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Clinical manifestations and location of brain metastases as prognostic markers

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A B S T R A C T

Background: Brain metastases (BM) are a frequent complication of cancer and are regularly seen in clinical practice. New treatment modalities are improving survival after diagnosis of BM. However, symptoms are rarely reported and their significance is not well established. The aim of the present study was to investigate neurologic indicators as prognostic markers in patients with brain metastases.
Patients and methods: A prospectively acquired database from 2 referral centers was analyzed. All patients had had at least 2 neuro-oncologic consultations and magnetic resonance imaging to confirm the diagnosis. Patients were classified according to universally used prognostic scores, gender, primary tumor, localization of BM, and clinical complaints. Univariate and multivariate analysis was used to evaluate associations.
Results: A total of 570 patients were included; 71% were female, and 91% had solid tumors. Median survival was 11 months (95% confidence interval 9.4-12.6). Of 1322 parenchymal lesions, 78% were supratentorial, and were most commonly in the frontal lobe. The most common symptoms were headache, vision changes, and weakness. Brain metastases in the brainstem were associated with a worse prognosis ($P = 0.04$). Visual complaints ($P = 0.005$), altered mental status, ($P < 0.0001$) and cranial neuropathy

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(*P* 0.001) were also associated with a poor outcome, as were poor performance status, more than 1 brain metastases, meningeal carcinomatosis, and uncontrolled primary cancer.
Conclusions: Both presenting symptoms and the location of brain metastases have prognostic significance and should be further studied, both as independent prognostic predictors and in conjunction with other factors used in prognostic scores.

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Introduction

Metastatic spread of cancer, particularly to the central nervous system, is a feared and often devastating complication.[1,2] Metastases to the brain are 10 times more frequent than are primary brain tumors in adults.[3] Estimates of the incidence of brain metastases (BM) vary widely, from 10%-40%, depending on the data source and the primary cancer site.[4,5] Lung and breast cancers are the most common malignancies associated with BMs, followed by melanoma, renal, colorectal, and germ cell malignancies.[4] Patients diagnosed with BM and treated only with steroids survive 1-2 months.[6] In the 1980s, median survival (MS) after the diagnosis of BM was 3.7 months[7]; in the 1990s it was reported as 2.85-5 months.[8] Late in the 1990s, the Radiation Therapy Oncology Group performed recursive partitioning analysis (RPA)[1] to develop a classification of BMs. In this system, MS ranges from 7.1 (RPA class 1) to 2.3 for the worst class (RPA III). In the 2000s, the MS was 5 months, with fewer than 6% of patients surviving more than 24 months.[9,10] Surgery followed by whole brain radiotherapy (WBRT) was considered the standard treatment for single BMs.[11] Stereotactic radiosurgery (SRS) has been increasingly used for patients with oligometastatic disease,[12] with MS after treatment ranging from 6-12 months.[6,13] Studies comparing surgery and SRS report similar outcomes. However, these studies were not randomized, and the results might have been affected by selection bias.[14] WBRT after surgery vs SRS is currently under investigation[15], although several well-designed randomized studies have already shown that stereotactic radiosurgery might be a suitable alternative for patients with up to 10 brain metastases.[16] For now, the choice of therapy should be individually tailored. According to the clinical manifestations, the most frequently reported in the literature were headache, motor weakness, decreased awareness, seizures, visual impairment, and cerebellar dysfunction.[17-19] The most common location of brain metastases described were supratentorial (frontal lobe [FL], followed by parietal lobe, and occipital lobe [OL]) and infratentorial (cerebellum).[20,21] Nevertheless, there is little information on how clinical manifestations and the precise location of BMs affect outcome. We designed this study to investigate the association between those 2 factors and outcome.

Material and methods

From January 2010-2017, data from patients seen at a neuro-oncologic clinic after referral from an oncology or neurology center were included in a database. Demographic, oncologic data, signs and symptoms, location of BMs, and prognostic information were collected and analyzed. All patients had at least 1 magnetic resonance imaging study (MRI) to confirm the diagnosis of BM. For the purpose of this study, urologic malignancies included testicular, prostate, and renal cancers. Synchronous cancer was defined in patients presenting with BM who had 2 primary cancers, for example, breast and lung cancer. Neoplastic meningitis diagnosis was made based on MRI and confirmed with cerebrospinal fluid analysis. Patients were also classi-

Table 1
Characteristics of patients with central nervous system metastases (CNSm) with a comparison between sexes.

