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Nested cohort study to identify characteristics that predict near-term disablement from lung cancer brain metastases

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Abstract

Objectives—To test whether the presence of patient- and imaging-level characteristics: 1) are associated with clinically meaningful changes in mobility among late stage cancer patients with metastatic brain involvement; and 2) can predict their risk of near-term functional decline.

Design—Prospective nested cohort study

Setting—Quaternary academic medical center

Participants—The study population consisted of a nested cohort of the 66 patients with imaging confirmed brain metastases among a larger cohort of 311 patients with late stage lung cancer.

Interventions—Not applicable

Main Outcomes—Functional evaluations with the Activity Measure for Post-Acute Care Computer Adaptive Test (AM-PAC-CAT) and symptom intensity ratings were collected at monthly intervals for up to 2 years.

Results—In exploratory univariate models, whole brain radiation therapy (WBRT) and imaging findings of cerebellar or brain stem involvement were associated with large AM-PAC-CAT declines in mobility (−4.55, SE 1.12; −2.87, SE 1.0; and −3.14, SE 1.47, respectively). Also in univariate models, participants with new neurological signs or symptoms at imaging (−2.48, SE 0.99), new brain metastases (−2.14, SE 0.99), or new and expanding metastases (−2.64, SE 1.14) declined significantly. Multivariate exploratory mixed logistic models including WBRT, cerebellar/brainstem location, presence of new and expanding metastases, and worst pain intensity

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had excellent predictive capabilities for AM-PAC-CAT score declines of 7.5 and 10 points, C statistics 0.8.

Conclusions—Among patients with lung cancer and brain metastases, a cerebellar/brainstem location, new and expanding metastases, and treatment with WBRT may predict severe, near-term mobility losses and indicate a need to consider rehabilitation services.

Introduction

Cancer and its treatment are associated with functional losses that profoundly reduce patients' quality of life, shorten their survival, and increase their healthcare utilization. The timely (and even preemptive) delivery of simple rehabilitation services is capable of lessening or even reversing a decline into functional dependency.^{1–3} However, only a small percentage of the patients who would benefit from these services receive them, and then only after a prolonged delay in their application.^{4,5} An important reason for this is our currently limited ability to anticipate the course and severity of this decline which would allow for the more timely referral of appropriate patients.

There is a compelling need for an early, simple, and nearly transparent way to identify and triage patients at risk for near-term functional loss. Some work supports the viability of this approach as robust associations between acute functional decline and the presence of specific clinical characteristics, e.g., brain and bone metastases, bladder dysfunction, and obesity, have been identified in a range of cancer populations.⁴ However, their predictive capabilities remain poorly explored. More specifically, while particularly strong associations have been found between the presence of brain metastases and functional loss, even in this setting we remain unable to accurately predict which patients with brain metastases could benefit from the timely administration of rehabilitation services.

Our team's work with a prospectively monitored cohort of patients with late stage lung cancer (LC) has already confirmed a strong association between the presence of brain metastases and disablement.⁶ This led us to speculate that an enhanced analysis of readily available data, e.g., imaging and patient reports, might improve our ability to predict the impact of brain metastases on a patient's function, and, thereby, identify those most likely to benefit from rehabilitation services. The goal of this study was, therefore, to conduct exploratory analyses using routinely available clinical and radiographic data in order to estimate associations of patient- and imaging-level characteristics with clinically meaningful changes in mobility among late stage cancer patients with metastatic brain involvement.

Methods

Subjects and enrollment

The data utilized in this study were collected from members of a previously described cohort of 311 patients with Stage IIIB or IV Non-Small Cell LC (NSCLC) or Extensive Stage Small Cell LC (SCLC).⁶ As previously described, the 311 cohort members were comprised of patients seen in initial consultation or follow-up at the Mayo Clinic, Rochester outpatient Medical Oncology Clinic. A total of 357 patients were telephonically invited to participate

and 311 consented and were enrolled. The Institutional Review Board approved both the initial cohort study and additional data collection for this study.

