Neuro-Oncology

Surgical and anatomic factors predict development of leptomeningeal disease in patients with melanoma brain metastases

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Abstract

Background. Leptomeningeal disease (LMD) is a devastating complication of systemic malignancy, of which there is an unclear etiology. The aim of this study is to determine if surgical or anatomic factors can predict LMD in patients with metastatic melanoma.

Methods. A retrospective chart review was performed of 1162 patients treated at single institution for melanoma brain metastases (MBM). Patients with fewer than 3 months follow-up or lacking appropriate imaging were excluded. Demographic information, surgical, and anatomic data were collected.

Results. Eight hundred and twenty-seven patients were included in the final review. On multivariate analysis for the entire cohort, female gender, dural-based and intraventricular metastasis, and tumor bordering CSF spaces were associated with increased risk of LMD. Surgical resection was not significant for risk of LMD. On multivariate analysis of patients who have undergone surgical resection of a metastatic tumor, dural-based and intraventricular metastasis, ventricular entry during surgery, and metastasis in the infratentorial space were associated with increased risk of LMD. On multivariate analysis of patients who did not undergo surgery, chemotherapy after initial diagnosis and metastasis bordering CSF spaces were associated with increased risk of LMD.

Conclusion. In a single-institution cohort of MBM, we found that surgical resection alone did not result in an increased risk of LMD. Anatomical factors such as dural-based and intraventricular metastasis were significant for developing LMD, as well as entry into a CSF space during surgical resection. These data suggest a strong correlation between anatomic location and tumor cell seeding in relation to the development of LMD.

Key Points

- Surgical resection alone is not associated with an increased risk developing LMD.
- Entrance into the ventricle space during surgical resection results in an increased risk of LMD.
- Metastasis near a CSF space is associated with risk of LMD and is facilitated by seeding during surgery.

Importance of the Study

This is the first study to examine how the relationship between anatomic location of brain metastases and surgical intervention may lead to the development of leptomeningeal disease (LMD) in a large cohort from a single type of malignancy. Our data suggest that, in contrast to previous reports, surgery is not the only risk for developing LMD. We have found that the presence dural-based and intraventricular metastasis, as well metastasis bordering a ventricle or CSF cistern, were associated with an increased risk of developing LMD. We also found in our cohort of patients who underwent surgical resection of their metastasis, that location adjacent to a CSF space as well as entry into the ventricle during surgery was associated with developing LMD. These findings highlight the complex relationship between natural and iatrogenic tumor cell seeding into a CSF space as a direct cause of the development of LMD.

Leptomeningeal disease (LMD) is a devastating complication of systemic malignancy. Prognosis is extremely poor, with a typical overall survival on the order of 4–6 weeks without treatment, and 3–6 months with treatment.[1] LMD can occur in several types of solid malignancies, in 10–25% of patients with breast cancer, 5% of patients with melanoma, and 3–5% of patients with non small cell lung cancer.[2–4] In particular, LMD from melanoma portends a very poor prognosis, with a reported mean survival of 3.5 months even with treatment.[5] The pathogenesis of melanoma LMD development is not fully delineated but is assumed to have mechanisms similar to those in other solid malignancies. These mechanisms include vascular spread to the leptomeninges or choroid plexus, direct extension from known metastases, or perineural invasion.[6–8]

There is evidence that surgical resection may result in an increased risk of leptomeningeal disease when compared to focal radiation therapy (i.e. stereotactic radiosurgery (SRS)).[9] Norris et al. first noted a correlation between surgical resection of posterior fossa metastases and the development of LMD.[10,11] This correlation was confirmed by Suki et al., who also suggested that piecemeal resection of metastatic lesions resulted in a higher incidence of LMD compared to en bloc resection.[9,12] More recent evidence has suggested that surgical resection may lead to higher rates of nodular-type LMD development, although this risk may be mitigated by use of neoadjuvant SRS.[13–16]

Given the previous findings relating surgical resection to development of LMD, we hypothesized that surgical and anatomical factors may play a role in the development of LMD in patients with metastatic melanoma. By examining a single institution's cohort of patients with melanoma brain metastases (MBM) and LMD, we assessed how surgical resection may influence the development of LMD. In particular, we evaluated how tumor seeding in the cerebrospinal fluid (CSF) may result in the development of LMD, by assessing the location of brain metastases and their proximity to a ventricle or CSF cistern, as well as entry into the ventricle during surgery.

