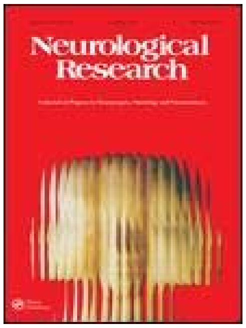

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Original Research Paper

Factors associated with survival and recurrence for patients undergoing surgery of cerebellar metastases

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Objective: Patients with cerebellar and non-cerebellar metastases are often included in the same study population, even though posterior fossa lesions typically have different presenting symptoms, clinical outcomes, and complications. This is because the outcomes for patients with cerebellar metastases are unclear.

Methods: Adult patients who underwent surgery for an intracranial metastasis (single or multiple) between 2007 and 2011 were retrospectively reviewed. Stepwise multivariate proportional hazards regression analysis was used to identify an association between cerebellar location with survival and recurrence.

Results: Of the 708 patients who underwent intracranial metastatic surgery, 140 (19.8%) had surgery for cerebellar metastasis. A cerebellar location was associated with poorer survival [RR (95% CI); 1.231 (1.016–1.523), $P = 0.04$] and increased spinal recurrence [RR (95% CI); 2.895 (1.491–5.409), $P = 0.002$], but not local ($P = 0.61$) or distal recurrence ($P = 0.88$). The factors independently associated with prolonged survival for patients with cerebellar metastases were: decreasing number of intracranial metastases ($P = 0.0002$), decreasing tumor size ($P = 0.002$), and radiation ($P = 0.0006$). The factors associated with prolonged local progression free survival were: decreasing tumor size ($P = 0.0009$), non small cell lung cancer (NSCLC) ($P = 0.006$), non-bladder cancer ($P = 0.0005$), and post-operative radiation therapy ($P = 0.02$). The factors independently associated with prolonged distal progression free survival were: age > 40 years ($P = 0.02$), surgical resection ($P = 0.01$), and whole brain radiation (WBRT) therapy ($P = 0.02$).

Discussion: Patients with cerebellar metastases have more distinct clinical presentations and outcomes than patients with non-cerebellar lesions. The findings of this study may help risk stratify and guide treatment regimens aimed at maximizing outcomes for patients with cerebellar metastases.

Introduction

The brain is a common metastatic site for several types of primary cancers. While the majority of these cancers metastasize to the supratentorial space, approximately 10–20% also metastasize to the posterior fossa.[1,2] Cerebellar metastases, unlike most of their supratentorial counterparts, can cause significant symptoms out of proportion with their size.[3–5] These cerebellar lesions can cause obstructive hydrocephalus, brainstem compression, and herniation with acute neurological decline.[3,4] This increased propensity for rapidly progressive symptoms make these lesions appear clinically distinct from supratentorial lesions, with different presenting symptoms, risk profiles, treatment strategies, and potential outcomes.[6,7] However, the effect of tumor location on survival and recurrence for metastatic lesions remains unclear, even though an infratentorial location has been associated with worse prognoses for other pathologies including gliomas, trauma, and intracranial hemorrhage, among others.[8–12]

Studies on brain metastases typically group patients with supra- and infratentorial metastases into the same study cohort even though patients with infratentorial lesions may be clinically distinct.[11,12] This grouping means that patients with cerebellar metastases are treated similarly as their supratentorial counterparts, which may be erroneous.[13–20] The goals of this study were therefore to: (i) identify factors more common in patients with cerebellar metastases than other intracranial metastases, (ii) ascertain if a cerebellar location was independently associated with worse outcomes, and (iii) identify

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factors independently associated with survival, local recurrence, and distal recurrence for patients with cerebellar metastases. A better understanding of these facets may help guide treatment regimens aimed at maximizing outcomes for patients with cerebellar metastases, which may be more distinct than metastases that occur elsewhere.

Methods

Patient selection

Institutional Review Board (IRB) approval was obtained prior to conducting this study (36875). A total of 708 adult patients (age $>$ 18 years) underwent surgery of a single or multiple intracranial metastases between 1997 and 2011. The pathology was determined by a senior neuro-pathologist in all cases. Of these 708 patients, 140 underwent surgery of a non-brainstem, cerebellar metastasis.

Recorded variables

The clinical, operative, and hospital course records of these 708 patients were retrospectively reviewed. The information collected from neurosurgery and neuro-oncology clinical notes included patient demographics, co-morbidities, presenting symptoms, neuro-imaging, neurological function, body imaging, and adjuvant therapy. The Karnofsky performance scale (KPS) index was used to classify patients' pre-operative functional status, and was assigned by a reviewer blinded to patient outcomes at the clinical visit prior to surgery during a chart review.[21] A motor deficit was defined as decreased strength, while a language deficit was defined as any combination of receptive and/or expressive aphasia. A cognitive deficit was defined as any complaint of decreased mental status or ability, while a vision deficit was defined as any decrease in visual acuity or visual field perception. Recursive partitioning analysis (RPA) classification group, control of primary tumor, and presence of extra cranial spread were assigned as previously defined.[22]

The MRI images were obtained and reviewed. The characteristics that were recorded included the lesion's size (largest diameter based on gadolinium enhancement), specific lobe involvement, number of intracranial metastases, and presence of hydrocephalus. Extent of resection was classified from comparing pre- and post-operative MRIs obtained $<$ 48 hours after surgical resection as gross total resection (GTR) if no residual enhancement, near total resection (NTR) in case of only rim enhancement of the resection cavity, or subtotal resection (STR) if residual nodular enhancement was noted on post-operative MRI.[23] The presence of hydrocephalus was defined as the presence of dilated ventricles with transependymal flow on MRI. In addition to brain MRIs, all patients underwent computed tomography (CT) scans of the chest, abdomen, pelvis, and spine with and without contrast. This was used to identify control of primary tumor and presence of extra-cranial spread. It was also used to assess the number of metastatic sites.

