



Clinical factors associated with mortality within three months after radiosurgery of asymptomatic brain metastases from non-small cell lung cancer

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Abstract

Purpose Routine brain MRI surveillance frequently diagnoses small, asymptomatic brain metastases from non-small cell lung cancer (NSCLC) that are effectively treated with stereotactic radiosurgery (SRS). A subset of patients, however, may die prior to the onset of symptoms. This study identifies clinical features that distinguish neurologically-asymptomatic NSCLC brain metastases patients that die prior to routine 3 month follow-up after SRS.

Methods Retrospective chart review from 2007 to 2017 identified 18 patients with neurologically-asymptomatic NSCLC brain metastases who died <3 months after SRS. Twenty-eight additional patients meeting criteria and surviving >6 months after SRS were identified. Clinical factors were examined to determine characteristics correlated with survival using cox proportional hazards and nominal logistic regression models. Logistic regression models using salient factors were trained with 10-fold cross-validation and compared to the graded prognostic assessment (GPA) and score index of radiosurgery (SIR) using the AUC from receiver operant characteristic curves.

Results The median survival following SRS was 1.4 and 9.2 months for the <3 months and >6 months groups, respectively. Age, number of brain metastases, and Karnofsky performance status were associated with overall survival while gender and interval between primary cancer and first brain metastasis diagnoses were associated with <3 months and >6 months survival, respectively. Models using GPA and SIR performed poorly compared to preliminary metrics generated in this study for prognosis of both <3 months and >6 months survival.

Conclusion Physicians require data to provide high-value, cost-conscious health care. Clinical metrics can screen patients with asymptomatic NSCLC brain metastases likely to die prior to the standard screening interval and observation could be considered.

Keywords Brain metastasis · Clinical metric · NSCLC · Neurologically asymptomatic · Prognostic · Stereotactic radiosurgery

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Introduction

Brain metastases from non-small cell lung cancer (NSCLC) occur in 20–40% of patients at some point in the disease course [1–4]. Patients with neurologically-symptomatic brain metastases require definitive treatment with options including SRS, tyrosine kinase inhibitors (TKIs), whole-brain radiation therapy (WBRT). However, routine follow up with increasingly sensitive MRI imaging has increased the likelihood of the early detection of small, neurologically-asymptomatic brain metastases [5–7]. Currently, there are no standard treatment or observation guidelines for these patients.

The decision to treat these lesions involves a multidisciplinary team guided by patient characteristics, disease profile, and clinical metrics. Several clinical features have been proposed in the literature as predictors of overall survival (OS) in cancer patients with brain metastases [2, 8–12]. In addition, a number of established prognostic metrics are in frequent clinical use including the disease-specific graded prognostic assessment (GPA) and the score index of radiosurgery (SIR) [9, 13]. However, most studies do not stratify their cohorts based on neurologic symptomatic status and therefore, these metrics may fail to capture these patients [12].

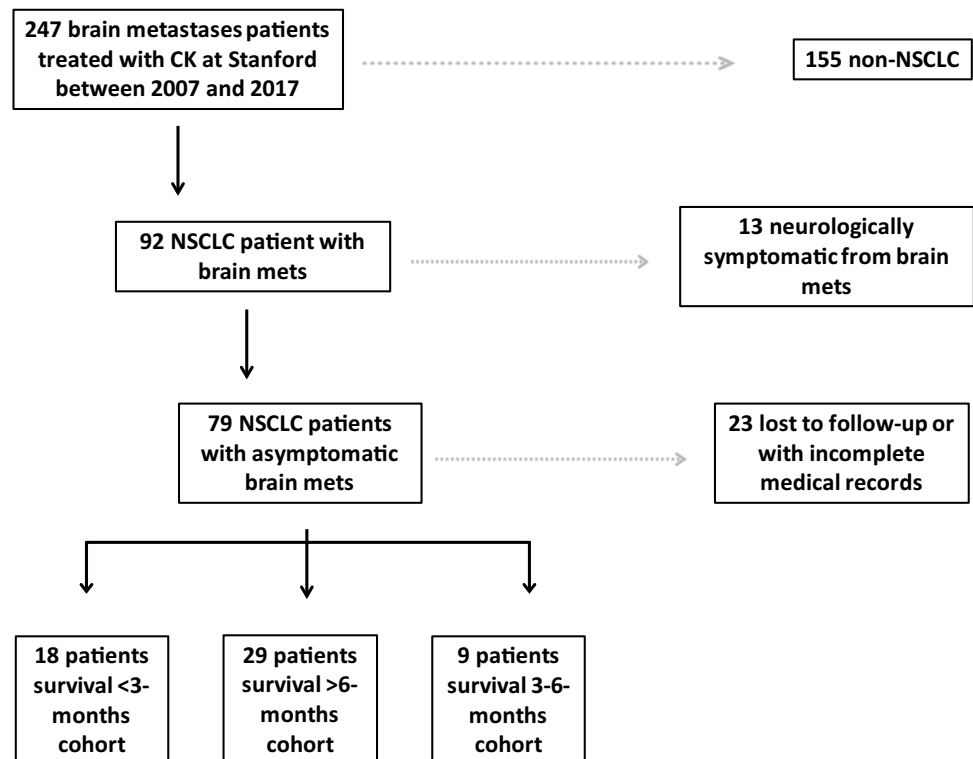
At our medical center, NSCLC patients with small, neurologically-asymptomatic brain metastases may be treated with SRS, a choice therapy for several small brain metastases (< 3 cm each, < 12 total) [8, 14, 15]. Our experience suggested that despite treatment with SRS, a subset of NSCLC patients with small, neurologically-asymptomatic brain metastases would die prior to routine 3-month follow-up, and that observation could have been considered. This study aimed to identify clinical and tumor characteristics to identify these patients. We then developed preliminary prognostic metrics to compare to the GPA and SIR.