Data collection

Data were collected from three sources: 1) telephonically from patients via the Activity Measure for Post Acute Care Computer Adaptive Test (AM-PAC-CAT) and numerical rating scales (NRS's) of "worst pain," as well as average fatigue and dyspnea over the previous week, 2) review of Mayo Clinic and outside medical records, and 3) interpretation of neuroradiologic imaging studies. AM-PAC-CAT and NRS scores were collected for the cohort as a whole by research assistants at enrollment and every 3–4 weeks thereafter. Efforts to contact participants continued for up to two years or until a patient's withdrawal, death, or study completion. Eighty four percent of the 2543 assessments were completed among surviving, enrolled participants (311 -member cohort) within four weeks of their prior assessment.⁶

Information abstracted from the records included LC type and stage, participant demographics, comorbidities, extra-cranial disease status, brain metastasis treatment (observation, surgery, stereotactic and/or whole brain radiation therapy (WBRT)), and Charlson comorbidity indices.⁷ For purposes of the analyses described below, treatments were linked to the scan that precipitated either a change or the consideration of a change in management. All records were abstracted separately by two cancer rehabilitation physicians (AC and KD) with disagreements resolved through an in-person consensus process.

Brain imaging studies obtained from the time of participants' study enrollment until the termination of data collection were reviewed by an experienced (>5 years post fellowship), board-certified neuroradiologist (FD) to determine: 1) whether the image revealed the initial detection of a brain metastasis, or a progression pattern defined as including brain metastases in a new location, expanding metastases or new metastases in association with expanding metastases; 2) size of the largest brain metastasis; 3) location of metastases (hemispheric (frontal, parietal, temporal, or occipital lobe), cerebellum, brainstem, or basal ganglia/thalamus; 4) number of metastases (1–2, 3–5, and >5); and 5) unilateral or bilateral involvement. If a metastasis had previously been treated, it was counted as a metastasis in subsequent scans if a residual or growing lesion was noted. When a metastasis spanned across more than one of the locations noted in point 3 above, the location of it greatest expanse was recorded. Imaging studies obtained within 10 days of a scan that noted new or progressive brain metastases, and solely for treatment planning purposes, e.g., stereotactic radiosurgery, were not reviewed or included in the analyses.

Measures

AM-PAC-CAT—The AM-PAC is a widely used item response theory-based functional assessment tool which was established through factor, modified parallel and Rasch analysis.^{8,9} Each item queries respondents regarding the amount of difficulty they experience performing an activity with four response options ranging from "none," to "unable." The AM-PAC Basic Mobility item bank demonstrates validity, reliability, and responsiveness when administered via the computer adaptive testing (CAT) platform used in

this study.^{6,8–14} Because our work did not confirm these properties for the AM-PAC's additional Daily Activities and Applied Cognition item banks among patients with late stage LC in the initial study,⁶ only data from the Basic Mobility item bank were utilized.

Symptom Numerical Rating Scale (NRS)—The eleven-point NRS has been extensively validated as a means to assess symptom intensity among patients with cancer.^{15,16} The scale ranges from 0 (none) to 10 (as bad as it can be). Participants were asked to rate their “worst pain,” as well as their average fatigue and level of dyspnea over the past seven days preceding each assessment point.

Statistical Analyses

Construction of assessment intervals—The primary unit of analysis in this study was the change in AM-PAC-CAT score between two assessment points – with larger negative quantities reflecting larger declines in mobility. Changes were calculated between all AM-PAC-CAT scores that occurred within 3 months of each other. The telephonic collection of AM-PAC-CAT and NRS scores was not correlated with a participant's clinical care or imaging. In order to link AM-PAC-CAT intervals with imaging that revealed new or expanding brain metastases, scans were coupled to all score intervals that occurred within 6 weeks of imaging. This linkage strategy was based on previous work suggesting that the impact of a brain metastasis precedes and extends beyond the acute detection and treatment period.¹⁷ Additionally, prior statistical scholarship from the 1980s–90s established that including overlapping intervals in a sampling scheme increases precision.¹⁸

Patient-level descriptive statistics were calculated for the demographic and clinical characteristics of the study participants. AM-PAC-CAT score and NRS descriptive statistics were also calculated for each AM-PAC-CAT score interval. Scan-level descriptive statistics were calculated for all scans that revealed new or expanding brain metastases and could be linked to an AM-PAC-CAT score interval (N=96).

General estimating equation (GEE) models, with an exchangeable correlation matrix and identity link, were used to estimate associations between change in AM-PAC-CAT scores, the dependent variable. In all models, and 1) patient clinical and demographic information, 2) NRS scores, and 3) brain metastasis characteristics. All models were adjusted for AM-PAC-CAT interval lengths and score at the beginning of an interval. Univariate models were constructed initially and followed by multivariate GEE models in a stepwise fashion. The ordering of variable entry into the multivariate models was based on the Wald test p value of coefficients in univariate models. The threshold for inclusion was a coefficient Wald test p value 0.10 as has been previously described.¹⁹ To assess robustness, an additional multivariate GEE model was constructed to estimate the contribution of brain metastasis characteristics to patients' functional decline relative to other factors known to undermine function: symptomatic bone metastases and extracranial disease progression.