Outcome definitions

The date of death was recorded for all patients, where survival data was obtained from the social security index database.[24] Time to death was defined as the time from cranial surgery to death. Patients whose deaths were unconfirmed were classified as lost to follow-up at the time of the last clinic visit. Local recurrence was defined as the presence of recurrence or progression of tumor in the previous surgical cavity. Distal and spinal recurrence was defined as the presence of new tumor in the brain and spine not adjacent to the previous surgical cavity, respectively. Time to local, distal, or spinal recurrence was defined as the time from surgery to MRI diagnosis of recurrence. Patients whose recurrence was unconfirmed were classified as lost to follow-up at the time of their last neuro-imaging.

Perioperative and adjuvant treatment

Surgery was generally advocated for patients with cerebellar masses that pose the threat of causing obstructive hydrocephalus or symptoms attributable to their lesion. This included lesions near the ventricular system or with significant vasogenic edema. For all tumors, the general aim of surgery was to achieve GTR of the tumor when possible. Subtotal resection was achieved primarily when the tumor involved eloquent brain as confirmed by intra-operative mapping and/or monitoring (awake/speech language mapping, direct cortical motor or brainstem stimulation, and motor evoked or somatosensory evoked potentials). Surgery was pursued for multiple metastases when the metastases were easily accessible and/or causing symptoms. Motor and somatosensory evoked potentials were routinely used in the majority of cases, while surgical navigation (CT and/or MRI wand) was used in all cases after 2001.

The uses of radiation therapy, either whole brain radiation (WBRT) and/or stereotactic radiosurgery (SRS), and chemotherapy were determined by a multi-disciplinary team consisting of the neurosurgeon, neuro-oncologist, medical oncologist, radiation oncologist, and the patient themselves. Post-operative MRI was typically performed at three-month intervals following surgery, or when symptoms developed including increased headaches, weakness, or other deficits.

Statistical analysis

Summary data were presented as mean $\pm$ standard deviation for parametric data and as median [interquartile range (IQR)] for non-parametric data. For inter-group comparisons between patients with cerebellar and non-cerebellar metastases, student's *t*-test was used for continuous data and Fisher's exact test for categorical data. Stepwise multivariate proportional hazards regression analyses were performed to identify the role of the cerebellar location and recurrence (local, distal, and spinal) as well as survival among patients with supratentorial and infratentorial metastases. In these analyses, stepwise multivariate analysis was done after controlling for factors consistently shown to be associated with survival for patients with intracranial metastases (age, KPS, primary tumor control, extracranial spread, number of intracranial metastases, and radiation therapy). Similar analyses were used to identify factors independently associated with survival and recurrence for patients with cerebellar metastases. In these analyses, univariate analysis was first performed to evaluate associations between radiographic, pre-operative, operative, perioperative, and pathologic variables with outcomes only for patients with cerebellar metastases. All variables associated with survival ($P < 0.10$) in univariate analysis were then included in a stepwise multivariate proportional hazards regression model. This same model was also used to identify independent associations for local and distal recurrence. Survival as a function of time was plotted using the Kaplan–Meier method, and the Log-rank analysis was used to compare Kaplan–Meier plots (GraphPad Prism 5, La Jolla, CA). Values with $P < 0.05$ in these analyses were considered statistically significant. JMP 9 (SAS, Cary, NC) was used unless otherwise specified.

Results

Pre-, peri-, and post-operative characteristics of all patients

The pre-operative characteristics of the patients in this study are summarized in Table 1. A total of 708 patients underwent surgery for an intracranial metastasis during the review period. The average age was 58.4 ± 12.1 years at the time of surgery, and 336 (47%) were male. The median [IQR] pre-operative KPS was 80 [70–80], and the major presenting symptoms were headaches in 293 (41%), seizures in 110 (16%), motor deficits in 254 (36%), language deficits in 111 (16%), cognitive deficits in 146 (21%), and vision deficits in 120 (17%). At the time of surgery, 502 (71%) patients had control of their primary tumor, 324 (46%) had extracranial spread, and the median [IQR] number of metastatic sites was 1 [1–3]. Among the patients, 152 (21%), 421 (59%), and 135 (19%) presented with an RPA class of 1, 2, and 3, respectively. The average size of the operated tumor was 3.2 ± 1.5 cm, and 256 (36%) involved the frontal lobe, 154 (22%) the parietal lobe, 102 (14%) the temporal lobe, 101 (14%) the occipital lobe, and 140 (20%) the cerebellum. The median [IQR] number of intracranial metastases was 1 [1–2], and 460 (65%) had solitary metastasis.

The peri- and post-operative outcomes are summarized in Table 2. Gross total resection was achieved in 502 (71%) patients and 80 (11%) underwent resection of multiple intracranial metastases. Perioperatively, 65 (9%), 20 (3%), and 16 (2%) developed a new motor, language, and vision deficit, respectively. Wound infection developed in 13 (2%) patients and 10 (1%) had an intracranial hemorrhage requiring operative exploration. Pre-operative craniospinal radiation was performed in 111 (16%) patients, 249 (35%) patients underwent post-operative chemotherapy, and 450 (64%) underwent radiation therapy, in which 340 (48%) underwent WBRT and 222 (31%) underwent SRS. At last follow-up, 51 (7%) patients developed leptomeningeal disease, 8 (1%) required a shunt, and 4 (1%) underwent Ommaya placement.

At last follow-up, 514 (73%) patients had died. The median [IQR] follow-up time for surviving patients was 10.2 [2.8–22.8] months. The median survival of the entire cohort was 9.3 months, where the 6-, 12-, and 24-month survival rates were 61, 42, and 26%, respectively and 107 (15%) developed local recurrence. The 6-, 12-, and 24-month local progression free survival rates were 87, 77, and 69%, respectively. Distal recurrence developed in 226 (32%). The median distal progression free survival was 15.7 months. The 6-, 12-, and 24-month distal progression free survival rates were 72, 55, and 42%, respectively. Spinal recurrence developed in 50 (7%), where 30 (60%), 11 (22%), and 20 (40%) of these patients had recurrence in the bone, epidural space, or intradurally, respectively. The 6-, 12-, and 24-month spinal progression free survival rates were 93, 88, and 83%, respectively.