Methods

Clinical Review

Approval from the institutional review board at H. Lee Moffitt Cancer Center and Research Institute was obtained for a retrospective review of patient clinical data. 1162 patients were identified with a primary diagnosis of melanoma and brain metastases between 1999 and 2020 (Figure 1). Patients included in the study required a minimal follow-up of 3 months from the time of initial diagnosis of brain metastasis, as well as the presence of magnetic resonance imaging (MRI) for review of brain metastases and leptomeningeal disease. Patients with evidence of LMD at the time of their initial MBM diagnosis were excluded. General demographic information, as well as survival data, were obtained. First-line radiation treatment was also obtained, to determine whether whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), or fractionated stereotactic radiation therapy (FSRT), or WBRT with SRS boost was administered. Development of LMD was determined based on MRI or CSF cytology when available.

In patients who underwent multiple resections of intracranial metastases, the initial surgery was used for determination for development of LMD. Surgical data were reviewed with emphasis on determining whether the ventricular space was entered during the resection. This determination was made via a combination of operative report review and evaluation of the postoperative imaging.

Imaging Review

Imaging was reviewed independently by a neurosurgeon (SL) and a neuroradiologist (JA). MRIs were reviewed to determine the presence of dural-based metastases, as well as the presence of metastatic lesions bordering a ventricular or major CSF cistern (e.g. basal cisterns, cisterna magna). Patients whose MRIs were not available for our independent review were excluded from the analysis. Patients without appropriate imaging to ascertain detailed radiographic or anatomic location characteristics (e.g., MRI without contrast) were excluded from the analysis. Patients were described as having a metastasis bordering a ventricle or major CSF cistern if the tumor was located in the parenchyma and noted to be in direct contact with the CSF space or its ependymal lining, without intervening brain parenchyma (Figure 2B). Lesions categorized as intraventricular were required to have an isolated metastatic deposit that was located entirely within the ventricle (Figure 2C). The latter two types of metastases were distinguished from nodular LMD which consisted of multiple enhancing nodular lesions along the ventricular or CSF cistern (Figure 2D). Opening of the ventricle was