To avoid conflation of explanation and prediction we used a similar approach to construct models that best predicted 2.5-, 5.0-, 7.5-, and 10.0-point declines in AM-PAC-CAT scores as has been previously suggested.²⁰

We utilized four levels of AM-PAC-CAT score decline in order to examine the granularity of our predicative capacity. Multivariate logistic mixed models were sequentially constructed. For inclusion in the multivariate models, coefficients' Wald test p values had to be ≤ 0.10 in at least two of the four univariate models. In order to create a single model, covariates were retained in the final multivariate model if their coefficient Wald test p values were ≤ 0.10 in all four models. C statistics were calculated for each model and bootstrapping was used to estimate a 95% confidence interval for the C statistics. Standard errors were estimated using the jackknife and bootstrap approaches. Conventional diagnostics were performed for all models. Analyses were conducted in STATA version 13.0.^a

Results

Participants

Table 1 outlines the demographic and clinical characteristics of the 66 nested cohort members whose brain scans revealed metastases at some point during the study period. Participant mean age was 61 years. A majority (61%) was female and 83% had NSCLC. The 66 members of the brain metastases subgroup differed only in the higher proportion of women, 61% vs. 46%, $p=0.04$ from the 245 members of overall cohort whose imaging did not reveal brain metastases. Thirty two cohort members (48%) had known brain metastases at the time of study enrollment, while 34 (52%) did not.

Intervals

For a majority of the 66 participants with brain metastasis, multiple of their scans and telephonic assessments were used to construct the 209 AM-PAC-CAT score intervals. The within-individual characteristics of these intervals changed over the course of follow up, e.g., AM-PAC-CAT and NRS scores, and brain imaging findings. Figure 1 depicts the frequency with which unique participants (Panel A), scans (Panel B), and assessments (Panel C) contributed to the AM-PAC-CAT intervals. Unique participants contributed to an average of 5.0 intervals, unique scans to an average of 2.7 intervals, and unique assessments to an average of 1.1 intervals. The mean interval length was 37 days, (SD 13.2), with durations ranging from 17 to 93 days. On average, at the outset of each interval, participants' AM-PAC-CAT scores were 69.9 (SD 9.3, min 33.0, max 94.0), suggesting that they were high level household and low level community ambulators.²¹ Their worst pain, average fatigue, and average dyspnea scores were 3.1 (SD 3.4), 4.2 (SD 2.7), and 2.5 (SD 2.6), respectively (min 0 and max 10 for all symptoms). The mean AM-PAC-CAT score change over the 209 intervals was -2.25 (SD 7.55, min -45.60 , max 11.42).

Brain scans

Table 2 describes the imaging findings of the 96 scans among the 66 patients with brain metastases that were obtained during the study interval, revealed new or expanding brain metastases, and could be linked to an AM-PAC-CAT score. A majority (76%) of the imaging studies was enhanced MRIs, with almost all of the remainder (20%) being computed

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tomography (CT) scans. Among these 96 scans, multiple metastases were noted on a majority, with over one third (34%) revealing 5 metastases. Metastases were most frequently detected in the frontal lobe, 71%. However, the parietal lobe (58%) and cerebellum (52%) were also frequently involved. The largest brain metastasis was an average of 1.6 cm (SD 1.1) in greatest diameter. Forty percent of scans led to participants' initial diagnoses with brain metastases. Almost two thirds (61%) had been obtained due to changes in a patient's signs or symptoms. Observation was the most common management approach, 38%, followed by WBRT, 30%. In order to assess for potential bias, the 96 scans that could be linked to AM-PAC-CAT score intervals were compared to imaging studies obtained between participants' initial LC diagnoses and study enrollment, and to imaging studies that could not be linked to an AM-PAC-CAT score interval. These latter scans (N=104) differed in that linked scans were less likely to result in patients receiving WBRT, and more likely to result in patients being observed. Unlinked scans were also more likely to lead to an initial diagnosis with metastatic disease to the brain and to reveal new metastatic sites, rather than expanding sites.

