better outcomes, whereas men fared worse when compared to women (HR 1.17 95% CI 10.5–1.31, $p = 0.006$). Of note, location of EPMS did not predict survival (HR 1.1–1.2, 95% CI 0.83–1.5, all $p > 0.3$) (Fig. 2b). In the subgroup with multiple EPMS, the mOS of 1, 2, 3, and ≥ 4 EPMS was 3.9, 2.9, 2.2, and 1.7 months, respectively. There was a statistically and clinically significant inverse association between increasing number of EPMS and worse mOS ($p < 0.001$) (Fig. 3a). In a multivariate model, this observation persisted after adjusting for confounders whereby those with 4 EPMS fared the worst when compared to those with only one EPMS (HR 2.6, 95% CI 2.0–3.3, $p < 0.001$) (Fig. 3b). In addition, histology other than adenocarcinoma or squamous cell (HR 0.76, 95% CI 0.64–0.92, $p = 0.004$) and receipt of treatment, such as surgical resection of metastatic disease (received by 3% of cohort, HR 0.28, 95% CI 0.22–0.37, $p < 0.001$), systemic anti-cancer therapy (received by

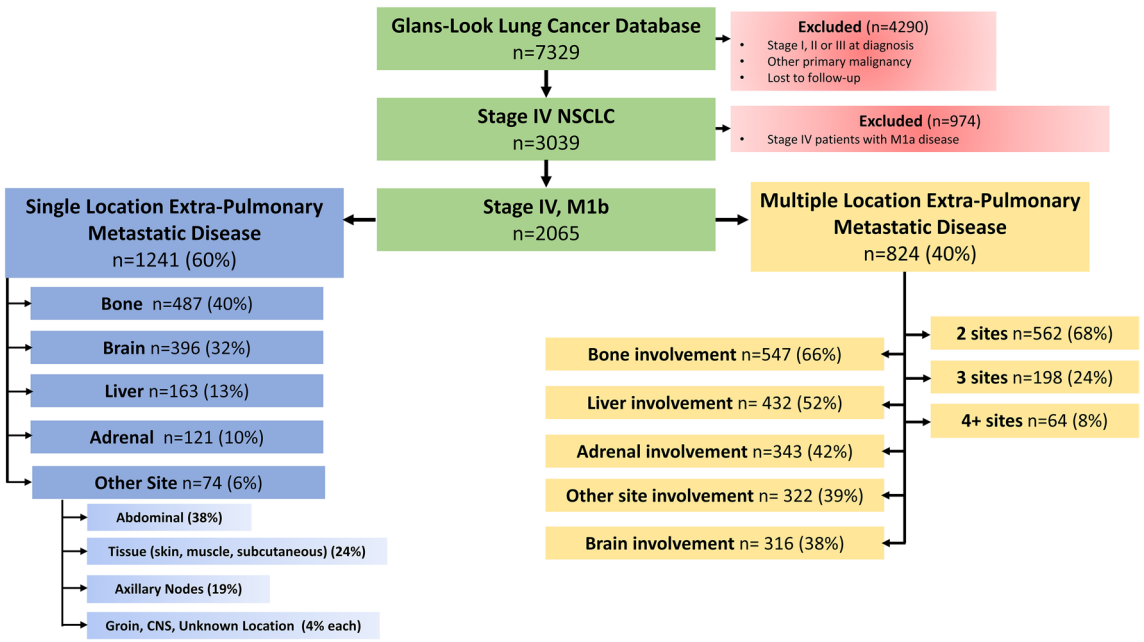

Fig. 1 Location, number, and distribution of extra-pulmonary metastatic sites at diagnosis, in M1b patients, 1999–2013

Table 1 Demographic, tumor, and treatment characteristics of patients with single-site metastatic disease