	Female (n = 405)	Male (n = 165)	Total (n = 570)	
Age at diagnosis of cancer, mean ± SD (years)	49 ± 12	47 ± 17	48 ± 14	p NS
Age at diagnosis of CNSm, mean ± SD* (years)	51 ± 12	48 ± 17	50 ± 14	p NS
KPS, mean ± SD	70 ± 20	70 ± 20	70 ± 20	
KPS ≥ 70, n (%)	266 (66)	94 (57)	360 (63)	p NS
KPS < 70, n (%)	139 (34)	71 (43)	210 (37)	
Median overall survival (95% CI), months	12 (10–13.9)	7 (5.2–8.8)	11 (9.4–12.6)	p 0.025
Primary cancer site, n (%)				**Median OS, months (95% CI)**
– Breast	203 (50)	1 (0.6)	204 (36)	12 (9.4–14.6)
– Lung	75 (19)	45 (27)	120 (21)	14 (11.1–16.6)
– Gynecologic	53 (13)	-	53 (9)	
◦ *Ovarian*	18 (4)	-	18 (3)	15 (2.5–27.5)
◦ *Cervix uteri*	24 (6)	-	24 (4)	7 (2.2–11.8)
◦ *Other*	11 (3)	-	11 (2)	4 (0.7–7.2)
– Hematologic	27 (7)	25 (15)	52 (9)	12 (6.6–17.4)
– Head and neck	13 (3)	19 (12)	32 (6)	8 (5.3–10.8)
Thyroid	2 (0.5)	5 (3)	7 (1)	6 (0–18.8)
– Sarcoma	2 (0.5)	1 (0.6)	3 (0.5)	8 (–)
– Urologic	7 (2)	45 (27)	52 (9)	7 (4.3–9.7)
– Skin/melanoma	13 (3)	8 (5)	21 (4)	6 (1.6–10.4)
– Gastrointestinal	4 (1)	10 (6)	14 (3)	3 (1.8–4.2)
– Synchronous	3 (0.7)	1 (0.6)	4 (0.7)	15 (2.3–27.7)
– Other	3 (0.7)	4 (3)	7 (1)	5 (1.2–8.8)
Therapeutic line				
Before first-line treatment, n (%)°	76 (19)	44 (27)	120 (21)	19 (15.1–22.9)
During first-line treatment, n (%)	148 (36)	74 (45)	222 (39)	9 (6.5–11.5)
During second-line treatment, n (%)	93 (23)	37 (22)	130 (23)	8 (5.8–10.2)
After third-line treatment, n (%)	88 (22)	10 (6)	98 (17)	8 (5.1–10.9)
Localization of CNSm°				
Supratentorial only	189 (47)	93 (56)	282 (50)	12 (8.9–15.1)
Infratentorial only	29 (7)	15 (9)	44 (8)	12 (7.9–16.1)
Both	127 (31)	21 (19)	158 (28)	12 (9.7–14.3)
Carcinomatosis only	61 (15)	27 (16)	88 (15)	4 (2.3–5.6)

* SD, standard deviation.
° $P < 0.001$

fied by RPA,[1] in which a lower score is associated with better survival, and the Graded Prognostic Assessment (GPA),[2] including the individualized GPA (iGPA),[22] where a higher score is associated with a better survival. Kaplan-Meier curves with log-rank analysis were used to compare survival. T and Mann-Whitney U tests were used to compare continuous variables with or without a normal distribution. ANOVA and Tukey correction were used to analyze more than 3 variables. Relative risk (RR) with 95% confidence interval (CI) was calculated to assess prognostic associations. A P value < 0.05 was considered statistically significant. The study did not raise ethical concerns and was approved by the IRB (Ethics and Scientific Investigation Committees).

Results

Records of a total of 570 patients with BM were included, of whom 405 were women (71%). The mean age at the time of cancer diagnosis was 48 years (range 17-85), and the mean age at the time of BM diagnosis was 50 years (range 17-85) (Table 1).