Association between cerebellar location and outcomes

In stepwise multivariate analysis, after controlling for factors consistently known to be associated with survival (age, KPS, primary tumor control, extracranial spread, number of intracranial metastases, post-operative radiation), cerebellar location was independently associated with increased risk of spinal recurrence [RR (95% CI); 2.895 (1.491–5.409), $P = 0.002$] and poorer survival [RR (95% CI); 1.231 (1.016–1.523), $P = 0.04$], but not local recurrence [RR (95% CI); 1.145 (0.663–1.877), $P = 0.61$] or distal recurrence [RR (95% CI); 0.974 (0.670–1.377), $P = 0.88$]. The effects of local, distal, and spinal recurrence was not changed after controlling for *en bloc* resection and leptomeningeal disease in separate analyses.

Differences between patients undergoing surgery for cerebellar and non-cerebellar metastases

The differences between patients undergoing resection of cerebellar and non-cerebellar metastases are summarized in Tables 1 and 2. Pre-operatively, patients undergoing resection of a cerebellar metastasis more commonly presented with headaches ($P = 0.0001$), and less commonly presented with seizures ($P = 0.0001$), language deficit ($P = 0.02$), and vision deficit ($P = 0.006$). Moreover, patients undergoing resection of a cerebellar metastasis were less likely to have solitary metastasis ($P = 0.02$), but had less number of intracranial metastases ($P = 0.02$). Patients with melanoma less frequently had metastases to the cerebellum than the supratentorial space ($P = 0.006$). There were no differences between the cohorts in regards to age, KPS, control of primary tumor, extracranial spread, and RPA classification.

Perioperatively, patients who underwent resection of a cerebellar metastasis were more likely to undergo resection of multiple intracranial metastases ($P = 0.004$) and develop a wound infection ($P = 0.006$). Among patients undergoing one metastatic tumor

Table 1 Pre-operative characteristics of patients undergoing surgery of cerebellar and supratentorial metastases from 1997–2011

	Cerebellar metastases (n = 140)	Supratentorial metastases (n = 568)	
Characteristics	Number (%)	Number (%)	P-value
Demographics			
Age*	58.3 ± 11.2	58.4 ± 12.3	0.89
Male	67 (48%)	269 (47%)	0.93
KPS**	80 (70–80)	80 (70–80)	0.87
Headaches	85 (61%)	208 (37%)	**0.0001**
Seizures	4 (3%)	106 (19%)	**0.0001**
Motor deficit	41 (29%)	213 (38%)	0.08
Language deficit	13 (9%)	98 (17%)	**0.02**
Cognitive deficit	21 (15%)	125 (22%)	0.08
Vision deficit	13 (9%)	107 (19%)	**0.006**
Tumor characteristics			
Control of Primary	100 (71%)	402 (71%)	0.92
Extracranial Spread	71 (51%)	253 (45%)	0.22
No. of body met sites**	2 (1–3)	1 (1–3)	0.21
RPA Class			
RPA Class 1	27 (19%)	125 (22%)	0.57
RPA Class 2	86 (61%)	335 (59%)	0.63
RPA Class 3	27 (19%)	108 (19%)	0.99
Solitary metastasis	79 (56%)	381 (67%)	**0.02**
Primary cancer			
NSCLC	55 (39%)	214 (38%)	0.77
Breast	26 (19%)	80 (14%)	0.19
Gastrointestinal	20 (14%)	52 (9%)	0.09
Melanoma	8 (6%)	80 (14%)	**0.006**
Renal cell	10 (7%)	41 (7%)	0.99
Bladder	4 (2%)	8 (1%)	0.27
Primary bone	2 (1%)	15 (3%)	0.55
Other	15 (11%)	78 (14%)	0.40
Radiographics			
Tumor size*	3.1 ± 1.0	3.2 ± 1.6	0.41
Location			
Frontal lobe	10 (7%)	246 (43%)	**0.0001**
Temporal lobe	4 (3%)	98 (17%)	**0.0001**
Parietal lobe	8 (6%)	146 (26%)	**0.0001**
Occipital lobe	2 (1%)	99 (17%)	**0.0001**
Cerebellum	140 (100%)	0 (0%)	**0.0001**
Brainstem	1 (0.7%)	11 (2%)	0.48
Skull base	2 (1%)	23 (4%)	0.20
Bone involvement	3 (2%)	38 (7%)	**0.04**
Eloquent			
Motor cortex	4 (3%)	89 (16%)	**0.0001**
Language cortex	2 (1%)	46 (8%)	**0.002**
Basal ganglia	0 (0%)	6 (1%)	0.60
No. of brain mets**	1 (1–2)	2 (2–3)	**0.02**
Hemorrhagic	25 (18%)	114 (20%)	0.64
Hydrocephalus	29 (21%)	24 (4%)	**0.0001**

Bold indicates statistical significance ($p < 0.05$).
NSCLC, non-small cell lung cancer; KPS, Karnofsky performance score.
Study population (n = 708)*mean±standard deviation, ** median (interquartile range).

resection, the frequency of wound infections was still more common among patients with cerebellar metastases as compared to metastases elsewhere (6 vs 1%, $P = 0.004$). There were no statistical differences between patients who underwent resection of a cerebellar or a supratentorial metastasis with regard to the extent of resection, development of iatrogenic deficits, and use of adjuvant therapies.

At last follow-up, patients undergoing resection of a cerebellar metastasis had shorter median survival times than patients who underwent supratentorial metastatic tumor resection, but did not achieve statistical significance (8.2 vs 9.9 months, $P = 0.11$) (Fig. 1). There was no difference between the cohorts with regard to local ($P = 0.86$) (Fig. 2) and distal recurrence ($P = 0.84$) (Fig. 3). However, patients who underwent resection of a cerebellar metastasis had lower 12-month spinal progression free survival than patients who underwent resection of a supratentorial metastasis (75.0 vs 90.8%, $P = 0.0006$) (Fig. 4).

In a separate analysis to analyze the impact of *en bloc* resection for cerebellar metastases, there were no differences in local recurrence (8 vs 15%, $P = 0.99$), spinal recurrence (25 vs 11%, $P = 0.16$), epidural spinal recurrence (8 vs 2%, $P = 0.24$), intradural spinal recurrence (0 vs 5%, $P = 0.99$), and distal recurrence (25 vs 29%, $P = 0.99$) between patients with *en bloc* and piecemeal resection.