Univariate models

Table 3 lists the results of the univariate GEE models. Treatment with WBRT (−4.55, SE 1.12) as well as the presence of brain stem (−3.14, SE 1.47) metastases were associated with large and significant decrements in patients' mobility scores, all exceeding twice the AM-PAC-CAT's 1.5 minimal clinically important different (MCID) for LC.⁶ Cerebellar location of metastases was also associated with significant declines in mobility (−2.87, SE 1.0). Additionally, the mobility of participants with neurological signs or symptoms at diagnosis declined (−2.48, SE 0.99), as did those whose brain scans revealed expanding (−2.14, SE 0.99) or a combination of new and expanding and metastatic sites (−2.64, SE 1.14).

Multivariate model

Covariates included in the final multivariate model are also presented in Table 3. The model included three variables; receipt of WBRT (−4.05, SE 1.11), the presence of cerebellar metastases (−1.77, SE 0.94), and the presence of expanding and new metastatic sites (−2.04, SE 1.08). The co-occurrence of all three characteristics would, on average, be associated with an 8-point decrement in a patient's AM-PAC-CAT score.

Logistic regression models

Output from the univariate logistic mixed models that examined associations between AM-PAC-CAT score declines 2.5, 5.0, 7.5, and 10.0 points are listed in Table 4. Results of the final multivariate logistic mixed models with robust jackknife- and bootstrap-estimated standard errors are listed in Table 5. C statistics for predicting mobility declines 2.5, 5.0, 7.5 and 10.0 points, ranged from 0.75 to 0.83 (0.7 – 0.8 acceptable to good, 0.8 – 0.9 excellent, 0.9 outstanding),²² with the model being more predictive of large declines in mobility, e.g., 7.5- and 10.0-point.

Discussion

This study advances understanding of cancer-related disablement by estimating the impact of the clinical, radiographic, and treatment characteristics of brain metastases on the function of patients with cancer. We found that cerebellar/brainstem involvement, the presence of both new and expanding metastases, as well as metastasis size and treatment with WBRT were associated with large near-term decreases in patient mobility.²¹ We believe that these findings may facilitate timely and appropriate efforts to preserve functionality among patients with lung cancer brain metastases because: 1) patients with brain metastases, particularly those treated in an outpatient setting, inconsistently receive proven and effective rehabilitation services;⁵ 2) timely referral for rehabilitation services can enhance function and quality of life while reducing utilization;²³ and 3) the characteristics identified in the logistic mixed models (Table 5) accurately identify patients at high risk of large, near-term declines in function.

Although the AM-PAC is widely utilized in rehabilitation, neither it, nor the import of its scores, are known to most oncological clinicians. Our previous work established that the MCID for the AM-PAC is 1.5 among patients with LC.⁶ Given this, the 4.05 point decrease associated with WBRT represents a marked and clinically important decline in functionality.²⁴ As reflected in the logistic mixed models (Tables 4 and 5), patients that needed/received WBRT for cerebellar/brainstem metastases and new and expanding metastases, even when relatively small; e.g., 0.1 cm, are at an over 10-fold risk of experiencing mobility declines greater than four times the AM-PAC's MCID, a catastrophic level of functional loss that increases a patient's risk of falls, institutionalization, and other adverse outcomes.²¹

Prior reports describe functional deterioration among patients with brain metastases,²⁵ but none appear to have examined linkages between specific metastasis or patient characteristics and impending disablement. Characteristics reported to be associated with reduced survival, e.g., number of metastases, were not predictive of declining mobility in our study, apart from performance status,²⁴ possibly due to the more limited time intervals examined, mean 36.6 days.

An extensive literature has examined associations between WBRT and diverse QOL domains, including physical function. While general functional deterioration has been noted,^{26,27} findings have varied across study cohorts and with measurement strategy. Two randomized trials compared the impact of WBRT following stereotactic radiosurgery,²⁸ and surgical resection,²⁹ on brain metastases (roughly 2/3 due to lung cancer). Both found that WBRT did not impact the proportion of independently functioning patients, although participants were higher functioning at baseline than patients in the current study and the use of a binary KPS <70 variable, obviated discrimination among lower functioning patients. More recently, a Phase III trial (North Central Cooperative Trials Group N0574) of WBRT in addition to stereotactic radiosurgery for brain metastases (again about 2/3rds due to lung cancer) found that WBRT was associated with larger degradations in cognitive functioning and QOL than radiosurgery alone.³⁰ It is pertinent that others have found that brain

metastasis-related deterioration in neurocognitive functioning is strongly correlated with degradations in ADL performance³¹ and mobility.³²