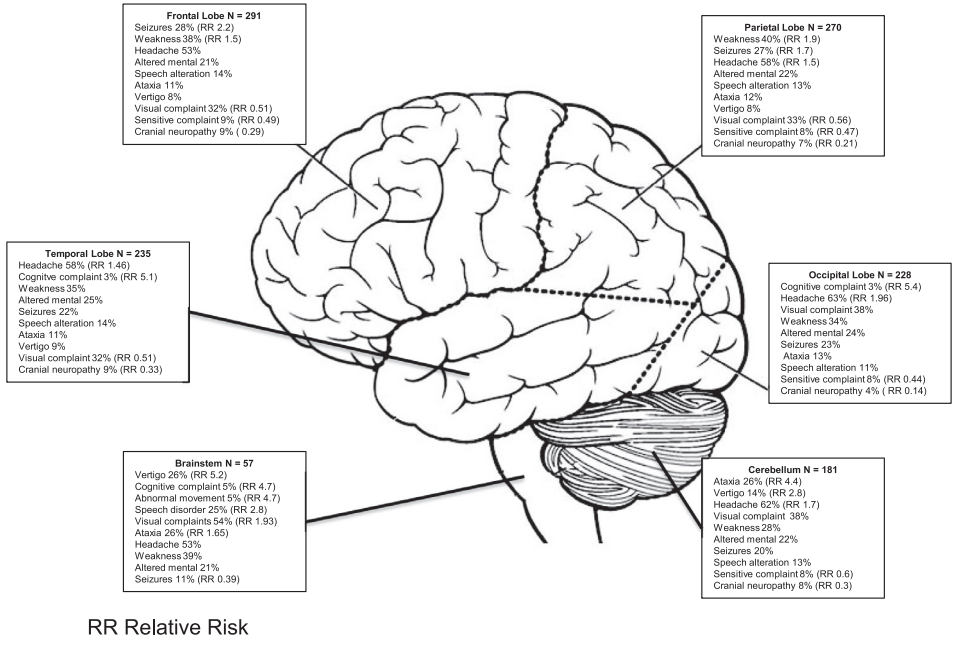


Fig. 1. Clinical symptoms according to brain metastases localization.

Location

BMs were more frequently parenchymal and supratentorial (n = 440, 78%); infratentorial lesions were seen in 202 patients, and 158 (28%) had both supra- and infratentorial metastases (Table 2). The most common primary cancer sites metastasizing to infratentorial structures were breast (n = 99), lung (n = 51), gynecologic (n = 15), and urologic (n = 13). Other primary cancers such as cervix uteri, thyroid, and sarcoma, were also included. A primary site of cancer could not be found in only 3 patients (0.7%). Skull base lesions affecting the brain were seen in 23 and cavernous sinus metastases in 37. We did not include lesions of the skull only. The median survival (MS) was higher in patients with OL metastases, although not significantly so, and worse for those with brainstem lesions. Meningeal carcinomatosis was seen in 107 (19%) patients, of whom 88 (82%) had no parenchymal BMs and 19 (18%) had both parenchymal and meningeal tumor activity. Carcinomatosis was more frequently associated with breast (n = 47), hematologic (n = 36), lung (n = 9), gastrointestinal (n = 4), cervico-uterine (n = 3), and urologic (n = 3) malignancies. Table 2 and Fig. 1 describe the relationship between symptoms and BM location. The *FL* was affected in 291 patients. Symptoms positively associated with this location were seizures in 28% (RR 2.2, 95% CI 1.5-3.4, $P < 0.001$) and focal motor weakness in 38% (RR 1.5, 95% CI 1.05-2.12, $P = 0.016$). Symptoms unlikely to be associated with FL lesions included vision changes in 32%, (RR 0.51, 95% CI 0.36-0.71, $P < 0.001$), sensory complaints in 9% (RR 0.49, 95% CI 0.29-0.82, $P = 0.004$), and cranial neuropathy in 9% (RR 0.29, 95% CI 0.18-0.47, $P < 0.001$). The *parietal lobe* was affected in 270 patients, with the following associated symptoms: focal weakness in 40% (RR 1.86, 95% CI 1.3-2.6, $P < 0.001$), seizures in 27% (RR 1.7, 95% CI 1.16-2.6, $P = 0.005$), and headache in 58% (RR 1.46, 95% CI 1.05-2.04, $P = 0.015$). Negatively associated symptoms included visual complaints in 33%, (RR 0.56, 95% CI 0.4-0.8, $P < 0.001$), sensory complaints in 8% (RR 0.47, 95% CI 0.27-0.79, $P = 0.003$), and cranial neuropathy in 7% (RR 0.21, 95% CI 0.12-0.36, $P < 0.001$). The *temporal lobe* was affected by metastases in 235 patients, with positively associated complaints including headache in 58% (RR 1.46, 95% CI 1.04-