Factors independently associated with prolonged survival

In univariate analysis, the factors associated with survival were: age, congestive heart failure, KPS, seizures, language deficit, cognitive deficit, non small cell lung cancer (NSCLC), GI cancer, melanoma, bone cancer, prostate cancer, pre-operative chemotherapy, number of intracranial metastases, hydrocephalus, tumor size, new motor deficit, post-operative chemotherapy, post-operative brain radiation, WBRT, and distal recurrence. No other clinical or imaging variables were found to be associated with

Table 2 Peri- and post-operative characteristics of patients undergoing surgery of a cerebellar or supratentorial metastasis from 1997 to 2011. Study population (n = 708)

	Cerebellar metastases (n = 140)	Supratentorial metastases (n = 568)	
Characteristics	Number (%)	Number (%)	P-value
Surgery			
Gross total resection	102 (73%)	400 (70%)	0.60
Near total resection	21 (5%)	105 (18%)	0.39
Subtotal resection	16 (11%)	43 (8%)	0.17
Biopsy	4 (3%)	26 (5%)	0.35
En bloc resection	12 (9%)	48 (8%)	0.99
Cortical mapping	1 (0.7%)	20 (4%)	0.10
Multiple mets resected	26 (19%)	54 (10%)	0.004
New symptoms			
Motor deficit	16 (11%)	49 (9%)	0.33
Language deficit	4 (3%)	16 (3%)	0.99
Vision deficit	3 (2%)	13 (2%)	0.99
Adjuvant therapy			
Chemotherapy	51 (36%)	198 (35%)	0.77
Pre-op craniospinal radiation	16 (11%)	95 (17%)	0.15
Post-op radiation therapy	88 (63%)	362 (64%)	0.85
Whole brain XRT	66 (47%)	274 (48%)	0.85
Stereotactic XRT	36 (26%)	186 (33%)	0.13
Complications			
Wound infection	7 (5%)	6 (1%)	0.006
Intracranial hemorrhage	4 (3%)	6 (1%)	0.12
Leptomeningeal disease	13 (9%)	38 (7%)	0.28
DVT/PE	5 (4%)	24 (4%)	0.82
Pneumonia	0 (0%)	7 (1%)	0.36
Shunt placement	2 (1%)	6 (1%)	0.66
Ommaya placement	2 (1%)	2 (0.4%)	0.18
Survival			
Deaths	104 (74%)	410 (72%)	0.67
Median survival	8.2	9.9	0.11
Local recurrence	20 (14%)	87 (15%)	0.90
12-month local PFS rate	80.2%	76.0%	0.86
Distal recurrence	40 (29%)	186 (33%)	0.36
12-month distal PFS rate	50.8%	55.3%	0.84
Spine recurrence	17 (12%)	33 (6%)	0.02
Bone recurrence	11 (8%)	19 (3%)	0.03
Epidural recurrence	3 (2%)	8 (1%)	0.46
Intradural recurrence	6 (4%)	14 (3%)	0.26
12-month spine PFS rate	75.0%	90.8%	0.0006

DVT, deep vein thrombosis; PE: pulmonary embolism; XRT, radiation therapy.
*mean ± standard deviation, ** median (interquartile range).

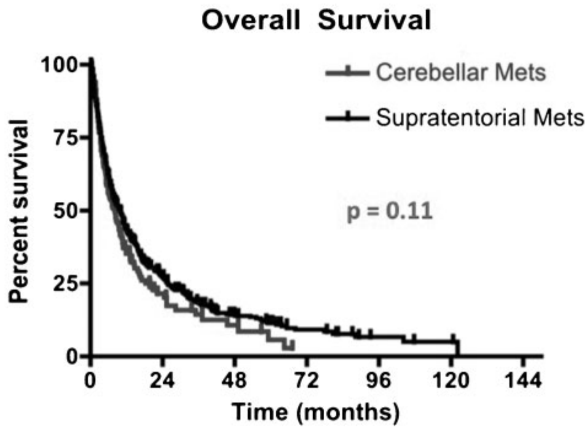

Figure 1 Kaplan–Meier survival curves for patients undergoing surgery of an intracranial cerebellar versus supratentorial metastasis. The median survival for patients undergoing surgery of a cerebellar metastasis was 8.2 months as compared to 9.9 months for patients with supratentorial metastasis (P = 0.11). The 6-, 12-, and 24-month overall survival rates for patients undergoing surgery of an intracranial cerebellar metastasis were 56.2, 35.3, and 21.5%, respectfully. The 6-, 12-, and 24-month overall survival rates for patients undergoing surgery of a supratentorial metastasis were 61.8, 43.1, and 27.2%, respectively. In multivariate analysis, however, after controlling for factors consistently shown to be associated with survival (age, KPS, primary tumor control, extracranial spread, number of intracranial metastases, radiation therapy), cerebellar location was associated with poorer survival [RR(95% CI); 1.231 (1.016–1.523), P = 0.04].

survival. This included RPA class, *en bloc* resection, and extent of resection.

In stepwise multivariate analysis (Table 3), the factors that remained significantly associated with prolonged survival were: decreasing number of intracranial metastases [RR (95% CI); 0.819 (0.753–0.903), $P = 0.0002$], decreasing tumor size [RR (95% CI); 0.681 (0.539–0.858), $P = 0.002$], and post-operative brain radiation [RR (95% CI); 0.309 (0.197–0.490), $P < 0.0001$]. In separate analyses, number of intracranial metastases, tumor size, and

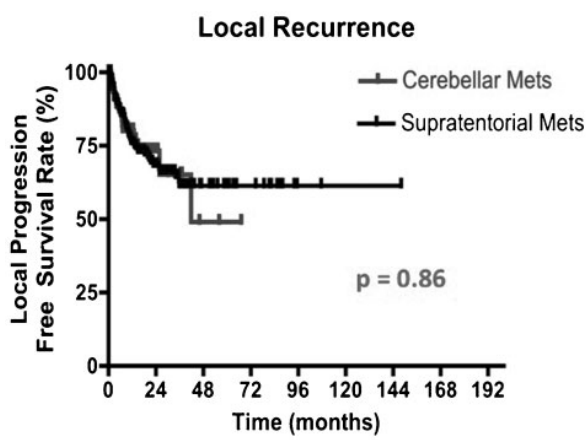

Figure 2 Kaplan–Meier local progression free survival curves for patients undergoing surgery of an intracranial cerebellar versus supratentorial metastasis. The 6-, 12-, and 24-month local progression free survival rates for patients undergoing surgery of an intracranial cerebellar metastasis were 86.9, 80.2, and 73.4%, respectively. The 6-, 12-, and 24-month local progression free survival rates for patients undergoing surgery of a supratentorial metastasis were 86.4, 76.0, and 68.4%, respectively (P = 0.86).