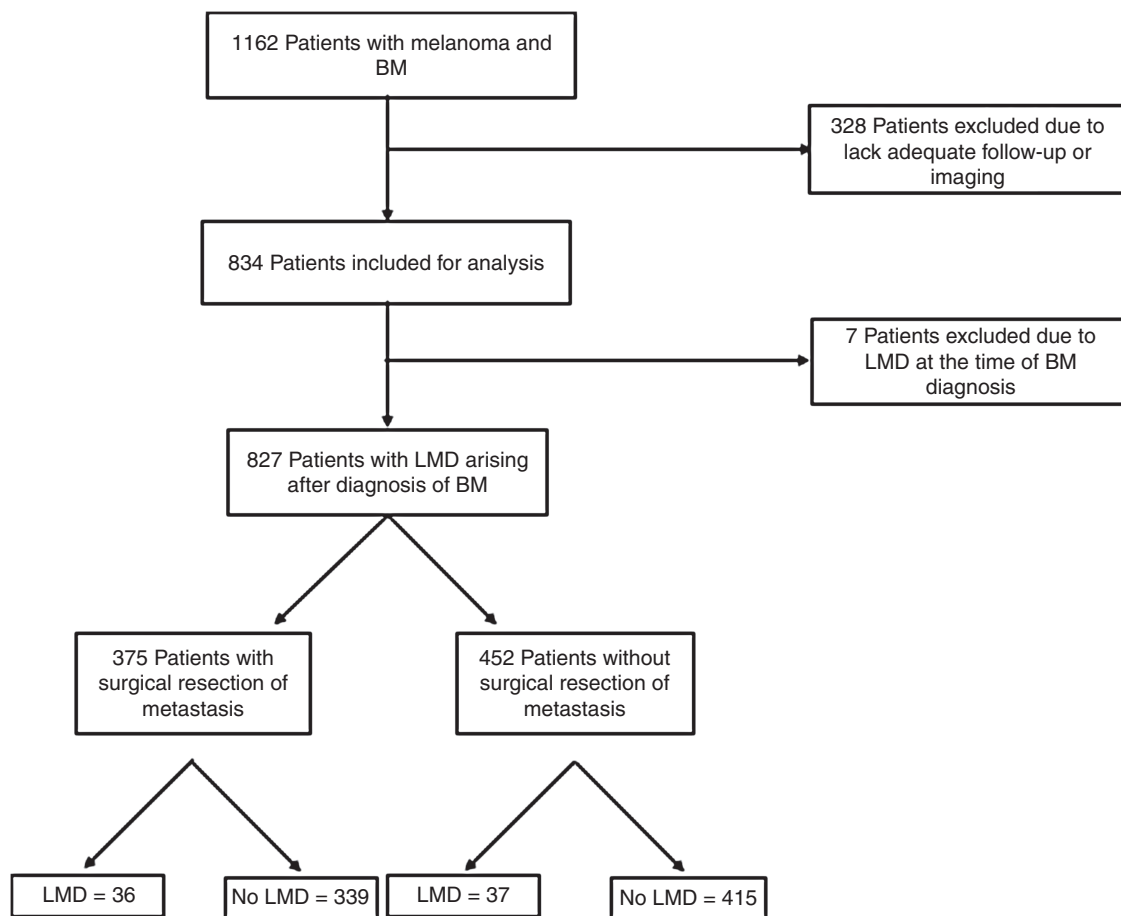
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┌─────────────────────────┐
│ 1162 Patients with       │
│ melanoma and BM          │
└─────────────────────────┘
            │
            │─────────────────────►  ┌──────────────────────────┐
            │                         │ 328 Patients excluded due │
            │                         │ to lack adequate follow-up│
            │                         │ or imaging                │
            ▼                         └──────────────────────────┘
┌─────────────────────────┐
│ 834 Patients included    │
│ for analysis             │
└─────────────────────────┘
            │
            │─────────────────────►  ┌──────────────────────────┐
            │                         │ 7 Patients excluded due to │
            │                         │ LMD at the time of BM      │
            │                         │ diagnosis                  │
            ▼                         └──────────────────────────┘
┌─────────────────────────┐
│ 827 Patients with LMD    │
│ arising after diagnosis  │
│ of BM                    │
└─────────────────────────┘
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375 Patients with surgical resection of metastasis | **452 Patients without surgical resection of metastasis**

LMD = 36   No LMD = 339   LMD = 37   No LMD = 415

Fig. 1 Flowchart demonstrating patient selection.

determined radiographically, if on postoperative imaging, clear ventricular entry was seen and/or the operative report described ventricular entry during the procedure (Figure 2 E,F). If neither of these criteria were satisfied, the patient was not considered to have entry into the ventricle during surgery. LMD was defined by clear radiographic evidence of LMD on imaging as defined by the radiology report, and/or by presence of positive CSF cytology after completion of a lumbar puncture and subsequent clinical diagnosis of LMD by the treating physician.

Statistical Analysis

Patient characteristics were summarized using descriptive statistics including mean, standard deviation, median, and range for continuous measures and proportions and frequencies for categorical measures.