Table 2
Comparison between clinical symptoms and localization with the outcome according to the symptom.

Symptom/sign	Localization						Median OS, months (95% CI)	*P*
	Frontal	Temporal	Parietal	Occipital	Cerebellar	Brainstem		
Headache								
Yes, 301 (53%)	155	137*	156*	143*	112*	30	11 (8.8–13.2)	0.54
No, 269							9 (6.7–11.3)	
Visual symptoms/diplopia								
Yes, 227 (40%)	93*	81*	88*	86	68	31*	7 (5.1–8.9)	0.005
No, 343							12 (9.9–14)	
Weakness								
Yes, 189 (33%)	109*	82	109*	77	51	22	9 (6.1–11.9)	0.17
No, 381							12 (10–13.9)	
Sensitive complaint								
Yes, 70 (12%)	25*	22*	22*	17*	15*	8	7 (4.5–9.5)	0.07
No, 500							12 (10.2–13.8)	
Cranial neuropathy								
Yes, 94 (17%)	25*	20*	18*	10*	14*	11	5 (3.5–6.5)	0.001
No, 476							12 (10.2–13.8)	
Altered mental state								
Yes, 125 (22%)	61	59	60	54	39	12	5 (2.9–7.1)	<0.001
No, 445							12 (10.1–13.9)	
Seizure								
Yes, 124 (22%)	82*	52	72*	53	36	6*	9 (5.5–12.5)	0.46
No, 446							11 (9.2–12.8)	
Ataxia								
Yes, 76 (13%)	33	25	31	30	47*	15*	10 (6.2–13.8)	0.3
No, 494							11 (9.2–12.8)	
Altered speech								
Yes, 68 (12%)	41	30	35	25	23	14*	12 (5.2–18.8)	0.4
No, 502							11 (9.4–12.6)	
Vertigo								
Yes, 48 (8%)	23	22	22	22	26*	15*	17 (8.3–25.7)	0.06
No, 522							10 (8.2–11.8)	
Abnormal movement								
Yes, 9 (2%)	6	4	7	6	5	3	7 (4.1–9.9)	0.13
No, 561							11 (9.4–12.7)	
Cognitive complaint								
Yes, 9 (2%)	6	7*	6	7	4	3	7 (1.5–12.5)	0.13
No, 561							11 (9.3–12.7)	
Total	291 (51%)	235 (41%)	270 (47%)	228 (40%)	181 (32%)	57 (10%)		
Median OS, months (95% CI)	11 (8.8–13.2)	11 (9–12.9)	12 (10.1–13.9)	13 (11–14.9)	12 (9.9–14)	8 (4.4–11.7)	11 (9.4–12.6)	
P	0.48	0.8	0.3	0.8	0.4	0.04		

* $P < 0.05$.