Whether the predictors of functional decline identified in this study are simply markers of impending disablement or contribute to its occurrence is largely moot, as their identification alone provides the opportunity to deliver rehabilitation services in a proactive rather than a reactive, and often too late, manner.^{4,33}

We believe that our findings are of sufficient quality to inform future research and, potentially, even decision making regarding the referral of patients with lung cancer brain metastases for rehabilitation services. First, we used the only functional PRO with established precision and responsiveness in patients with metastatic cancer (including brain metastases) to estimate mobility. Second, measurements were obtained in advance of the detection of brain metastases, yielding more accurate assessment of total functional decline than can be obtained at the time of diagnosis or treatment. Third, our data have limited missingness with 84% of scheduled PRO collections having been conducted, with a resultant reduced risk of bias. Though selection bias is a concern, the study sample differed from the overall LC cohort solely by it having a higher proportion of women (gender has not been associated with functional change in cancer populations, making it unlikely that this female preponderance biased coefficient estimates). Fourth, our estimates are robust across analytic methods (e.g., jackknife and bootstrap), and they are in accord with prior studies, including the anatomic distribution of brain metastases.³⁴ Last, 20–40% of patients with non-skin cancers develop brain metastases annually,²⁷ and only a minority receive validated rehabilitation services; this situation becomes less acceptable as cancer patients increase in terms of age, number, and survival duration.

Limitations

This study, inevitably, has limitations. The fact that we did not collect clinician-rated function or objective performance data could be considered one of these. This concern is mitigated by the growing body of findings that patient reported outcomes (PROs) are at least as discriminative in distinguishing patients' functional capabilities as either clinician-or performance-rated assessments.³⁵ Another concern is that a larger cohort may have yielded more precise and potentially robust estimates. However, the number of subjects (66), data collection points, and scans involved in this report is relatively large. Further, the granularity and frequency of assessments that characterize this study would likely not be possible with a larger sample. Gains from a larger sample may therefore be limited.

That our study population was comprised solely of patients with LC, which is known to have a more limited prognosis and to engender a heavier symptom burden than many other cancers,³⁶ limits its generalizability. However, our focus on LC with its more rapid progression likely enabled us to detect near-term changes that may not have been detected in a more heterogeneous cancer population. It can also be argued that our findings are not particularly surprising, as most practitioners would intuitively agree that tumors at high risk of causing symptoms and appropriate for WBRT are generally poor prognostic factors, both with respect to survival and function. However, as ubiquitous as this awareness may be, it

has proven insufficient to prompt clinicians to refer their patients for validated rehabilitation services to prevent costly and needless disablement.

Conclusion

Among patients with LC and brain metastases, a cerebellar/brainstem location, new and expanding metastases, treatment with WBRT, and size of the largest metastasis may predict severe, near-term mobility losses that will likely benefit from rehabilitation services.

Acknowledgments

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Glossary

AM-PAC-CAT	Activity Measure for Post Acute Care Computer Adaptive Test
CAT	Computer adaptive testing
GEE	General estimating equation
LC	Lung cancer
MCID	Minimal clinically important different
NSCLC	Non-Small Cell LC
NRS's	Numerical rating scales
SCLC	Small Cell LC
WBRT	Whole brain radiation therapy

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Figure 1.

The contribution of unique participants (Panel A), imaging studies (Panel B), and assessments (Panel C) to intervals between AM-PAC-CAT assessment points.

Table 1

Subject demographic and clinical characteristics

Total N	66
Female N (%)	40 (60.6%)
Age mean (SD)	61.1 (10.8)
Charlson Index mean (SD)	7.97 (2.15)
Medical co-morbidities N (%)	
COPD	14 (21.2%)
Stroke	2 (3.0%)
CAD	5 (7.6%)
Connective tissue or musculoskeletal disorder	22 (33.3%)
Neurological disorder	6 (9.1%)
Primary Caregiver N (%)	
Spouse	47 (71.2%)
Child	12 (18.2%)
Parent	2 (3.0%)
Sibling	1 (1.5%)
Other	4 (6.1%)
Lung Cancer N (%)	
Small Cell	11 (16.7%)
Non-small cell	55 (83.3%)