	$N=1241$ (%)	Adrenal ($n=121$)	Bone ($n=487$)	Brain ($n=396$)	Liver ($n=163$)	Other ($n=74$)	p value
Age (years), median (IQR)	67.4 (59.0–76.0)	70.3 (61.5–78.0)	68.0 (60.0–76.0)	64.8 (56.0–73.0)	72.0 (66.0–79.0)	67.4 (59.3–75.3)	< 0.001*
≤ 65 years	531 (43%)	41 (34%)	194 (40%)	224 (57%)	39 (24%)	33 (45%)	< 0.001*
> 65 years	710 (57%)	80 (66%)	293 (60%)	172 (43%)	124 (76%)	41 (55%)	
Gender							
Female	600 (48%)	54 (45%)	232 (48%)	197 (50%)	80 (49%)	37 (50%)	0.879
Male	641 (52%)	67 (65%)	255 (52%)	199 (50%)	83 (51%)	37 (50%)	
Histology							
Adenocarcinoma	554 (45%)	48 (40%)	251 (52%)	170 (43%)	57 (35%)	28 (38%)	< 0.001*
Not otherwise specified	408 (33%)	32 (26%)	138 (28%)	154 (39%)	66 (40%)	18 (24%)	
Other	87 (7%)	10 (8%)	30 (6%)	23 (6%)	15 (9%)	9 (12%)	
Squamous cell	192 (15%)	31 (26%)	68 (14%)	49 (12%)	25 (16%)	19 (26%)	
Smoking history							
Current	405 (33%)	52 (43%)	119 (24%)	162 (41%)	46 (28%)	26 (35%)	< 0.001*
Former	560 (45%)	54 (45%)	246 (51%)	164 (41%)	67 (41%)	29 (39%)	
Never	276 (22%)	15 (12%)	122 (25%)	70 (18%)	50 (31%)	19 (26%)	
Calendar year of diagnosis							
1999–2004	462 (37%)	51 (42%)	190 (39%)	155 (39%)	44 (27%)	22 (30%)	0.028*
2005–2009	456 (37%)	41 (34%)	168 (35%)	139 (35%)	70 (43%)	38 (51%)	
2010–2013	323 (26%)	29 (24%)	129 (26%)	102 (26%)	49 (30%)	14 (19%)	
Treatment for metastatic disease							
No	321 (26%)	40 (33%)	76 (16%)	77 (19%)	107 (66%)	21 (28%)	< 0.001*
Yes	920 (74%)	81 (77%)	411 (84%)	319 (81%)	56 (34%)	53 (72%)	
Systemic treatment							
No	992 (80%)	100 (83%)	356 (73%)	350 (88%)	134 (82%)	52 (70%)	< 0.001*
Yes	249 (20%)	21 (17%)	131 (27%)	46 (12%)	29 (18%)	22 (30%)	
Radiation treatment							
No	398 (32%)	45 (37%)	94 (19%)	102 (26%)	127 (78%)	30 (41%)	< 0.001*
Yes	843 (68%)	76 (63%)	393 (81%)	294 (74%)	36 (22%)	44 (59%)	
Surgical treatment							
No	1187 (96%)	121 (100%)	485 (99%)	345 (87%)	163 (100%)	73 (99%)	< 0.001*
Yes	54 (4%)	0 (0%)	2 (< 1%)	51 (13%)	0 (0%)	1 (1%)	

IQR interquartile range

*Denotes significant result

25% of cohort, HR 0.3, 95% CI 0.27–0.34, $p < 0.001$), and radiation therapy (received by 70% of cohort, HR 0.54, 95% CI 0.49–0.60, $p < 0.001$) also correlated with superior survival, but men experienced poorer prognosis than women (HR 1.2, 95% CI 1.1–1.3, $p = 0.002$). Receipt of systemic therapy and surgical resection for metastatic disease, regardless of number or location of EPMS, demonstrated the most improved mOS (10.0 vs. 2.0 months, $p < 0.001$, and 9.0 vs. 3.0 months, $p < 0.001$, respectively).

Discussion

In this population-based study of mNSCLC patients with extra-pulmonary metastasis at diagnosis, we investigated the clinical characteristics and outcomes of patients with either single or multiple extra-pulmonary metastatic disease. In the subgroup with single organ involvement, we observed in univariate analysis that liver metastases demonstrated the shortest mOS, whereas adrenal metastases

Table 2 Demographic, tumor, and treatment characteristics of patients with multi-site metastatic disease