2.04, $P = 0.017$) and cognitive complaints in 3% (RR 5.1, 95% CI 1.05-24.8, $P = 0.03$). Negatively associated symptoms were visual complaints in 35%, (RR 0.68, 95% CI 0.48-0.96, $P = 0.018$) and cranial neuropathy in 9% (RR 0.33, 95% CI 0.19-0.56, $P < 0.001$). *OL* metastases were seen in 228 patients, with positively associated symptoms of cognitive complaints in 3% (RR 5.4, 95% CI 1.1-26.2. $P = 0.024$) and headache in 63% (RR 1.96, 95% CI 1.4-2.8, $P < 0.001$) and negatively associated sensory complaints in 8% (RR 0.44, 95% CI 0.25-0.78. $P = 0.003$) and cranial neuropathy in 4% (RR 0.14, 95% CI 0.071-0.27, $P < 0.001$). *Cerebellar* metastases occurred in 181 patients, with positively associated symptoms of ataxia in 26% (RR 4.4, 95% CI 2.6-7.2, $P < 0.001$), vertigo in 14% (RR 2.8, 95% CI 1.5-5.1, $P < 0.001$), and headache in 62% (RR 1.7, 95% CI 1.2-2.5, $P = 0.002$). Less likely symptoms included sensory complaints in 8% (RR 0.55, 95% CI 0.3-0.99, $P = 0.03$) and cranial neuropathy in 8% (RR 0.3, 95% CI 0.2-0.6, $P < 0.001$). *Brainstem* metastases were seen in 57 patients, with positively associated symptoms of vertigo in 26% (RR 5.2, 95% CI 2.6-10.3, $P < 0.001$), cognitive complaints in 5% (RR 4.7, 95% CI 1.2-19.3, $P = 0.048$), abnormal movements in 5% (RR 4.7, 95% CI 1.2-19.3, $P = 0.048$), speech problems in 25% (RR 2.77, 95% CI 1.4-5.4, $P = 0.004$), visual complaints in 54% (RR 1.93, 95% CI 1.12-3.35, $P = 0.014$), and ataxia in 26% (RR 1.65, 95% CI 1.4-5.1, $P = 0.004$). Seizures, seen in 11%, were negatively associated with this location (RR 0.39, 95% CI 0.16-0.94, $P = 0.018$). Patients with BM in the brainstem had a significantly worse MS (12.7 vs 29.7 months, $P = 0.04$) than did patients without brainstem involvement.

Symptoms

Symptoms that led to the diagnosis of BM are shown in Table 2. The majority of patients had more than 1 symptom. The most common complaints were headache, visual defect or diplopia, localized weakness, altered mental status, and seizures. BMs most commonly associated with seizures originated from endometrial (46%), melanoma (38%), sarcomas (33%), urologic (29%), cervico-uterine (25%), and lung (23%) cancers. BMs most commonly associated with altered mental status were endometrial (46%), skin (33%), ovarian (33%), gastrointestinal (29%), breast (23%), and hematologic (21%). MSs were significantly worse for those with cranial neuropathy ($P = 0.001$), vision changes ($P = 0.005$), and altered mental status ($P < 0.001$) (Table 2). Fig. 2 describes the most important associations found. *Headache* was reported in 301 patients, 32% had BMs; multivariate analysis showed a significant association between headache and occipital ($P < 0.001$), cerebellum ($P = 0.003$), parietal ($P = 0.024$), and temporal ($P = 0.028$) lobe lesions. *Visual complaints* were reported by 227 patients, multivariate analysis showed a significant relationship with frontal ($P < 0.001$), parietal ($P = 0.001$), brainstem ($P = 0.018$), and temporal ($P = 0.029$) lobe lesions. *Focal motor weakness* was reported in 189 patients, multivariate analysis showed a significant relationship between weakness and parietal ($P < 0.001$) and frontal ($P = 0.026$) lobe BMs. *Altered metal status or a decreased level of consciousness* was reported in 125 patients, multivariate analysis showed no significant relationship between altered metal status and specific BM locations. *Seizures* were seen in 124 patients, multivariate analysis showed a significant relationship between seizures and BMs located in the frontal ($P < 0.001$) and parietal ($P = 0.007$) lobes and the brainstem ($P = 0.030$). *Cranial neuropathy* was found in 94 patients, multivariate analysis showed a significant relationship between cranial neuropathy and BMs in the frontal, temporal, parietal, OL and the cerebellum ($P < 0.001$). *Ataxia* occurred in 76 patients, multivariate analysis showed a significant relationship between ataxia and BMs in the cerebellum ($P < 0.001$) and brainstem ($P = 0.002$). *Sensory complaints* were described by 70 patients, multivariate analysis showed a significant relationship between sensory complaints and BMs in the parietal ($P = 0.004$), occipital ($P = 0.004$), frontal ($P = 0.006$) lobes, and the cerebellum (0.048). Dysarthria was found in 68 patients and was significantly associated with BMs in the brainstem ($P = 0.002$). *Vertigo* was reported in 48 patients and was significantly associated with BMs in the cerebellum ($P < 0.001$) and brainstem ($P < 0.001$). Among patients with solid tumors, 85% had metastases at sites other than the central nervous system (Table 3).