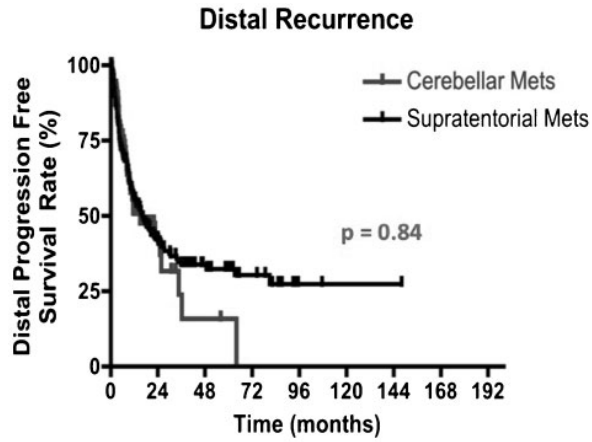

Figure 3 Kaplan–Meier distal progression free survival curves for patients undergoing surgery of an intracranial cerebellar versus supratentorial metastasis. The 6-, 12-, and 24-month distal progression free survival rates for patients undergoing surgery of an intracranial cerebellar metastasis were 76.3, 50.8, and 42.3%, respectively. The 6-, 12-, and 24-month distal progression free survival rates for patients undergoing surgery of a supratentorial metastasis were 70.6, 55.3, and 41.6%, respectively (P = 0.84).

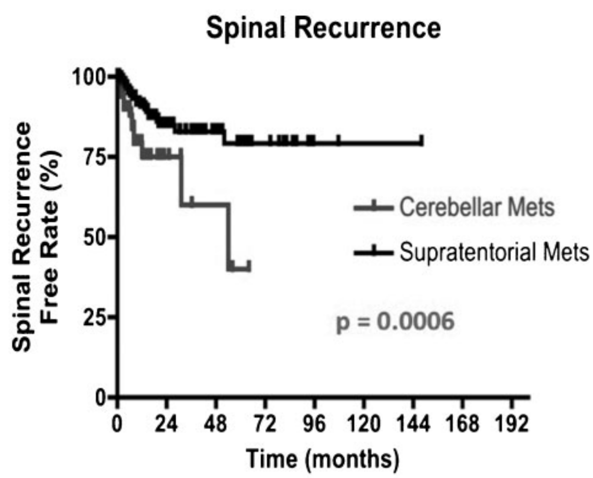

Figure 4 Kaplan–Meier spinal progression free survival curves for patients undergoing surgery of an intracranial cerebellar versus supratentorial metastasis. The 6-, 12-, and 24-month spinal progression free survival rates for patients undergoing surgery of an intracranial cerebellar metastasis were 88.0, 75.0, and 75.0%, respectfully. The 6-, 12-, and 24-month spinal progression free survival rates for patients undergoing surgery of a supratentorial metastasis were 94.3, 90.8, and 84.9%, respectively (P = 0.0006). In multivariate analysis, after controlling for factors consistently shown to be associated with survival (age, KPS, primary tumor control, extracranial spread, number of intracranial metastases, and radiation therapy), this difference remained significant [RR (95% CI); 2.895 (1.491–5.409), P = 0.002].

Table 3 Multivariate associations with prolonged survival for patients undergoing surgery of a cerebellar metastasis from 1997–2011

Multivariate associations with prolonged survival		
Variable	Relative risk (95% CI)	P-value
Decreasing number of intracranial metastases	0.819 (0.753–0.903)	0.0002
≤3 intracranial metastases*	0.265 (0.136–0.557)	0.0009
Decreasing tumor size	0.681 (0.539–0.858)	0.002
Tumor size ≤3 cm*	0.506 (0.316–0.810)	0.005
Post-op brain radiation	0.309 (0.197–0.490)	< 0.0001
Whole brain radiation therapy*	0.458 (0.291–0.715)	0.0006

*Analysis done in a separate multivariate analysis to find the greatest association with prolonged survival.

type of brain radiation were dichotomized to find the greatest statistical association with survival in the multivariate model. In these separate analyses, patients with ≤ 3 intracranial metastases [RR (95% CI); 0.265 (0.136–0.557), $P = 0.0009$], tumor size ≤ 3 cm [RR (95% CI), 0.506 (0.316–0.810), $P = 0.005$], and WBRT [RR (95% CI); 0.458 (0.291–0.715), $P = 0.0006$] had the greatest associations with prolonged survival.

Factors independently associated with prolonged local recurrence

In univariate analysis, the factors associated with local recurrence were: age, chronic obstructive pulmonary disorder, hypertension, motor deficit, NSCLC, renal cancer, bone cancer, bladder cancer, control of primary cancer, number of intracranial metastases, tumor size, post-operative brain radiation, and WBRT. No other clinical or imaging variables were found to be associated with local recurrence. This included RPA class, *en bloc* resection, and extent of resection.

In stepwise multivariate analysis (Table 4), the factors that remained significantly associated with prolonged local progression free survival were: decreasing tumor size [RR (95% CI); 0.415 (0.236–0.703), $P = 0.0009$], non-NSCLC primary [RR (95% CI); 0.189 (0.046–0.629), $P = 0.0062$], non-bladder primary [RR (95% CI); 0.027 (0.004–0.184), $P = 0.0005$], and post-operative brain radiation [RR (95% CI); 0.178 (0.044–0.752), $P = 0.02$]. In separate analyses, tumor size and type of brain radiation were dichotomized to find the greatest statistical association with survival in the multivariate model. In these separate analyses, patients with tumor size ≤ 3 cm [RR (95% CI), 0.182 (0.052–0.539), $P = 0.002$] and WBRT [RR (95% CI); 0.143 (0.042–0.429), $P = 0.0005$] had the greatest associations with prolonged survival.