Methods

We conducted a retrospective chart review of patients with brain metastases treated with SRS (CyberKnife®, Accuray, Sunnyvale, CA, USA) at Stanford Hospital between 2007 and 2017 (Fig. 1). Exclusion criteria included non-NSCLC histology, neurologically-symptomatic brain metastases, loss to follow-up prior to 6-months, and incomplete medical records. We identified 18 patients that met criteria and died within 3-months of SRS (<3 months group), the standard and National Comprehensive Cancer Network recommended follow-up period [16]. We then identified 29 patients that met criteria and were alive at 6-month follow-up (> 6 months group) and included 9 patients that died between 3 and 6 months of SRS. For each patient, we collected information on disease time-course, therapeutic management, patient demographics, and tumor characteristics. As patients may undergo multiple SRS treatments, clinical features were calculated from the time of the most recent SRS procedure. The IRB at Stanford University approved this study.

All analyses were performed in the R (v3.4.4) statistical environment [17]. Clinical features were compared between survival groups using Fisher exact test for categorical variables and analysis of variance for continuous variables. Disease progression and survival time were estimated using the Kaplan–Meier (KM) method. Univariate and multivariate associations of clinical features and survival

Fig. 1 Patient flow chart



were evaluated with Cox proportional hazards regression model. Complimentary analyses were carried out with nominal logistic regression for the <3 months (vs others) and for the >6-months (vs others) models, independently. GPA and SIR were excluded from all multivariate analyses. Factors that had a univariate p value <0.1 were considered for multivariate analysis. Results of all modeling were reported with a 95% confidence interval and a p value of <0.05 was considered significant.

ROC analysis was carried to determine the prognostic value of our clinical metrics compared to the GPA and SIR. Nominal logistic regression models based on a single variable of the GPA and SIR were generated to examine <3 months and >6 months prognostic value. The models were tuned with their respective variables using 10-fold cross-validation over the entire cohort.

Results

Patient and disease characteristics

Patient demographics

After applying exclusion criteria, 56 (57% female, median age: 64.4 years) patients remained for analysis (Table 1). A history of cigarette smoking was present in 48% of the patients. Patients in the <3-months group (median age: 72 years) were significantly older than those in the >6 months (median age: 60) group ($p=0.008$). Ethnic composition was largely Asian (48%) and white (45%) with Hispanic/Latino, black/African-American, and others making up the remaining 7%. This demographic composition reflects that expected for our region²².

Primary and extracranial disease profile

At the time of the most recent SRS, 73% of patients had progressive extracranial disease as described on imaging immediately prior to treatment, 25% had liver metastases, and 50% had bone metastases. Of the 56 patients, 47 had available mutation panel testing. In this group, epidermal growth factor receptor (EGFR) mutations were the most prevalent somatic mutation (55%). ALK fusions were rare (7.1%). There were no differences across the groups along these factors.

Brain tumor profile

Overall, patients had a median of 3.5 metastases prior to the most recent SRS. Patients in the <3-months group presented with a greater number of brain metastases than those in the >6-months (median: 4.5 vs 2, respectively, $p=0.04$).

However, when stratified by the two most common extracranial metastases, this difference was only present in patients with bone (median if present: 9 vs 3, $p=0.02$; if absent: 2 vs 2, $p=0.39$) and liver metastases (median if present: 15 vs 4, $p=0.003$; if absent: 2 vs 2, $p=0.36$). The difference did not reach significance when stratified by extracranial disease status (if progressive: $p=0.059$, if stable: $p=0.11$). The largest brain metastasis volumes (median: 0.55 cm³) and total brain metastasis volumes (median: 1.4 cm³) were both distributed similarly across the three groups ($p=0.7$ and $p=0.41$, respectively). Over half of the largest lesions were localized to either the frontal lobe (32%) or cerebellum (23%) with no differences across groups ($p=0.41$). Histology revealed most tumors were adenocarcinomas (94.6%). Further analysis did not stratify by histology.