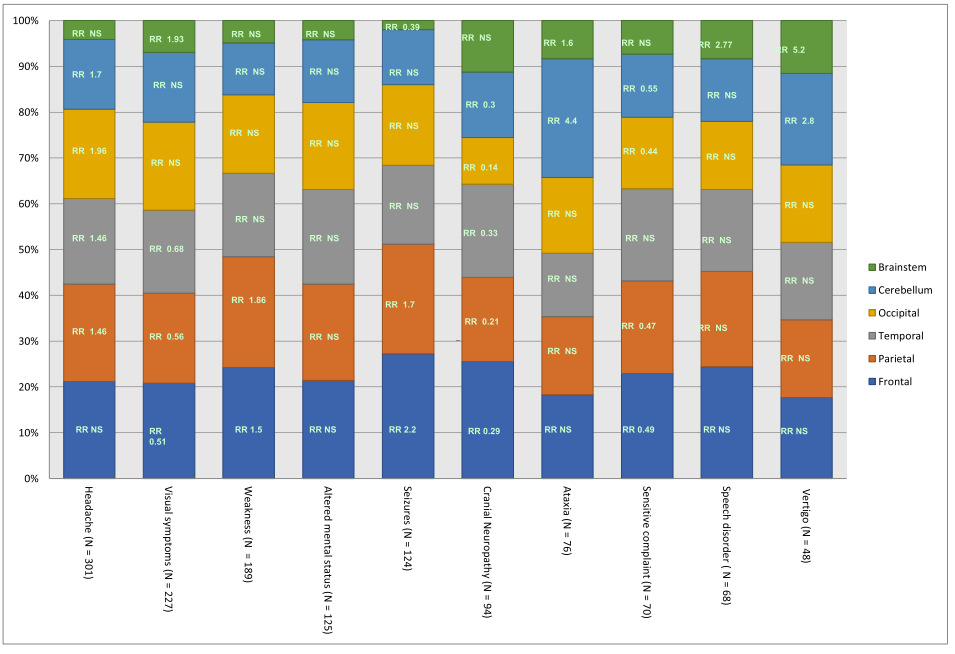
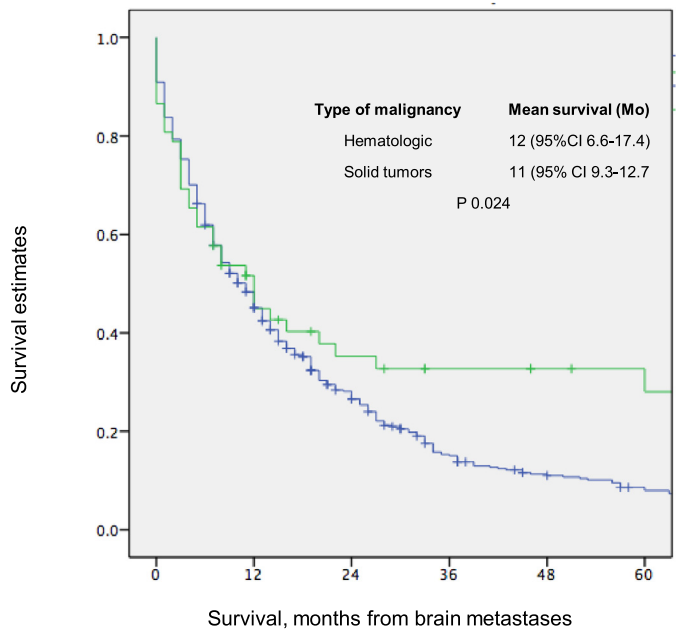


Fig. 2. Localization according to clinical symptoms.

Table 3
Comparison of OS among patients with solid and hematologic tumors.