	N = 2065 (%)	1 Site (*n* = 1241)	2 Sites (*n* = 562)	3 Sites (*n* = 198)	≥ 4 sites (*n* = 64)	*p* value
Age (years), median (IQR)	67.0 (58.0–75.0)	68.0 (59.0–76.0)	66.0 (58.0–74.0)	64.0 (54.8–73.3)	63.0 (55.0–70.0)	0.02*
≤ 65 years	954 (46%)	531 (43%)	279 (50%)	108 (55%)	36 (56%)	0.01*
> 65 years	1111 (54%)	710 (57%)	283 (50%)	90 (45%)	28 (44%)	
Gender						
Female	992 (48%)	600 (48%)	271 (48%)	94 (47%)	27 (42%)	0.811
Male	1073 (52%)	641 (52%)	291 (52%)	104 (53%)	37 (58%)	
Histology						
Adenocarcinoma	967 (47%)	554 (45%)	271 (48%)	104 (53%)	38 (59%)	0.073
Not otherwise specified	670 (32%)	408 (33%)	194 (35%)	54 (27%)	14 (22%)	
Other	139 (7%)	87 (7%)	33 (6%)	15 (7%)	4 (6%)	
Squamous cell	289 (14%)	192 (15%)	64 (11%)	25 (13%)	8 (13%)	
Smoking history						
Current	671 (32%)	405 (33%)	182 (32%)	64 (32%)	20 (32%)	0.984
Former	945 (46%)	560 (45%)	265 (47%)	91 (46%)	29 (45%)	
Never	449 (22%)	276 (22%)	115 (21%)	43 (22%)	15 (23%)	
Calendar year of diagnosis						
1999–2004	682 (33%)	462 (37%)	157 (28%)	49 (25%)	14 (22%)	< 0.001*
2005–2009	792 (38%)	456 (37%)	221 (39%)	82 (41%)	33 (51%)	
2010–2013	591 (29%)	323 (26%)	184 (33%)	67 (34%)	17 (27%)	
Treatment for metastatic disease						
No	521 (25%)	321 (26%)	135 (24%)	50 (25%)	15 (23%)	0.847
Yes	1544 (75%)	920 (74%)	427 (76%)	148 (75%)	49 (77%)	
Systemic treatment						
No	1651 (80%)	992 (80%)	448 (80%)	157 (79%)	54 (84%)	0.836
Yes	414 (20%)	249 (20%)	113 (20%)	41 (21%)	10 (16%)	
Radiation treatment						
No	628 (30%)	398 (32%)	160 (28%)	55 (28%)	15 (23%)	0.192
Yes	1437 (70%)	843 (68%)	402 (82%)	143 (72%)	49 (77%)	
Surgical treatment						
No	1995 (97%)	1187 (96%)	549 (98%)	195 (98%)	64 (100%)	0.02*
Yes	70 (3%)	54 (4%)	13 (2%)	3 (2%)	0 (0%)	

IQR interquartile range

*Denotes significant result

showed the longest survival; however, site of metastasis was ultimately not found to be a useful prognosticator after controlling for other measured confounders. Conversely, in the subgroup with multiple organ involvement, the number of EPMS appeared to be significantly associated with outcomes whereby an increasing number of sites correlated with worse mOS, which persisted in a multivariate model. Female gender, older age at diagnosis, and receipt of treatment, particularly systemic therapy, were also favorable prognostic factors. Our findings suggest that number of metastatic sites should be used to determine prognosis, guide treatment decision making, and facilitate timely and appropriate palliative care for patients.

Our unadjusted univariate results show consistency with prior studies, both in terms of mOS of the cohort as a whole and systemic therapy uptake rates [12]. However, we found that adrenal metastasis had a more favorable survival than other organs, such as bone and liver [3]. This finding is unexpected since adrenal metastases are often considered to have poor outcomes. Even when metastatic disease is surgically resected, [9, 10, 13] the adrenals represent a distant organ and may serve an anatomic conduit for further spread of primary lung cancer [14]. It is important to note that many of the previous studies did not adjust for confounders, and differentiation between those with only adrenal metastases and those with metastases in the adrenal(s) and other organs was not always performed, which could have impacted results [16]. For this reason, past investigations frequently provided inconsistent findings [3, 9, 10, 15]. In the current analysis, one of