Factors independently associated with prolonged distal recurrence

In univariate analysis, the factors associated with distal recurrence were: age, KPS, sensory deficit, adenocarcinoma, bone cancer, RPA class, tumor size, new motor deficit, pre-operative brain radiation, WBRT, and SRS. No other clinical or imaging variables were found to be associated with distal recurrence. This included *en bloc* resection and extent of resection.

In stepwise multivariate analysis (Table 4), the factors that remained significantly associated with prolonged distal progression free survival were: age > 40 years [RR (95% CI); 0.281 (0.120–0.771), $P = 0.02$], non-biopsy surgical resection [RR (95% CI); 0.012 (0.002–0.248), $P = 0.01$], and WBRT [RR (95% CI); 0.432 (0.212–0.881), $P = 0.02$].

Table 4 Multivariate associations with delayed local and distal recurrence for patients undergoing surgery of a cerebellar metastasis from 1997–2011

Multivariate associations with delayed local recurrence		
Variable	Relative risk (95%CI)	P-value
Decreasing tumor size	0.415 (0.236–0.703)	0.0009
Tumor size ≤ 3 cm*	0.182 (0.052–0.539)	0.002
Non-NSCLC	0.189 (0.046–0.629)	0.006
Non-bladder cancer	0.027 (0.004–0.184)	0.0005
Any post-operative brain radiation	0.178 (0.044–0.752)	0.02
Whole brain radiation therapy*	0.143 (0.042–0.429)	0.0005
Multivariate associations with delayed distal recurrence		
Variable	Relative risk (95%CI)	P-value
Age > 40	0.281 (0.120–0.771)	0.02
Non-biopsy, surgical resection	0.012 (0.002–0.248)	0.01
Whole brain radiation therapy	0.432 (0.212–0.881)	0.02

Discussion

Metastatic tumors are one of the most common lesions in the brain and occurs in approximately 25–45% of patients with metastatic disease.[1–3] Among intracranial metastases, cerebellar metastases occur in 10–20% of patients with metastatic disease.[1,2] Cerebellar metastases are considered to have poorer prognoses than metastases that occur elsewhere.[11,12] This assumed poorer prognosis is believed to be due to the fact that they can cause rapid progression of symptoms by causing obstructive hydrocephalus, brainstem compression, and tonsillar herniation.[11,12,25] These disastrous outcomes are magnified by the inability of the posterior fossa to accommodate mass effect as much as the supratentorial compartment.[11,12,25] As a result, cerebellar metastases can cause symptoms out of proportion with their tumor size.[11,12] These lesions therefore behave clinically different than metastases elsewhere in the brain, but are often included into the same discussion of metastatic brain disease.[22,26–31] This potentially erroneous grouping may prevent the optimization of care for patients with this less common location for intracranial metastases.

Previous studies on cerebellar metastases

Despite the relative commonality of cerebellar metastases, studies devoted to the clinical outcomes for these lesions are limited (Table 5).[32–38] The majority of these studies combine infratentorial and supratentorial lesions into the same study cohort, which masks the outcomes for patients with cerebellar metastases.[13–20] Moreover, the majority of the cerebellar studies aim to compare different modalities rather than understand differences between cerebellar and non-cerebellar patients and identify factors associated with outcomes for these patients.[33,34,36,38] Yoshida and Takahashi compared 38 patients who underwent surgery alone with 27 patients who underwent surgery plus radiation.[36] They found that survival was significantly improved with the addition of radiation therapy to surgical resection.[36] Ampil *et al.* found similar results in comparing 11 patients who underwent aggressive therapy with 34 patients who underwent only radiation.[38] Javalkar *et al.* compared surgery plus WBRT versus SRS only, and found no difference in outcomes.[33] Besides differences in treatment modalities, other studies evaluated the risk of leptomeningeal disease for patients with cerebellar metastases.[32,35] Chamberlain *et al.* found no increased incidence of leptomeningeal disease in patients who underwent surgery vs radiation treatment.[32] Suki *et al.* evaluated the risk of leptomeningeal disease among patients who underwent surgical resection.[35] They found that leptomeningeal disease occurred in 10% of the patients who underwent resection, and that piecemeal resection was associated with a greater risk as compared to *en bloc* resection and SRS.[35]

Studies devoted to evaluating risk factors for survival and recurrence of cerebellar metastases remain few and limited. Pompili and colleagues evaluated factors associated with survival for patients with cerebellar metastases, and found that only KPS was associated with survival in the 44 patients they studied.[37] Kanner *et al.* studied 93 patients, of whom 66 underwent surgery.[34] By comparing groups, they found that RPA class and use of multimodality treatment were associated with improved survival.[34] These previous studies, however, are limited by relatively small patient numbers,[32–34,37,38] only compared different treatment modalities,[32–34,37,38] and did not use multivariate analyses.[32–38] Therefore, it still remains unclear if cerebellar location is associated with poorer survival and which factors are associated with survival and recurrence for patients with cerebellar metastases.