Table 2

Radiographic findings, treatment characteristics, and functional levels of participants with scans showing brain metastases

	Scans linked to AM-PAC-CAT scores
	N = 96
Number of Mets	
1–2	37 (38.5%)
3–5	26 (27.1%)
6	33 (34.4%)
Actual Number of Mets	
Mean (SD)	3.0 (2.1)
Frontal Lobe	68 (70.8%)
Parietal Lobe	56 (58.3%)
Temporal Lobe	44 (45.8%)
Occipital Lobe	34 (35.4%)
Cerebellum	50 (52.1%)
Brainstem	14 (14.6%)
Basal ganglia and thalamus	13 (14%)
Hemisphere	
N/A	8 (8.3%)
Right	11 (11.5%)
Left	23 (24.0%)
Bilateral	54 (56.3%)
Diameter of Largest Met	
Mean (SD) cm	1.6 (1.1)
Symptomatic Brain Mets	
Unknown	7 (7.3%)
No	29 (30.2%)
Yes	60 (62.5%)
Progression of Brain Mets	
Initial Diagnosis	38 (39.6%)
Expanding	28 (29.2%)
New Site(s)	8 (8.3%)
Expanding + New	22 (22.9%)
Gamma Knife	28 (29.2%)
Craniotomy	6 (6.3%)
Observation	36 (37.5%)
VVBRT	29 (30.2%)

Table 3

Results of uni- and multivariate explanatory models

Variable	Coefficient	Robust Standard Error	p value	95% confidence interval	
				Lower bound	Upper bound
Univariate models					
Demographics					
Gender (male comparator)	0.83	1.04	0.423	-1.20	2.87
Clinical characteristics					
Musculoskeletal and connective tissue disorder	-1.76	1.17	0.132	-4.04	0.53
Neurological condition	2.70	2.34	0.248	-1.89	7.29
Chronic obstructive pulmonary disease	-0.92	1.26	0.466	-3.40	1.56
Coronary artery disease	2.53	2.40	0.292	-2.18	7.25
NSCLC (SCLC comparator)	-0.55	1.49	0.714	-3.48	2.38
Symptomatic brain metastases [†]	-2.48	0.99	0.012	-4.43	-0.54
Neuroradiographic characteristics					
Diameter of largest metastasis (cm)	-0.67	0.53	0.202	-1.70	0.36
Number of metastases					
1-2 [*]					
3-5	0.26	1.17	0.826	-2.04	2.56
innumerable	-1.83	1.16	0.114	-4.11	0.44
Location					
Brain stem	-3.14	1.47	0.033	-6.03	-0.26
Cerebellum	-2.87	1.00	0.004	-4.84	-0.91
Frontal lobe	-0.05	1.13	0.965	-2.26	2.16
Parietal lobe	-0.72	1.01	0.479	-2.70	1.27
Temporal lobe	-1.40	1.01	0.164	-3.38	0.57
Basal ganglia & thalamus	0.93	1.45	0.52	-1.92	3.77
Occipital lobe	-0.40	1.05	0.704	-2.46	1.66
Hemisphere					
Left [*]					
Right	-0.45	1.56	0.77	-3.51	2.61
Bilateral	-2.13	1.45	0.14	-4.97	0.71

Variable	Coefficient	Robust Standard Error	p value	95% confidence interval	
				Lower bound	Upper bound
Progression					
Expansion	2.14	0.99	0.031	0.20	4.08
Expansion + new site(s)	-2.64	1.14	0.02	-4.87	-0.42
New site(s)	1.58	1.75	0.367	-1.85	5.01
Initial diagnosis	-0.65	1.14	0.568	-2.89	1.59
Treatment					
Stereotactic radiotherapy	1.63	1.10	0.139	-0.53	3.78
Craniotomy	-0.81	2.16	0.708	-5.05	3.43
WBRT	-4.55	1.12	<0.001	-6.74	-2.36
Observation	2.40	1.04	0.02	0.37	4.43
Multivariate model					
Cerebellar metastasis	-1.77	0.94	0.059	-3.61	0.06
Expansion + New site(s) detected	-2.04	1.08	0.059	-4.15	0.08
WBRT	-4.05	1.11	<0.001	-6.24	-1.87