Prior therapeutic management

The majority (56%) of patients had no history of prior SRS. There was no difference in prior brain radiation between the <3-months (77%) and the >6-months groups (56%, $p=0.21$). Of the patients that received prior brain radiation (44.6%), the majority (87.9%) received 1–5 rounds of SRS treatment only. Prior to the most recent SRS, patients received rounds of chemotherapy (76.8%), immunotherapy (41%), and/or targeted therapy (54.6%). Of the patients that received EGFR-TKIs as targeted therapy, 87.6% received first generation medications.

Disease time-course and survival

At the time of analysis, 23% of patients were alive. The KM method was used to examine the disease time course divided into three intervals: primary cancer diagnosis to death or last follow-up (median time of 1.13 and 2.75 years for <3-months and >6-months groups, respectively; $p=0.02$), primary cancer diagnosis to first brain metastasis diagnosis (median time of 0.09 and 1.27 years for <3-months and >6-months groups, respectively; $p=0.02$), and most recent SRS to time of death or last follow-up (median time of 1.32 and 9.24 months for <3-months and >6-months groups, respectively; $p<0.001$) (Fig. 2). Time to last SRS from primary cancer diagnosis (median: 15.9 months) and from first brain metastasis diagnosis (median: 4.9 months) did not differ between groups (Table 1).

Clinical metric characteristics

The mean KPS recorded prior to the most recent SRS was lower for the <3-months than the >6-months group (median: 70 vs 90, respectively, $p<0.001$). GPA (median: 2.0 vs 1.0, $p=0.003$) and SIR (median: 5.0 vs 4.0, $p=0.004$)

Table 1 Clinical features

	Total	Survival			p value*
		> 6 months	3–6 months	< 3 months	
Number patients, N	56	29	9	18	
Patient characteristics					
Gender, % F	57.1%	65.5%	66.7%	38.9%	0.13
Age at last CK date, median in years (range)	64.4 (35.8–84.4)	59.5 (35.8–79)	69.2 (42.3–84.4)	71.8 (40.2–84.1)	0.008
Race/Ethnicity, %					0.45
White	44.6%	37.9%	44.4%	55.6%	
Asian	48.2%	55.2%	55.2%	33.3%	
OtheR	7.1%	6.9%	0%	11.1%	
Smoking history	48.2%	44.8%	44.4%	55.6%	0.56
Time to last CK, median months					
From primary DX	15.9 (0.5–88.3)	18.5 (0.5–88.3)	25.1 (1.4–38)	11.7 (1.1–79.3)	0.42
From first brain metastasis DX	4.9 (0.2–79.3)	4 (0.3–35.8)	8.4 (0.2–37.7)	4 (0.2–79.3)	0.27
Alive at time of analysis, %	23.2%	44.8%	0%	0%	
Therapeutic management prior to last CK date					
Chemotherapy	76.8%	82.3%	88.9%	61.1%	0.17
Immunotherapy	41%	37.9%	66.7%	33.3%	0.75
Targeted therapy	54.6%	55.2%	66.7%	44.4%	0.56
Targetted therapy: EGFR TKIs	42.8%	37.9%	66.7%	38.9%	0.73
First generation	37.5%	34.5%	55.6%	33.3%	
Second generation	10.7%	6.9%	22.2%	11.1%	
Third generation	8.9%	3.4%	33.3%	5.6%	
Brain radiation	44.6%	44.8%	66.7%	33.3%	0.55
WBRT only	3.6%	0%	0%	11.1%	
SRS only	39.2%	44.8%	66.7%	22.2%	
Both	1.8%	0%	0%	0%	
Prior SRS courses					0.75
0	59%	55.2%	33.3%	77.8%	
1–2	35.7%	34.5%	66.7%	16.6%	
3–5	5.3%	10.3%	0%	5.6%	
Tumor characteristics					
Primary tumor molecular profile (N=47)					
Presence of EGFR mutation, %	55.3%	56%	71.4%	46.7%	0.56
ALK mutation, %					0.63
Positive	7.1%	6.9%	0%	11.1%	
Unspecified	3.6%	0%	22.2%	0%	
Extracranial disease at time of CK consult					
Overall status					0.32
Progressive	73.2%	69%	66.7%	83.3%	
Stable	26.8%	31%	33.3%	16.7%	
Presence of liver metastases	25%	17.2%	44.4%	27.8%	0.24
Presence of bone metastases	50%	44.8%	55.6%	55.6%	0.72
Brain mets characteristics at time of CK consult					
Histology					0.55
Adenocarcinoma	94.6%	96.6%	100%	88.9%	
Squamous	5.4%	3.4%	0%	11.1%	
Number, median (range)	3.5 (1–22)	2 (1–14)	6 (1–12)	4.5 (1–22)	0.04
By extracranial disease status					
Stable	3 (1–16)	1 (1–13)	3 (2–9)	10 (2–16)	0.11