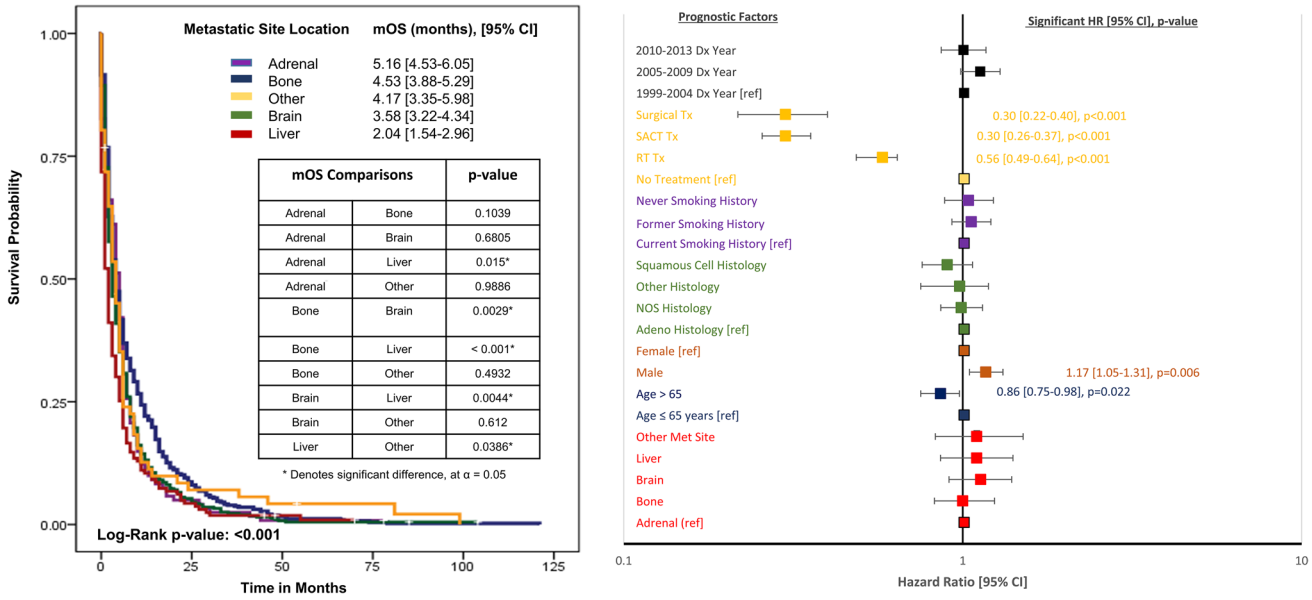

Fig. 2 **a** Survival analysis: median overall survival by location of EPMS, in single-site disease. **b** Forest plot: hazard ratio of patient factors and location of EPMS

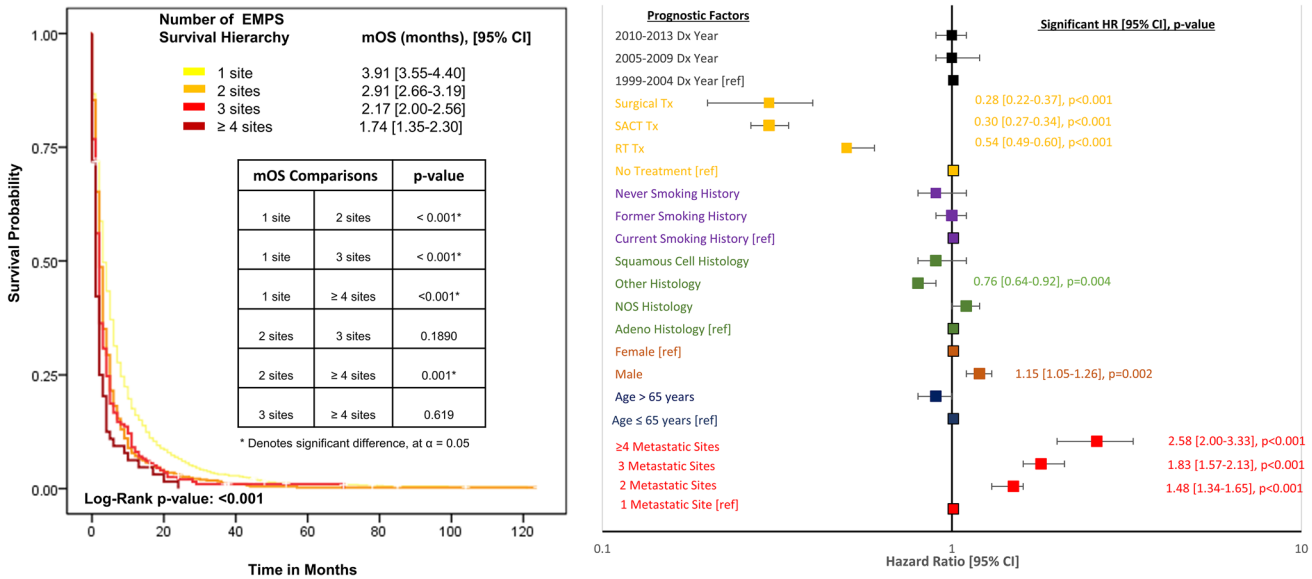

Fig. 3 **a** Survival analysis: median overall survival by number of EPMS. **b** Forest plot: hazard ratio of patient factors and number of EPMS

the noteworthy features is that we were able to control for measured confounders, after which location of metastasis no longer correlated with prognosis among patients with only a single site of metastatic disease. Part of this could be driven by the inclusion of some patients treated in the more contemporary era where tyrosine kinase inhibitors were used. These agents have been shown to be more effective than conventional cytotoxic drugs in managing some metastases, such as the brain and bone [17–19]. Also of note was the finding that among single-location EPMS, older age (> 65 years) at diagnosis was a favorable prognostic factor, even without consideration of performance status. This suggests that slower cell proliferation, decreased cell responsiveness to hormones and impaired angiogenesis which may develop as part of the aging process can impact the ability of the tumor to grow and vascularize, thus creating more indolent tumors and resulting in more favorable prognosis in this age group [3].