Univariable and multivariable logistic regressions were also performed to test the association of development of LMD and other variables. The variables with p≤0.1 from univariable logistic regression model analysis were added into initial model, then backward selection was conducted, and the variables with $P \geq .05$ were removed from the final model. Odds ratios, with 95% confidence

intervals, and P values were calculated. For categorical variables with more than two levels, P values are presented for each level compared to a referent level, and an overall p value using the type-III analysis of variance result. Data analysis was completed using SAS Institute Inc. (2021), version 9.4.

Results

Patient Population

A total of 827 patients with melanoma and intracranial metastatic disease with appropriate imaging and follow-up were identified and included for analysis (Table 1). Five hundred and forty-seven (66.1%) of the patients were male. Average age at last follow-up was 60.0 years, and average follow-up time was 22.4 months.

On imaging review, 49 (5.9%) of patients were recorded as having a dural-based metastasis, 23 (2.8%) of patients had an intraventricular metastatic tumor, and 192 (23.2%) of patients had one or more lesions bordering a ventricle or major CSF cistern. Six hundred and sixty-five (80.4%) patients had only MBM in the supratentorial space, while
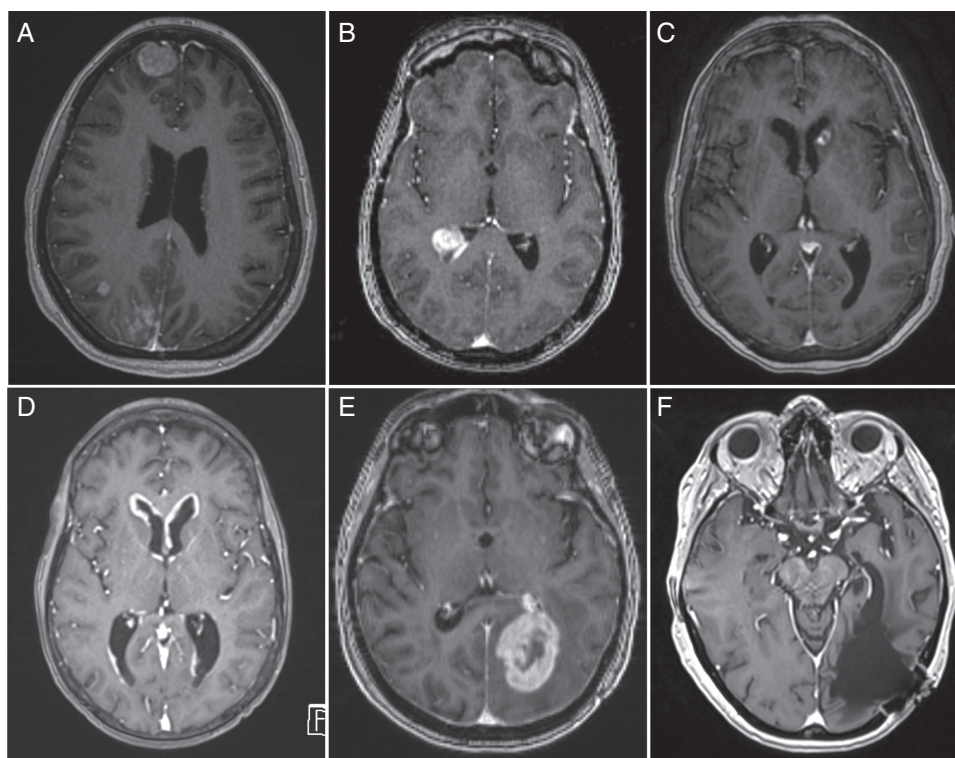
Fig. 2 T1 MRI with contrast of various types of brain metastases. A) Dural-based metastatic tumor in the left frontal lobe. B) An intraventricular metastasis in the atrium of the right lateral ventricle. C) A peri-ventricular metastasis bordering the ependyma of the left lateral ventricle. D) Nodular leptomeningeal disease in the bilateral frontal horns of the lateral ventricles. D and E) Pre- and postoperative imaging of a left occipital metastases. Note the entry into the temporal horn of the left lateral ventricle in the postoperative imaging.