Table 1 (continued)

	Total	Survival			p value*
		> 6 months	3–6 months	< 3 months	
Progressive	4 (1–22)	2 (1–14)	6.5 (1–12)	4.5 (1–22)	0.059
BY presence of liver metastases					
Present	2 (5.5–22)	4 (2–5)	7.5 (3–12)	15 (4–22)	0.003
Absent	2 (1–18)	2 (1–14)	5 (1–7)	2 (1–18)	0.36
By presence of bone metastases					
Present	4.5 (1–22)	3 (1–14)	7 (6–12)	9 (2–22)	0.02
Absent	2 (1–18)	2 (1–14)	2 (1–13)	2 (1–18)	0.39
Largest volume, median in cm ³ (range)	0.55 (0.008–11.96)	0.56 (0.008–11.96)	0.43 (0.29–5.94)	0.85 (0.1–11.4)	0.7
Total volume, Median in cm ³ (range)	1.4 (0.008–43.62)	1.39 (0.008–14.88)	1.12 (0.7–7.38)	1.66 (0.12–43.62)	0.41
Location of largest, % of Group					0.41
Cerebellum	23.2%	17.2%	33.3%	27.8%	
Frontal lobe	32.1%	34.5%	33.3%	27.8%	
Occipital lobe	17.9%	20.7%	11.1%	16.7%	
Parietal lobe	10.7%	13.8%	11.1%	5.6%	
Temporal lobe	7.1%	6.9%	0%	11.1%	
Subcortical	8.9%	6.9%	11.1%	11.1%	
Clinical metrics					
KPS, median (range)	80 (60–100)	90 (70–100)	90 (70–100)	70 (60–90)	<0.001
GPA, median (range)	1.5 (0–3.5)	2 (1–3.5)	1.5 (0.5–3)	1 (0–3)	0.003
SIR, median (range)	5 (3.0–8)	5 (3–8)	5 (3–6)	4.0 (3–6)	0.004

*p value calculated using Fisher Exact test

were also lower for the <3-months vs >6-months group (Table 1).

Clinical features associated with survival

In univariate analysis using cox proportional hazard models, age, male gender, the interval between primary cancer and first brain metastasis diagnoses, number of brain metastases, and KPS were associated with survival following the most recent SRS (Table 2). Male gender, number of brain metastases, and KPS remained significant in multivariate analyses.

Nominal logistic regression was carried out to separate factors associated with the <3-months model (Table S1) and with the >6-months model (Table S2). In univariate analysis for the <3-months model, age, male gender, number of brain metastases, and KPS were significantly correlated with <3-months survival. In the >6-months model, age, interval between primary cancer and first brain metastasis diagnoses, number of brain metastases, and KPS were correlated with survival >6-months. In multivariate analysis for the <3-months model, gender and KPS remained as significant factors. For the >6-months model, age, and interval between primary cancer and first brain metastasis diagnosis remained as significant factors. GPA and SIR were excluded from multivariate analysis as their values depended on other

parameters (KPS, age, gender, number of brain metastases) in the model.

Clinical metrics associated with survival

Common clinical metrics (GPA and SIR) were evaluated using both cox proportional hazards on the whole cohort and nominal logistic regression between the three groups. GPA and SIR were prognostic of overall survival following SRS (Table 2). Additionally, the two metrics were significantly associated with odds of falling into the <3-months group (vs others) (Table S1) and with odds of falling into the >6-months group (vs others) (Table S2).

Prognostic value of clinical features and metrics

The <3-months and >6-months logistic regression models were trained using 10-fold cross-validation to generate ROCs to compare to logistic regression models trained using GPA and SIR. The <3-months model was created using age, gender, number of brain metastases, and KPS as factors and the >6-months model was created using age, interval between primary cancer and brain tumor diagnoses, number of brain metastases, and KPS as factors. These custom models (AUC for <3-months: 0.84, 95% CI 0.8–0.87; >6-months: 0.77, 95% CI 0.73–0.81) were