	Solid tumors		Hematologic tumors		Total		*P*
	n	Median OS, months	n	Median OS, months	n	Median OS, months	
RPA							
I	35	238	12	-	47	238	<0.001
II	291	14	21	11	312	14	
III	192	5	19	5	211	5	
KPS							
<70	191	5	19	5	210	5	0.026
≥70	327	15	33	20	360	15	
ECOG							
1	249	17	27	27	276	18	0.039
2	156	8	13	7	169	8	
3	83	3	9	5	92	3	
4	30	2	3	3	33	2	
At the time of cancer diagnosis	111	17	9	*	120	19	0.09
During first line of treatment	192	9	30	7	222	9	
During second line of treatment	118	8	12	7	130	8	
≥Third line of treatment	97	8	1	14	98	8	
Parenchymal	447	12	16	*	463	12	<0.001
Carcinomatosis	56	2	32	7	88	3	
Both	15	4	4	*	19	6	
Systemic disease	440	10	28	5	468	10	<0.001
Lung metastases	208	9	7	7	215	8	0.014
Bone metastases	218	12	7	7	225	12	0.42
Liver metastases	136	8	2	5	138	8	0.04
Total	*518*	*11 (96% CI 9.3–12.7)*	*52*	*12 (95% CI 6.6–17.4)*	*570*	*11 (95% CI 9.4–12.6)*	*0.024*

* Patients were still alive after 32 months of follow-up.



	0 mo	12 mo	24 mo	36 mo	48 mo	60 mo
Solid Tumors	518	241	124	61	39	27
Hematologic	52	23	14	10	8	7

Fig. 3. Comparison of survival between hematologic and solid tumors with brain metastases.

The present study included both solid and hematologic tumors, but we analyzed them as different groups; MS was 11 months (95% CI 9.3-12.7) for solid tumors and 12 (95% CI 6.6-17.4) for hematologic malignancies ($P = 0.024$) (Fig. 3). Many inconsistencies were found when solid and hematologic tumors were compared.

A better MS was seen in patients with BM detected at the time of cancer diagnosis, as well as patients with solid tumors who had single metastases compared with those with multiple metastases ($P < 0.001$).

Treatment modalities for BM included WBRT in 95%, systemic chemotherapy in 14%, intrathecal chemotherapy in 9%, surgical resection in 8%, and radiosurgery in 3%. In 26% of patients, initial management included combined treatment modalities. Of the 181 patients with a single type of treatment, 96% had WBRT, 22% surgery, and 6% SRS.

RPA and GPA were helpful tools for estimating survival in our patients, for both solid and hematologic tumors (Table 4). The same was true for iGPA, except for the groups with a small number of patients ($n < 10$).

Discussion

The frequency of patients with BMs is increasing. Current care involves radiotherapy (SRS or WBRT) and/or surgery when indicated, with or without systemic chemotherapy.[8,23] Survival of patients with BMs has increased due to new diagnostic and treatment options,[24] although these might not be available in all centers around the world.

It has been reported that over three-quarters of parenchymal BMs were supratentorial (78%), with half in the frontal lobe, similar to our results.[1,25,26]. A single metastasis was found in about

Table 4
Individualized Graded Prognostic Assessment in patients with brain metastases.

	Median OS, months (95% CI)	*P*
Lung GPA		
0, 0.5-1 (n = 46)	12 (8.3-15.7)	0.005
1.5-2 (n = 50)	12 (8.2-15.8)	
2.5-3 (n = 23)	24 (16.3-31.7)	
3.5-4 (n = 4)	37 (11.5-62.5)	
Breast GPA		
0, 0.5-1 (n = 29)	4 (1.4-6.6)	0.001
1.5-2 (n = 73)	8 (2.1-13.9)	
2.5-3 (n = 78)	15 (9.9-20)	
3.5-4 (n = 25)	20 (5.5-34.5)	
Melanoma GPA		
0, 0.5-1 (n = 7)	0	0.016
1.5-2 (n = 9)	6 (0.16-11.8)	
2.5-3 (n = 2)	6	
3.5-4 (n = 2)	16	
Renal GPA		
0, 0.5-1 (n = 8)	4 (0-8.1)	0.12
1.5-2 (n = 6)	3 (0-7.8)	
2.5-3 (n = 2)	27	
3.5-4 (n = 1)	13	

one-third of patients, probably because BMs were diagnosed in all our patients by MRI. Having a single BM vs multiple BMs in solid cancer remains a helpful prognostic indicator.[1,14] The MS for patients with solid tumors who had single metastases was better than for those with multiple metastases ($P < 0.001$) but worse than for those with hematologic tumors ($P < 0.001$). After reviewing and comparing the outcomes,[8,9,13,27,28] we emphasize the fact that solid and hematologic tumors should be addressed separately in clinical trials as well as in management guidelines since there have different biology and prognosis.