* Comparator 1–2 metastases

Table 4

Results of univariate predictive models

Covariate	2.5			5.0			7.5			10		
	Coefficient	Robust SE	P value	Coefficient	Robust SE	P value	Coefficient	Robust SE	P value	Coefficient	Robust SE	P value
Number of metastases*												
3–5	1.39	0.53	0.386	1.68	0.76	0.249	0.94	0.64	0.925	0.93	0.66	0.924
6	2.32	0.84	0.020	1.96	0.87	0.127	2.08	1.34	0.252	1.84	1.11	0.311
Diameter of largest metastasis	1.39	0.16	0.015	1.36	0.24	0.074	1.81	0.43	0.013	1.62	0.33	0.020
Cerebellar/Brain stem location	2.32	0.24	0.008	2.79	1.19	0.016	3.51	2.61	0.091	3.27	2.36	0.101
Bilateral†	2.00	0.67	0.039	2.29	1.12	0.089	3.73	2.76	0.075	4.34	3.80	0.093
Treated with:												
Craniotomy	1.59	1.00	0.462	2.37	1.77	0.246	7.30	7.53	0.054	4.21	3.12	0.052
WBRT	2.59	0.86	0.004	2.56	1.08	0.026	5.35	3.40	0.008	4.44	2.48	0.007
Observation	0.44	0.14	0.010	0.40	0.16	0.020	0.26	0.17	0.038	0.28	0.19	0.066
Scan to evaluate a symptom(s) or sign(s)	1.96	0.62	0.032	2.03	0.80	0.075	4.13	2.94	0.047	3.29	1.98	0.047
Pattern of new and expanding metastases	1.92	0.65	0.052	2.51	1.05	0.029	2.40	1.41	0.135	1.68	0.99	0.381
Worst pain NRS	1.09	0.05	0.065	1.07	0.06	0.224	1.12	0.08	0.129	1.14	0.09	0.100

Table 5

Results of multivariate predictive models

Covariate	Coeff.	2.5				Robust Variance Estimates			
		OIM*	p value	Boot-strap	p value	Jack-knife	p value		
Diameter of largest met	1.66	0.28	0.003	0.26	0.001	0.2807	0.004		
WBRT	2.39	0.85	0.014	0.84	0.013	0.9149	0.026		
Cerebellar and/or Brainstem met	2.07	0.74	0.042	0.77	0.051	0.6604	0.026		
Expanding + New sites	1.76	0.65	0.124	0.66	0.131	0.6394	0.125		
Worst Pain	1.12	0.06	0.040	0.07	0.075	0.0671	0.071		
C statistic, (bootstrap 95% CI)				0.75 (0.67 – 0.82)					
		5.0							
Diameter of largest met	1.58	0.30	0.016	0.259	0.005	0.3061	0.021		
WBRT	2.19	0.89	0.055	1.0799	0.112	1.0972	0.123		
Cerebellar and/or Brainstem met	2.38	1.04	0.048	1.2236	0.092	1.3285	0.126		
Expanding + New sites	2.45	1.07	0.041	1.6188	0.176	1.4238	0.129		
Worst Pain	1.08	0.07	0.221	0.1065	0.444	0.0856	0.345		
C statistic, (bootstrap 95% CI)				0.77 (0.67 – 0.84)					
		7.5							
Diameter of largest met	2.23	0.53	0.001	0.7153	0.012	0.613	0.005		
WBRT	3.93	1.95	0.006	2.9758	0.07	2.7786	0.057		
Cerebellar and/or Brainstem met	1.88	1.06	0.259	1.8293	0.514	1.4871	0.425		
Expanding + New sites	3.45	1.85	0.021	2.9356	0.145	2.3222	0.07		
Worst Pain	1.15	0.09	0.066	0.1518	0.278	0.1159	0.16		
C statistic, (bootstrap 95% CI)				0.83 (0.68 – 0.90)					
		10							
Diameter of largest met	1.96	0.48	0.006	0.6104	0.031	0.508	0.012		
WBRT	3.69	2.01	0.017	2.1764	0.027	2.3426	0.044		
Cerebellar and/or Brainstem met	2.72	1.79	0.128	3.0791	0.376	1.9453	0.165		
Expanding + New sites	1.69	1.04	0.392	1.17	0.447	1.1186	0.429		

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Covariate	Coeff.	Robust Variance Estimates				
		OIM [*]	p value	Boot-strap	p value	Jack-knife
Worst Pain	1.19	0.10	0.034	0.1725	0.225	0.1442
C statistic, (bootstrap 95% CI)				0.8 (0.65 – 0.90)		

* Observed Information Matrix