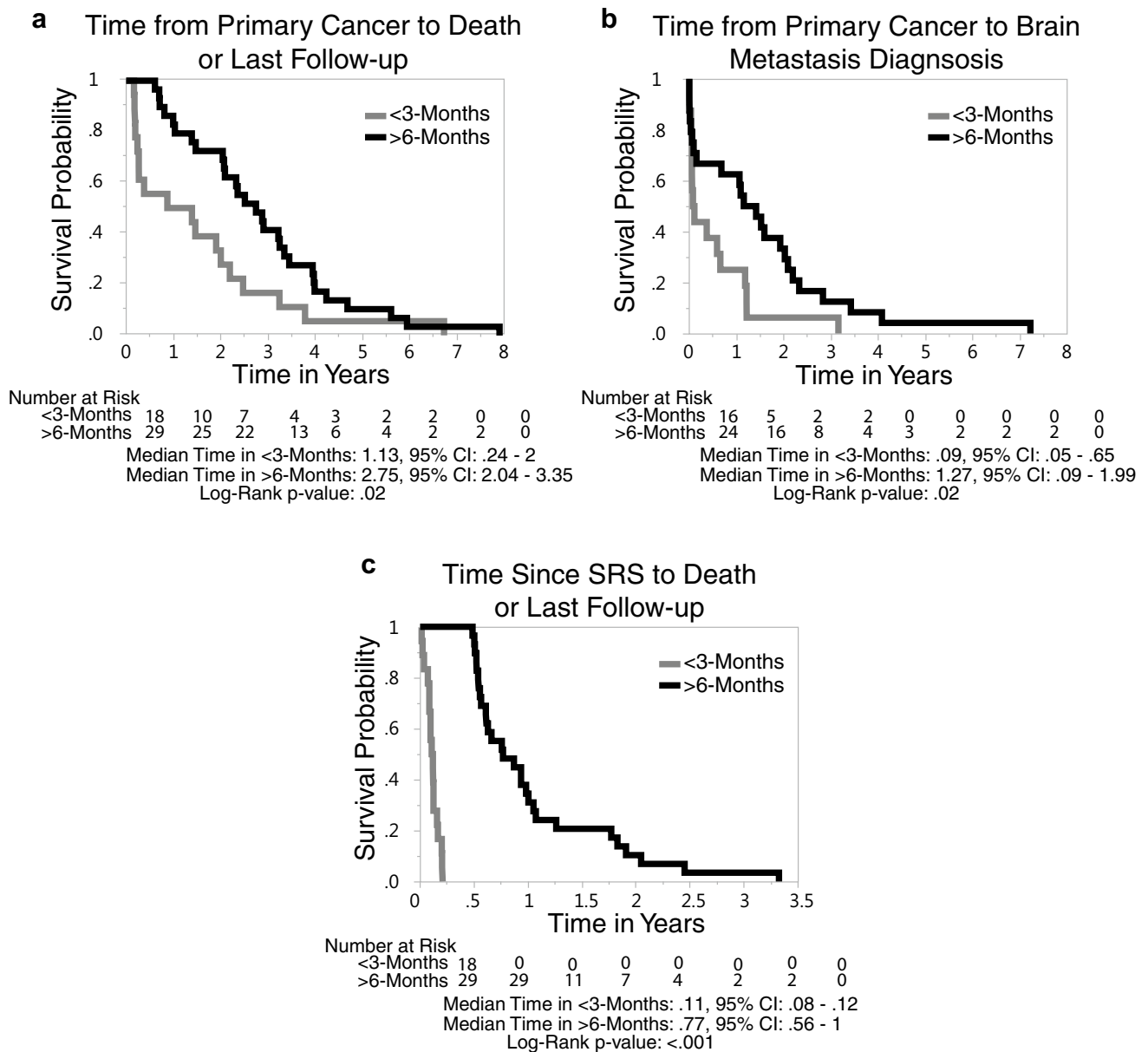


Fig. 2 Kaplan–Meier survival for disease time-course of patients that died within 3 months of SRS and those that survived for greater than 6 months. **a** OS probability of the two groups from time of primary cancer to death or last follow-up, **b** from time of primary cancer to brain metastasis diagnosis, and **c** from time of last SRS to death

or last follow-up. In **(b)**, 2 and 5 patients in the <3-months and >6-months, respectively, were diagnosed with brain metastases at the time of primary cancer diagnosis. *CI* confidence interval, *GPA* graded prognostic assessment, *SIR* stereotactic index of radiosurgery, *OS* overall survival, *SRS* stereotactic radiosurgery

trained independently and performed better than those using GPA (AUC for <3-months: 0.72, 95% CI 0.67–0.77; >6-months: 0.7, 95% CI: 0.65–0.74), SIR (AUC for <3-months: 0.69, 95% CI 0.64–0.73; >6-months: 0.68, 95% CI: 0.64–0.73), or KPS independently (AUC for <3-months: 0.8, 95% CI 0.8–0.87; >6-months: 0.69, 95% CI 0.64–0.73) (Fig. 3).