38 (4.6%) had only infratentorial tumors, and 124 (15.0%) had both.

The addition of chemotherapy or immunotherapy before or after initial diagnosis of brain metastasis was evaluated. 181 (21.9%) patients received some form of chemotherapy prior to their initial MBM diagnosis, while 392 (47.4%) received some form of chemotherapy following the diagnosis. 342 (41.4%) received some form of immunotherapy prior to the initial diagnosis while 390 (47.2%) received immunotherapy after. First-line radiation after initial MBM diagnosis was evaluated. 146 (17.7%) received only WBRT, 470 (56.8%) received either SRS or FSRT, 44 (5.3%) received a combination of WBRT and SRS.

Three hundred and seventy-five (45.3%) of patients underwent craniotomy for treatment of one or more metastatic tumors. 39 (10.5%) of patients had entry into the ventricular system during surgery. Univariate and multivariate analysis were performed on the entire cohort of patients, as well as on patients who received and did not receive surgery for their initial brain metastasis treatment.

Development of LMD

Seventy-three patients (8.8%) developed LMD after the initial diagnosis of a brain metastasis were included in further

analysis. Of these, 21 had positive CSF cytology, 12 had negative CSF cytology (6 of these had atypical cells on CSF analysis), and 40 did not have CSF analysis. Of these 73 patients, 36 (49.3%) had surgical resection of at least one metastatic tumor prior to the development of LMD, and 37 (50.7%) did not. Mean survival after LMD diagnosis was 4.1 months, with the longest-surviving patient expiring 38.5 months after LMD diagnosis.

On univariate logistic regression analysis for the entire cohort, females were more likely to develop LMD than males (OR 1.69, 95% CI 1.04–2.75, $P = .033$) (Table 2). Patients harboring a dural-based metastasis were more likely to develop LMD than those without (OR 2.52, 95% CI 1.17–5.43, $P = .018$). Patients with an intraventricular tumor (OR 6.06, 95% CI 2.48–14.84, $P < .001$) and a tumor bordering a ventricle or major CSF cistern (OR 3.73, 95% CI 2.28–6.10, $P < .001$) were more likely to develop LMD than those who did not. The presence of a metastasis in the infratentorial space location did not impact LMD rates. Chemotherapy given after initial MBM diagnosis resulted in an increased risk of developing LMD (OR 1.77, 95% CI 1.08–2.89, $P = .022$).

Interestingly, surgery for resection of a metastatic tumor was not a statistically significant predictor for the development of LMD (OR 1.19, 95% CI 0.74–1.93, $P = .476$). The type of first-line radiation also did not have an impact on the development of LMD on univariate analysis. When examining

Table 1 Cohort Demographics

Variable	Level	N = 827 (%)
Gender	Female	280 (33.9)
	Male	547 (66.1)
Dural-based metastases	No	769 (93.0)
	Yes	49 (5.9)
	Unknown	9 (1.1)
Intraventricular metastases	No	804 (97.2)
	Yes	23 (2.8)
Tumors bordering ventricle/cistern	0	635 (76.8)
	1	147 (17.8)
	2	28 (3.4)
	>2	17 (2.1)
Location of brain metastases	Supratentorial	665 (80.4)
	Infratentorial	38 (4.6)
	Both	124 (15.0)
Chemotherapy before initial MBM diagnosis	No	646 (78.1)
	Yes	181 (21.9)
Chemotherapy after initial MBM diagnosis	No	435 (52.6)
	Yes	392 (47.4)
Immune therapy before initial MBM diagnosis	No	485 (58.6)
	Yes	342 (41.4)
Immune therapy after initial MBM diagnosis	No	437 (52.8)
	Yes	390 (47.2)
Craniotomy for tumor resection	No	452 (54.7)
	Yes	375 (45.3)
Ventricular entry during surgery	No	332 (89.5)
	Yes	39 (10.5)
	Unknown/Not applicable	456
First-line radiation	WBRT	146 (17.7)
	SRS/FSRT	470 (56.8)
	WBRT±SRS	44 (5.3)
	None/Unknown	167 (20.2)
Development of LMD	No	754 (91.2)
	Yes	73 (8.8)
Survival time after LMD diagnosis (months)	Minimum	0.2
	Maximum	38.5
	Mean	4.1
	Median	2.1
	SD	6.4
Follow-up time (months)	Minimum	3.0
	Maximum	217
	Mean	22.4
	Median	12.6
	SD	25.6