Cerebellar location of a metastasis and its effect on survival and recurrence

This study found that a cerebellar location was independently associated with poorer survival, as seen in other pathologies including gliomas, trauma, and intracranial hemorrhage.[8–12] Among metastatic studies, Yardini *et al.* found that patients with cerebellar metastases had poorer survival than patients with supratentorial metastases by studying 74 patients with metastatic disease.[12] Sharr *et al.*

Table 5 Summary of previous studies focusing on cerebellar metastases

Studies	Year	No. patients with cerebellar metastases	No. of patients undergoing surgery	Identified factors associated with survival	Identified factors associated with recurrence	Multivariate analysis
Present study	*2012*	*140*	*140*	*Yes*	*Yes*	*Yes*
Javalkar *et al.*	2010	35	24	Yes	No	No
Yoshida *et al.*	2009	109	73	No	No	No
Chamberlain *et al.*	2008	90	30	No	No	No
Pompili *et al.*	2008	44	44	Yes	No	No
Suki *et al.*	2008	379	260	No	No	No
Kanner *et al.*	2003	93	66	Yes	No	Yes
Ampil *et al.*	1996	45	11	Yes	No	No

reported similar findings among patients with lung, melanoma, GI, and renal cancers, but not breast cancer.[11] Statistical comparisons, however, were not made in this study.[11] These previous metastatic studies are therefore limited because they did not conduct multivariate analyses, look at outcome measures other than survival, and had relatively small patient numbers.[11,12] This is especially important for metastatic disease because patient populations are extremely heterogeneous with disparate ages, functional statuses, primary cancer type, adjuvant therapy, etc. Additionally, the differences in survival were only seen in this study after using multivariate analyses, and not a direct comparison of survival times. Nonetheless, the worse outcome for cerebellar metastases could be attributed to numerous factors. The posterior fossa contains critical structures less tolerant of mass effect including the medulla, pons, respiratory centers, fourth ventricle, and other vital structures.[8–10] There is also limited space in the posterior fossa that can exacerbate these structures' ability to tolerate mass effect.[39–41] Additionally, the posterior fossa is different from supratentorial space in regard to cell types, tissue cytoarchitecture, and blood flow, which may also contribute to these differences in outcomes.[39–41]

In addition to survival, this study found an increased risk of spinal recurrence for patients with cerebellar metastases, but not local or distal recurrence. This was independent of *en bloc* resection and the development of leptomeningeal disease. This propensity for cerebellar metastases to later have spinal recurrences without an increased risk of distal intracranial recurrences suggests that the bony and epidural components of the spine and cerebellum may be seeded by similar sources (i.e. Batson's venous plexus) as compared to the supratentorial compartment. It may also suggest that metastatic tumors, once they acquire the ability to metastasize to the brain, have differential abilities to metastasize between the supratentorial and the infratentorial/spinal compartment. These findings may advocate for potentially monitoring the spine more vigilantly for recurrences, and may also suggest that the spine should potentially be considered in the radiation field for prophylactic treatment.

Differences between cerebellar and non-cerebellar metastases

Patients with cerebellar disease had distinct differences from patients with non-cerebellar disease in this study. Patients with cerebellar metastases more commonly presented with headaches, and less commonly vision deficits, language deficits, and seizures. This makes intuitive sense based on brain location where cerebellar lesions can more commonly obstruct CSF drainage pathways, leading to hydrocephalus and subsequent headaches.[11,12,25] In fact, prior to widespread neuro-imaging use, the presence of headaches in a patient with metastatic disease made it highly suspicious for cerebellar metastases.[3,10] Likewise, patients with cerebellar metastases rarely presented with vision deficits, language deficits, or seizures. This is because these lesions did not involve the occipital lobe, Wernicke's/Broca's area, and cerebral cortex or mesial temporal lobe structures, which are generally responsible for vision, language, and seizures, respectively.[42] However, these symptoms can still occur in patients with cerebellar lesions. Besides these symptoms, patients with melanoma less frequently had metastases to the cerebellum. Previous studies have found a propensity for lung and breast cancer to the cerebellum out of proportion to their primary tumor size.[1,10,34] The finding that melanoma rarely metastasizes to the cerebellum is especially interesting because the intracranial disease burden for patients with metastatic melanoma can be high, but they may have fewer propensities to metastasize to the cerebellum.[43,44]

Besides these presenting symptoms and primary tumor type, patients who underwent surgery for their cerebellar metastasis less commonly had solitary disease than patients who underwent surgery for a supratentorial lesion. Interestingly, however, patients with cerebellar metastases had less intracranial disease burden than patients with supratentorial metastases. This seems paradoxical, but implies that patients who develop cerebellar disease typically have less intracranial metastases but is less commonly in isolation. Perioperatively, patients with cerebellar metastases more commonly had wound infections. This is believed to be due to a higher risk of CSF leak, difficulty in dural repair, and more pressure on the wound for posterior fossa lesions than supratentorial lesions.[45]

At last follow-up, there were no differences between cerebellar and non-cerebellar patients in regard to survival, local recurrence, and distal recurrence when directly comparing cohorts. However, patients with metastases are heterogeneous, with different ages, functional statuses, presence of primary tumor control, systemic disease burden, and adjuvant therapy.[13–20] After controlling for factors consistently associated with survival, we found that survival is poorer in patients with cerebellar metastases, as seen in previous studies, which did not use multivariate analyses.[11,12] Besides survival, patients with cerebellar metastases also had shorter spinal progression free survival rates, which was supported in multivariate analyses. Interestingly, there were no differences between intradural spinal recurrence and leptomeningeal disease. This means this recurrence rate was less likely due to drop metastases. It supports the notion that systemic metastases, once they metastasize to the cerebellum, have a greater propensity for spinal rather than supratentorial recurrences.

Factors independently associated with survival, local recurrence, and distal recurrence for patients with cerebellar metastases

This study found that a decreased number of intracranial metastases was associated with improved survival. The association between the number of intracranial metastases and survival is the basis of several metastatic studies.[12,27,28,30,31,46] Several studies often subdivide their treatment comparisons into patients with different number of metastases, including solitary metastasis, multiple metastases (2–5), or numerous metastases (> 5).[12,27,28,30,31,46] Patients with solitary metastasis are considered to have the best prognoses, and patients who have more are considered to have poorer prognoses.[12,27,28,30,31,46–48] Patients, however, rarely only have one metastasis.[12,27,28,30,31,46] In fact, recent improvements in various treatment modalities have prolonged survival for patients with metastatic disease, and patients often present with more intracranial metastases than before.[47–50] This study found that the most significant cut-off was three metastases, where patients with three or less metastases had the best prognosis. This may mean patients with two and even three metastases may benefit from surgical resection, similar to those patients with solitary metastasis.

Patients with smaller tumors had better survival and local progression free survival. The size that had the greatest cut-off was 3 cm for both survival and local recurrence. This size is important because this is the same size cut-off used for radiation, where tumors larger than 3 cm typically do not respond to radiation therapy.[49,51] Surgery, as with radiation therapy, is most efficacious for smaller tumors. This supports the need for early surgical intervention before tumors increase in size, which may reduce intracranial tumor burden, decrease risk of local recurrence, and potentially prolong survival.