Discussion

Clinical features and metrics

SRS has been an effective treatment option for NSCLC patients with brain metastases, however, a subset of

Table 2 Factors associated with overall survival after CK based on univariate and multivariate cox regression models

Parameter	Variable	Univariate HR ^c	95% confidence interval	p value	Multivariate HR ^c	95% confidence interval	p value
Age ^a	Continuous no	1.05*	1.02–1.08	0.03	1.03	0.99–1.06	0.1
Gender	M vs F	2*	1.05–3.81	0.03	2.03*	1.03–4.06	0.04
Progression to first brain metastasis	Continuous no	0.98*	0.95 – 0.99	0.04	0.99	0.97–1.02	0.55
Smoking Hx	Yes vs no	0.94	0.44–2	0.54	–	–	–
Extracranial metastases ^a	Yes vs no	1.36	0.64–2.91	0.47	–	–	–
Presence of EGFR ^a	Yes vs no	1.21	0.68–2.36	0.58	–	–	–
Systemic disease status ^a	Stable vs progressive	1.11	0.56–2.12	0.76	–	–	–
No brain metastases ^a	Continuous no	1.14*	1.07–1.22	0.008	1.09*	1.01–1.18	0.03
Location of largest brain metastases ^a	Supratentorial vs infratentorial	1.08	0.46–2.85	0.87	–	–	–
Volume of largest brain metastases ^a	Continuous no	1.000	1–1	0.48	–	–	–
Total volume of brain metastases ^a	Continuous no	1.000	1–1	0.22	–	–	–
KPS ^a	Continuous no	0.93*	0.9 – 0.96	<0.001	0.95*	0.92–0.99	0.01
GPA ^d	Continuous no	0.53*	0.37 – 0.76	<0.001	–	–	–
SIR ^d	Continuous no	0.7*	0.56 – 0.87	0.001	–	–	–

*p value < 0.05

^aAt time of last CKT^bPrior to last CKT^cAdjusted for ethnicity, prior chemotherapy, prior immunotherapy, prior targeted therapy, and prior brain radiation^dNot included in multi-variate analysis due to high correlation with other parameters used to create these metrics

neurologically-asymptomatic patients die within a short period after treatment. In this study, we evaluated associations of clinical features with death < 3-months following SRS in 56 patients with small, neurologically-asymptomatic brain metastases from NSCLC. KPS, age, gender, number of brain metastases, and the time interval between primary cancer and brain tumor diagnoses were significantly associated with survival following SRS. Specifically, KPS and gender were correlated with < 3-months survival and age, interval of brain metastasis from primary cancer diagnoses, and KPS were associated with > 6-month survival.

KPS, age, gender, and number of brain metastases have been previously described as factors associated with survival in NSCLC brain metastases patients undergoing SRS and comprise calculations for the GPA and SIR clinical metrics [9, 13]. Patients in the < 3-months group had a shorter time interval between primary cancer diagnosis and identification of first brain metastasis than did those in the > 6-months group. This may suggest aggressive disease progression processes in the < 3-months group that better overcome the blood–brain barrier or other obstacles to metastasis. Once in the brain, both groups had neurologically-asymptomatic disease with a similar brain

metastasis burden and no statistical differences in brain metastasis volumes.

The time interval between primary tumor and brain metastases diagnoses is not captured by GPA or SIR. Furthermore, these metrics fail to account for neurologic-symptom status and tumor genetic profile. For the latter, we collected information on the largest brain metastasis location and somatic mutation profiles of the primary tumors. The distribution of locations for the largest lesions, with an overall bias towards the cerebral cortex (68%) followed by the cerebellum (23%) and subcortical regions (9%), did not differ between groups nor were locations associated with survival. The overall differences may not reflect disease malignancy, and instead, be due to differences in cerebral perfusion [18].

To examine the role of tumor genomic characteristics in survival, mutation panel testing results were collected and analyzed. Of the 47 patients with available mutation panel testing, EGFR mutations were prevalent (55% of patients), an incidence that is higher than the general American population (10–15% of NSCLC brain metastases) [19, 20]. However, 48% of our cohort identified as Asian and high rates of EGFR-mutations have been observed in East Asian NSCLC patients (20–55%) [21–23]. In addition, prolonged OS has