On multivariate logistic regression analysis, we found that female gender continued to be a risk for development of LMD (OR 1.69, 95% CI 1.05–2.81, P = .042). We also found that anatomic factors were significant drivers of LMD development. The presence of dural-based metastasis (OR 2.33, 95% CI 1.04–5.23, P = .041), intraventricular metastasis (OR 4.48, 95% CI 1.72–11.70, P = .002), and metastasis bordering a ventricle or major cistern (OR 3.17, 95% CI 1.90–5.30, P < .001) were all predictive for development of LMD.

LMD Risk in Surgical Patients

In the cohort of patients who underwent surgery, a similar trend on univariate logistic regression analysis was observed. Dural-based metastasis (OR 2.77, 95% CI 1.04–7.35, P = .041), intraventricular metastasis (OR 6.94, 95% CI 1.86–25.88, P = .004), metastasis bordering a ventricular space (OR 2.97, 95% CI 1.46–6.02, P = .003), and ventricular entry during surgery (OR 4.82, 95% CI 2.15–10.82, P < .001) were all significant predictors of LMD development (Table 3). In contrast to the entire cohort of LMD patients, gender was no longer a predictive variable. Presence of a metastasis in the infratentorial space was a predictor for LMD (OR 2.40, 95% CI 1.02–5.67, P = .045). As with the overall cohort, type of first-line radiation therapy did not impact on the odds of LMD development.

Further analysis of the 88 patients with a metastasis bordering the ventricle and undergoing surgery demonstrated that when the ventricle was entered, there was an increased risk of developing LMD (OR 3.12, 95% CI 1.03–9.48, P = .045). We also found that in this cohort of patients with metastasis bordering the ventricle undergoing surgery, that radiation therapy regardless of modality, SRS (OR = 0.29 (0.09–0.98) P = .047) or WBRT (OR 0.09, 95% CI 0.01–0.81, P = .032), resulted in a decreased risk of developing LMD (overall P = .040).

Multivariate logistic regression model found that dural-based metastasis (OR 3.49, 95% CI 1.20–10.14, P = .022), intraventricular metastasis (OR 5.38, 95% CI 1.21–23.81, P = .027), and ventricular entry during surgery (OR 5.43, 95% CI 2.18–13.52, P < .001) correlated with LMD development. Similar to the univariate analysis, presence of metastasis in the infratentorial space was predictive of LMD (OR 2.89, 95% CI 1.14–7.35, P = .025).

LMD Risk in Nonsurgical Patients

In the cohort of patients who did not undergo surgery, gender (OR 1.63 95% CI 0.83–3.32 P = .159), and presence of dural-based metastasis (OR 2.07, 95% CI 0.58–7.40, P = .265) were no longer associated with development of LMD (Table 4). The presence of intraventricular metastasis (OR 5.47, 95% CI 1.60–18.71, P = .007) and metastasis bordering a ventricular space or cistern (OR 4.64, 95% CI 2.33–9.24, P =< .001) was associated with LMD development. In this cohort, neither the presence of metastasis in the infratentorial space, radiation treatment, nor presence of tumor bordering the ventricle were associated with the development of LMD. Similar to the

only metastasis that border a ventricle or CSF space, there was a reduced risk of LMD in patients who received WBRT (OR 0.28, 95% CI 0.09–0.83), P = .022).