Conversely, we noted that the number of EPMS in the subset of patients with multiple organ involvement to be predictive of outcomes. There are several explanations for this, but it is likely that the number of EPMS is more representative of the overall disease burden and biology of the underlying lung cancer. Previous studies have described an association between a high number of metastatic sites and increased circulating tumor cell diversity, which can lead to reduced response and survival in patients undergoing systemic therapy [20–25]. Likewise, some have also proposed that a higher number of metastatic sites may signify that tumor cells are well adapted to colonizing distant organs and thus lead to treatment resistance [17].

The findings from the current study are important for several reasons. First, the treatment paradigm for mNSCLC has changed significantly over the past decade, and had a commensurate impact on outcomes [16]. While there have been prior studies that examined the impact of different metastatic sites on prognosis, we postulate that recent treatment advances, including the development of biomarkers, may alter the prognostic significance of location of EPMS. Specifically, the increasing use of targeted therapies for metastatic NSCLC has demonstrated disparate outcomes in patients with different sites of metastatic disease, even in the presence of favorable biology [17, 19, 26, 27]. Additionally, benefits associated with the use of targeted therapy have been detected in patients without targetable mutations [28, 29]. These findings suggest heterogeneity in metastatic NSCLC, of which metastatic burden, rather than location, might have a more prognostic value [30, 31]. Evolving treatment options for mNSCLC, which are expected to increase in both scope and uptake, [12] have likely altered the natural history of this disease, so a re-evaluation of the relationship between EPMS and outcomes is both timely and clinically relevant. The fact that previous studies are dated and do not always consider important confounders may further account for the variability seen in reports that describe the same organs as having the best or the worst prognosis.

Secondly, early integration of palliative care is increasingly recognized as being a critical component in delivering comprehensive care, especially in mNSCLC, since it represents a terminal condition. This study demonstrates a strong association between number of EPMS and median overall survival, suggesting that these patients would likely benefit most from prompt referrals to palliative care [18, 32, 33]. Additionally, this study validates, at a population-based level, the changes that have been introduced in the 8th Edition Staging Manual of the American Joint Commission on Cancer, underscoring that multiple distant metastatic sites have poorer prognosis than those with metastases limited to a single organ [34]. Moreover, this study uses a large representative patient population drawn from a population-based cancer registry, which includes all patients with a NSCLC diagnosis, not just those presenting to an oncology practice. Therefore, it serves to validate previous work that showed a possible correlation between prognosis and overall metastatic burden in highly selected patient populations [30].

This study should also be interpreted in the context of several limitations. First, it represents a retrospective review of mNSCLC cases managed at a single tertiary cancer center. Thus, results may not be generalizable to other jurisdictions; however, our center has catchment area of over 1 million residents from the southern portion of Alberta, Canada, where demographics are comparable to the rest of the country that share a similar single payer, universal healthcare system. Second, different assessment protocols and advances in diagnostic imaging techniques over the last two decades have improved the rate of detection for both number and site of metastatic disease. Depending on diagnostic year, all patients did not receive the same imaging or staging protocols, and certain sites of metastatic disease, or the frequency at which multiple metastatic sites were detected, may not be consistent throughout the entire study timeframe. Finally, as measures of patient performance status at the time of diagnosis was not available for patients in all years of the study, it is a potential confounding variable which may not have been fully addressed in the current study.

In summary, this study presents a large-scale, multi-year retrospective analysis of outcomes for patients with mNSCLC at diagnosis. Our study proposes that a simple count of metastatic sites at diagnosis may serve as an important prognostic tool in clinical practice and provides practical survival data that can be used to inform clinicians regarding patient prognosis, risks and benefits of treatment in an era of rapidly changing treatment options, and facilitate timely planning for and access to palliative care services. Considering that number of EPMS portends a worse median overall survival, consideration or stratification by the number of EPMS might play an important role in the future design of clinical trials. Altogether, these results suggest that while mNSCLC may not yet be amenable to complete eradication, consideration of number of EPMS may help identify patients who would benefit from either more aggressive treatment or best supportive care. Further efforts to determine and mitigate the factors predisposing patients to develop metastatic disease, along with initiatives to reduce the number of patients presenting with a high burden of disease, will help to improve future outcomes.

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