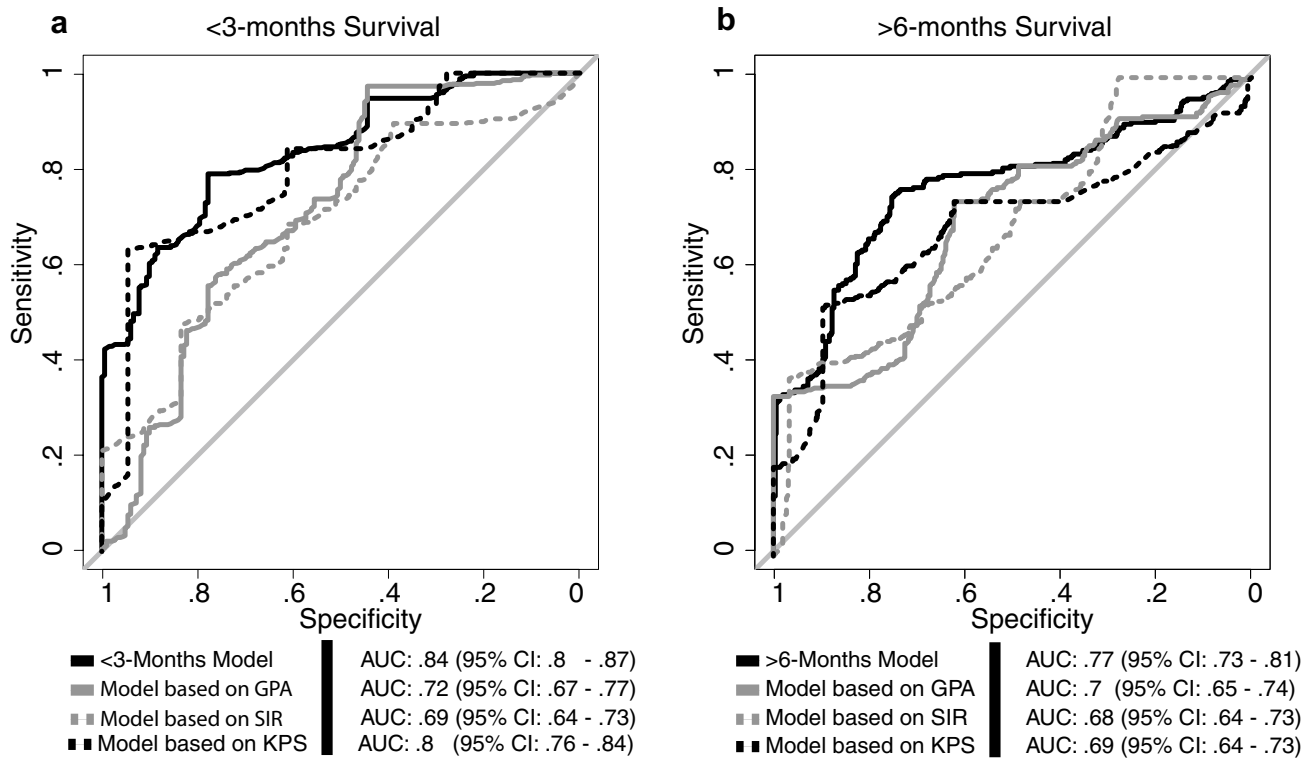


Fig. 3 ROC curves for prognostic models were developed by training logistic regression models with 10-fold cross-validation on the entire cohort. The < 3 months and > 6 months models were generated based on factors determined to be prognostic in univariate logistic regression (Table S1 and Table S2). These were compared to logistic regression models based on KPS, GPA and SIR to examine prognos-

tic value for **a** death within 3 months of SRS and for **b** survival of at least 6 months after SRS. *AUC* area under the curve, *CI* confidence interval, *GPA* graded prognostic assessment, *KPS* Karnofsky performance status, *SIR* stereotactic index of radiosurgery, *SRS* stereotactic radiosurgery

been observed generally in neurologically-asymptomatic patients and EGFR mutants, regardless of prior treatment [24, 25]. Regardless, the < 3-months and > 6-months groups had statistically similar distributions of EGFR mutations. Similar to the general population, ALK mutations were rare in our cohort. However, the importance of accounting for molecular features of NSCLC is highlighted in recent studies arguing for updates to clinical metrics including the GPA [26]. Spertudo and colleagues (2017) propose the lung-mol-GPA, a modified GPA metric that includes ALK and EGFR mutations statuses.

Guidance for therapeutic management

Clinical teams have little guidance when considering treatment vs observation for small, asymptomatic brain metastases identified on routine surveillance MRI. Identifying clinical characteristics associated with morbidity prior to neurologic symptom onset may help to avoid interventions that may not otherwise affect overall prognosis or quality of life. Under certain circumstances it may be reasonable for the treatment team to opt for short-interval, follow-up MRI

scans rather than immediate treatment. In some patients, the early detection and active therapeutic management of brain metastases, even prior to presentation of neurological symptoms, may improve clinical outcomes and reduce costs [27, 28].

Patients with brain metastases from EGFR-mutant NSCLC benefit from therapeutic regimens other than standard chemotherapy and often see prolonged survival. In fact, small, asymptomatic brain metastases respond well to TKI treatment alone in treatment naïve patients [29]. Liu et al. [29] analyzed overall survival in 96 neurologically-asymptomatic, EGFR-mutant NSCLC patients with brain metastases under three treatment groups: upfront radiation therapy (RT, both WBRT and SRS), delayed RT but upfront TKI treatment, or no RT. They argued for upfront EGFR-TKI followed by RT when appropriate as they found no significant impact on OS with delayed RT.