Table 2 Univariate and Multivariate Logistic Regression Analysis of LMD for all Patients with MBM

Univariate					
Covariate	**Level**	**N**	**Odds Ratio(95% CI)**	**OR P-value**	**Overall P-value**
Gender	Female	280	1.69 (1.04–2.75)	**.033**	**.033**
	Male	547	-	-	
Dural metastasis	Yes	49	2.52 (1.17–5.43)	**.018**	**.018**
	No	769	-	-	
Intraventricular metastasis	Yes	23	6.06 (2.48–14.84)	**<.001**	**<.001**
	No	804	-	-	
Tumor bordering ventricle/cistern	Yes	192	3.73 (2.28–6.10)	**<.001**	**<.001**
	No	635	-	-	
Number of lesions bordering ventricle/cistern	>2	17	4.97 (1.55–16.00)	**.007**	**<.001**
	2	28	4.41 (1.68–11.53)	**.003**	
	1	147	3.47 (2.03–5.95)	**<.001**	
	0	635	-	-	
Location of brain metastasis	Infratentorial/ Both	162	1.39 (0.79–2.43)	.254	.254
	Supratentorial	665	-	-	
Chemotherapy before initial MBM diagnosis	Yes	181	0.68 (0.36–1.29)	.241	.241
	No	646	-	-	
Chemotherapy after initial MBM diagnosis	Yes	392	1.77 (1.08–2.89)	**.022**	**.022**
	No	435	-	-	
Immune therapy before initial MBM diagnosis	Yes	342	1.12 (0.69–1.81)	.652	0.652
	No	485	-	-	
Immune therapy after initial MBM diagnosis	Yes	390	0.76 (0.47–1.24)	.278	.278
	No	437	-	-	
Craniotomy for tumor resection	Yes	375	1.19 (0.74–1.93)	.476	.476
	No	452	-	-	
Radiation for all metastasis	SRS/FSRT	470	0.77 (0.43–1.38)	.382	.592
	WBRT ± SRS	190	0.71 (0.35–1.46)	.349	
	None	167	-	-	
Radiation for metastasis bordering ventricle	SRS/FSRT	95	0.61 (0.26–1.45)	.267	.073
	WBRT ± SRS	59	0.28 (0.09–0.83)	**.022**	
	None	38	-	-	
Multivariate					
Covariate	**Level**		**Odds Ratio(95% CI)**	**OR P-value**	**Overall P-value**
Gender	Female		1.69 (1.02–2.81)	**.042**	**.042**
	Male		-	-	
Dural metastasis	Yes		2.33 (1.04–5.23)	**.041**	**.041**
	No		-	-	
Intraventricular metastasis	Yes		4.48 (1.72–11.70)	**.002**	**.002**
	No		-	-	
Tumor bordering ventricle/cistern	Yes		3.17 (1.90–5.30)	**<.001**	**<.001**
	No		-	-	

entire cohort of patients, chemotherapy given after initial MBM diagnosis resulted in an increased risk of developing LMD (OR 2.35, 95% CI 1.15–4.80, P = .019). Radiation treatment in this cohort did not affect the development of LMD.

On multivariate analysis, treatment with chemotherapy following initial MBM diagnosis (OR=2.12 95% CI 1.02–4.40 P = .044) and the presence of metastasis bordering a ventricle or cistern were associated with the development of LMD (OR 4.38, 95% CI 2.18–8.77, P < .001).

Table 3 Univariate and Multivariate Logistic Regression Analysis of LMD for Surgical Patients with MBM