Patients who underwent surgical resection had better distal recurrence rates than patients who underwent biopsy, regardless of use of adjuvant therapy. The current standard of care for patients with intracranial metastases is far from defined, but includes some combination of surgery, SRS, and/or WBRT.[52] Cerebellar lesions, more so than their supratentorial counterparts, have an increased risk of acute neurological decline and complications such as leptomeningeal disease.[12,31,39–41] This study supports the notion that surgical resection may also minimize the risk of distal recurrences. This may mean that sources of intracranial recurrences may be due to some combination of systemic as well as intracranial disease.

Patients with NSCLC and bladder cancer had the highest risk of local recurrence in this study. Non small cell lung cancer represents the highest proportion of brain metastases, where approximately 40% of these patients will develop brain metastases.[53] Interestingly, 20–40% can locally recur.[54,55] Al-Zabin and colleagues analyzed 181 patients who underwent resection of a lung metastasis, and 40% had recurrence.[54] Koutras *et al.* found that 13 (41%) patients had local recurrence following surgery in 32 patients with lung cancer.[55] Unlike lung cancer, bladder cancer does not frequently metastasize to the brain. The incidence ranges from 0–7%, and survival is typically dismal with median survivals that range from 2–4 months with aggressive treatment.[56,57] The rarity of this tumor type metastasizing to the brain has precluded an analysis of its effect on survival and recurrence. These findings suggest that more aggressive surgical therapy and/or adjuvant therapy might be warranted for patients with these primary cancers.

The use of any radiation therapy was associated with improved overall survival and local recurrence rates, while WBRT was associated with improved survival, local recurrence, and distal recurrence rates in this study. The use of SRS in combination with surgery was not found to be efficacious for any of these outcome measures. The positive effect of surgery with WBRT has been documented previously, but these studies did not use multivariate analyses to control for the disparate characteristics in patients with cerebellar metastases.[36] Other previous studies have compared surgery and WBRT to SRS alone, but have found no significant differences in outcomes.[33,38,58] The present study shows that the addition of WBRT to surgery may prolong survival and delay recurrence for patients who undergo resection of their cerebellar metastases.

Strengths and limitations

We believe this study provides several useful insights. First, the effects of cerebellar location on survival and recurrence remain unclear. This study shows that a cerebellar location is associated with poorer survival and increased spinal recurrence, but is not associated with local and/or distal intracranial recurrence for patients with metastatic disease. Second, this study identifies clinical differences between patients with cerebellar and non-cerebellar metastases. Patients with cerebellar metastases more commonly present with headaches and hydrocephalus, and less commonly vision deficit, language deficit, and seizures. Patients with cerebellar lesions also less commonly have melanoma and solitary lesions. Third, it uses multivariate analyses to identify factors independently associated with survival, local recurrence, and distal recurrence for patients who undergo surgical resection of their cerebellar lesion. Previous studies attempting to identify these factors are limited and do not use multivariate analyses, which is especially critical for patients with metastatic disease. Lastly, this study may provide useful information that may help guide treatment strategies aimed at prolonging survival and delaying recurrence for patients with cerebellar metastases. These patients appear to have different presenting symptoms, clinical courses, and outcomes than patients with the more common supratentorial metastases.

This study, however, has some limitations. One limitation is that these findings only apply to patients undergoing craniotomy for surgery for a cerebellar metastasis. Patients who did not undergo surgery were excluded. An additional limitation is that this study does not analyze the prognostic implication of molecular markers and receptors and isolated to primary tumor type, which may be a better indicator of patient outcomes. This includes hormonal receptors, epidermal growth factor receptors, and HER-2.[59–61] These molecular markers and others may also be associated with survival, but were not analyzed in this study. Furthermore, the patients in this study underwent disparate treatment regimens. A significant number of patients in this study did not undergo WBRT and/or SRS. As a result, the results of this study may be altered in the context of patients receiving more aggressive therapies. We attempted to control for these differences in adjuvant therapies by instituting multivariate analyses. Finally, this study is inherently limited by its retrospective design. As a result, it is not appropriate to infer direct causal relationships from this study. We acknowledge that there may be an inherent bias associated with patient selection, where patients who were offered surgery may have a propensity for better outcomes. However, we tried to create a uniform patient population by utilizing a strict inclusion and exclusion criteria, thus providing more relevant information for patients undergoing surgery for a cerebellar metastasis. We included only patients who underwent surgery, and excluded patients with incomplete medical records and pediatric patients. Furthermore, we performed multivariate analyses to control for potential confounding variables, which included disparate age, functional status, tumor pathology, primary tumor control, intracranial disease burden, and adjuvant treatment regimens. Given these statistical controls and a relatively precise outcome measure, we believe our findings offer useful insights into outcomes for patients with cerebellar metastases. However, prospective studies are needed to provide better data to guide clinical decision-making.

Conclusions

Studies on patients with intracranial metastases often combine patients with supra- and infratentorial lesions into the same study cohort. This combination may be erroneous since tumors in different tentorial compartments may behave differently, as seen in other intracranial pathologies. This study is the largest to perform multivariate analyses to analyze the role of cerebellar location on survival and recurrence as well as identify factors independently associated with these outcomes for patients with metastatic brain disease. This study found that a cerebellar location was associated with worse survival and greater risk of spinal recurrence. Patients with cerebellar metastases also present more commonly with headaches and hydrocephalus, and less frequently have melanoma primary cancer and present with vision deficits, language deficits, and/or seizures. The factors more commonly associated with prolonged survival include three or less intracranial metastasis, tumor size < 3 cm, and post-operative radiation therapy. The factors associated with prolonged local progression free survival include tumor size < 3 cm, non-NSCLC, non-bladder cancer, and radiation therapy. The factors associated with prolonged distal progression free survival include age $>$ 40, surgical resection, and radiation therapy. These factors can help risk stratify patients and potentially guide therapeutic regimens aimed at optimizing therapies and outcomes for patients with cerebellar metastases.

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