However, discrepancies exist in the literature over the timing of RT with some suggesting shorter OS with upfront EGFR-TKI and deferred SRS [19, 30]. In these studies, the distribution of patients with and without neurologic symptoms from brain metastases were uneven between

treatment branches. Magnuson et al. [30] retrospectively analyzed overall survival in 50 patients with EGFR-mutant NSCLC. In their study cohort, 94% vs 46% of patients were asymptomatic in the upfront-TKI and upfront-RT groups, respectively. In a later retrospective study on 351 patients with EGFR-mutant NSCLC and an identical design, Magnuson et al. [19] had similar distribution with 88% vs 51% of patients being asymptomatic in the upfront-TKI and upfront-RT groups, respectively. These discrepancies highlight the need for further investigation in neurologically-asymptomatic brain metastases patients to better understand treatment response and optimal management.

The landscape of non-surgical and non-SRS NSCLC brain metastasis treatment is rapidly evolving. Erlotinib is a first-line therapy used in most patients treated with EGFR-TKIs in this study as well as studies cited in this discussion. However, EGFR-TKIs represent a non-homogenous group of drugs and recent studies with new agents, such as osimertinib, show superior tumor control and progression free survival [31, 32]. In addition, the updated 2017 guidelines from the NCCN call for routine testing of PD-L1 expression in NSCLC diagnosis, a target of immunotherapy to combat NSCLC. In future studies, these new management strategies need to be taken into account as they will likely affect broad comparisons of efficacy between upfront-SRS and upfront-EGFR-TKI.

Updating clinical metrics

The clinical factors identified in this study could be used to create prognostic metrics that better reflect disease variability among this unique cohort of patients. Zindler et al. [33], using data from 495 NSCLC patients with 1–4, < 4 cm diameter brain metastasis lesions, developed two nomograms using ROC analysis for the prognosis of early death (< 3-months) and long-term survival (> 12-months). Their nomograms summed points from gender, age, presence of extracranial metastases, volume of largest brain metastasis, and the WHO performance scale. These metrics were significantly better at determining death in < 3-months (AUC: 70) than GPA and SIR. They did not report neurologic-symptom status within their cohort, limiting generalizability to our cohort.

However, as shown by the Zindler et al. [33] study and the results from our analysis, there is need to update the current metrics to more dynamic models that (1) better capture inter-patient variability and (2) distinguish factors for early death and long-term survival. As expected, both GPA and SIR were prognostic of overall survival. However, they performed poorly when compared to our more dynamic models. It should be noted that KPS performed quite well in univariate analysis and in model analysis. We argue that by independently selecting factors for early-death

and long-term survival, clinical metrics can increase the predictive potential of KPS and other clinical features. Further work is needed to refine clinical features correlated with early death and long-term survival and to better tune these models. External validation of our findings and prospective studies with larger sample sizes are needed to identify optimal management of patients with neurologically-asymptomatic brain metastases.

Study limitations and future directions

Unlike the present study, most of the literature has focused on outcomes following initial treatment of brain metastases, prior to any other intervention for these patient's intracranial disease. Physicians are often faced with making treatment decisions not only for patients with a new presentation of intracranial disease, but also in patients who continue to see disease progression following prior management. In our study design, OS, clinical features, and clinical metrics were obtained at the time prior to the most recent SRS procedure, providing a clinical context encountered daily by the treatment team. This design limits our ability to directly compare results with prior literature.

Further limitations of this study include those inherent in retrospective designs, including the risk of selection bias. Additionally, patients were excluded if they were lost to follow-up or had incomplete medical records, increasing the risk of selection bias. However, results were consistent following robust analyses using both cox proportional hazard and logistic regression models. Nevertheless, our results were obtained from a small single-institution dataset, resulting in the wide range of values observed in the cohort. Further work on larger cohorts is needed to externally validate the proposed metric and to test our claims.

Finally, while the cause of death could not be reported for the patients in this cohort, to our knowledge, patients did not report neurologic symptoms prior to death. However, the number of intracranial metastases was statistically greater in the < 3-months group compared with the > 6-months group. To further investigate this, the number of intracranial metastases was stratified by measures of systemic disease, namely, presence of bone and liver metastases, the two most common extracranial lesions. The difference in number of intracranial metastases was only significant in the presence of greater systemic disease burden. Therefore, patients who die early following SRS may have an overall increased disease burden. There were no differences in time interval between primary tumor or initial brain metastasis diagnoses and the most recent SRS reducing the risk that < 3-month patients simply had a longer disease time course. Nevertheless, lack of information on exact cause of death remains a major limitation of this manuscript.

Conclusion

Patients with brain metastases from NSCLC are a heterogeneous cohort, with diverse treatment exposures. Consideration of clinical characteristics correlated with decreased survival after SRS of small, asymptomatic NSCLC brain metastases may enable further refinement of high-value, patient-centered care.

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