Among notable observations in our study, we found that patients who had BM as the initial manifestation of their systemic cancer or occurring during initial treatment of their malignancy had better survival.[29] A better MS was found for BMs from hematologic cancers, as mentioned above, followed by endometrial, ovarian, lung, and head and neck tumors.

In our cohort, BMs were found more frequently with breast cancer, followed by lung, gynecologic, and urologic cancer. We compared this findings with some series.[10,30] The difference with some reports[1,2,9] may relate to selection bias, since we only included patients referred to neuro-oncologists. Rare primary cancers metastatic to the brain were also included, such as the cervix uteri, thyroid, and sarcoma.[31,32]

Breast cancer is the most common malignancy in women; 15%-20% of patients with this cancer develop BMs. In our centers, patients with breast cancer metastatic to the brain had an MS of 12 months (95% CI 9.4-14.6), similar to others.[27,33,34] Patients with BMs from lung cancer are the group most often reported in the medical literature, as almost half suffer from BM during their disease. Small-cell lung cancer metastasizes to the brain more frequently than nonsmall-cell lung cancer,[35] contrary to the findings in our study, probably because the majority our patients with small-cell cancer had prophylactic cranial irradiation. The MS of patients in our study with melanoma metastatic to the brain was 6 months (95% CI 1.6-10.4).[25,27]

According to the symptoms worse prognosis was seen in patients with vision changes (including diplopia), sensory complaints, cranial neuropathy, and altered mental status. To our knowledge, there are few studies investigating the prognostic significance of particular symptoms in patients with BM. Headache in patients with cancer is considered a red flag, as 30% of patients with cancer and headache have been found to have BMs.[24,36] In our study, 53% of patients with BMs had headache. We reviewed the last 1000 patients with can-

cer referred to our neuro-oncology units for evaluation of headache and who had at least 1 MRI, finding that 32% had BMs, while 68% did not. Therefore, a careful history, physical examination, and proper imaging studies remain the most important aspects of headache assessment.[37]

A worse prognosis was seen in patients with a poor performance status, multiple BMs, meningeal carcinomatosis, systemic disease, lung metastases, BMs in the brainstem, cranial neuropathy, vision changes, a high RPA, or a low GPA.[38,39] A better outcome was seen in patients whose cancer was diagnosed after they initially presented with BM, whose BMs were diagnosed on routine surveillance after cancer treatment, or who had a low RPA and a high GPA. Nearly half (264, 46%) of our patients had chronic brain metastases (ie, living $\geq$ 1 year after diagnosis of BM), with similar percentages for both solid tumors (n 241, 46.5%) and hematologic malignancies (n 23, 44%). It should be noted that our population consisted mainly of Hispanic patients, a population that is underrepresented in the literature.[25,40,41] It is beyond the scope of this study to determine whether Hispanic patients with BMs survive longer than those of other ethnicities. As this was a retrospective, multicenter observational study, the possibility of bias in selection and referral should be taken into account. Although some have postulated that a total brain metastasis volume is more predictive than the number of tumors[42] we used the first for the purpose of the study. Multicenter, multiethnic studies are encouraged to confirm our findings.

Conclusions

BMs are associated with significant morbidity and mortality. Advances in understanding their biology, early detection and management, and new treatment modalities have been shown to improve survival of patients with BMs. RPA, GPA, and iGPA are helpful tools in predicting outcomes. Our study confirmed that (1) certain symptoms (altered mental state, visual symptoms, and cranial neuropathy), and (2) the location (brainstem) have prognostic implications. Also, we shown others prognostic factors like: (3) number (single vs multiple) of BMs, (4) the timing of BM diagnosis (at the time of cancer diagnosis), and (5) the presence of metastatic disease in other locations.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2018.06.002.

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