Univariate					
Covariate	**Level**	**N**	**Odds Ratio(95% CI)**	**OR P-value**	**Overall P-value**
Gender	Female	132	1.74 (0.87–3.48)	.116	.116
	Male	243	-	-	
Dural metastasis	Yes	29	2.77 (1.04–7.35)	**.041**	**.041**
	No	337	-	-	
Intraventricular metastasis	Yes	10	6.94 (1.86–25.88)	**.004**	**.004**
	No	365	-	-	
Tumor bordering ventricle/ cistern	Yes	88	2.97 (1.46–6.02)	**.003**	**.003**
	No	287	-	-	
Number of lesions bordering ventricle/ cistern	>2	4	4.45 (0.44–44.76)	.205	**.019**
	2	7	5.34 (0.97–29.28)	.054	
	1	77	2.71 (1.28–5.74)	**.009**	
	0	287	-	-	
Ventricular entry during surgery	Yes	39	4.82 (2.15–10.82)	**<.001**	**<.001**
	No	332	-	-	
Location of brain metastases	Infratentorial/ Both	44	2.40 (1.02–5.67)	**.045**	**.045**
	Supratentorial	331	-	-	
Chemotherapy before initial MBM diagnosis	Yes	63	0.42 (0.13–1.42)	.165	.165
	No	312	-	-	
Chemotherapy after initial MBM diagnosis	Yes	172	1.36 (0.68–2.70)	.383	.383
	No	203	-	-	
Immune therapy before Initial MBM diagnosis	Yes	125	1.15 (0.56–2.35)	.710	.710
	No	250	-	-	
Immune therapy after initial MBM diagnosis	Yes	175	0.70 (0.35–1.42)	.327	.327
	No	200	-	-	
Radiation	SRS/FSRT	206	0.83 (0.37–1.84)	.645	.366
	WBRT ± SRS	86	0.45 (0.15–1.38)	.163	
	None	83	-	-	
Tumor bordering ventricle w/surgery & ventricular entry	Yes	30	3.12 (1.03–9.48)	**.045**	**.045**
	No	58	-	-	
Tumor bordering ventricle w/surgery	SRS/FSRT	51	0.29 (0.09–0.98)	**.047**	**.040**
	WBRT ± SRS	19	0.09 (0.01–0.81)	**.032**	
	None	18	-	-	
Multivariate					
Covariate	**Level**		**Odds Ratio(95% CI)**	**OR P-value**	**Overall P-value**
Dural metastasis	Yes		3.47 (1.22–9.85)	**.020**	**.020**
	No		-	-	
Intraventricular metastasis	Yes		4.56 (1.01–20.50)	**.048**	**.048**
	No		-	-	
Ventricular entry during surgery	Yes		4.52 (1.86–11.03)	**<.001**	**<.001**
	No		-	-	
Location of brain metastases	Infratentorial/ Both		2.89 (1.14–7.35)	**.025**	**.025**
	Supratentorial		-	-	

Table 4 Univariate and Multivariate Logistic Regression Analysis of LMD for Nonsurgical Patients with MBM

Univariate					
Covariate	**Level**	***N***	**Odds Ratio(95% CI)**	**OR *P*-value**	**Overall *P*-value**
Gender	Female	148	1.63 (0.83–3.23)	.159	.159
	Male	304	-	-	
Dural metastasis	Yes	20	2.07 (0.58–7.40)	.265	.265
	No	432	-	-	
Intraventricular metastasis	Yes	13	5.47 (1.60–18.71)	**.007**	**.007**
	No	439	-	-	
Tumor bordering ventricle/ cistern	Yes	104	4.64 (2.33–9.24)	**<.001**	**<.001**
	No	348	-	-	
Number of lesions bordering ventricle/ cistern	>2	13	5.84 (1.47–23.20)	**.012**	**<.001**
	2	21	4.58 (1.39–15.11)	**.012**	
	1	70	4.44 (2.05–9.64)	**<.001**	
	0	348	-	-	
Location of brain metastasis	Infratentorial/ Both	118	1.05 (0.49–2.25)	.894	.894
	Supratentorial	334	-	-	
Chemotherapy before initial MBM diagnosis	Yes	118	0.90 (0.41–1.97)	.797	.797
	No	334	-	-	
Chemotherapy after initial MBM diagnosis	Yes	220	2.35 (1.15–4.80)	**.019**	**.019**
	No	232	-	-	
Immune therapy before initial MBMdiagnosis	Yes	217	1.16 (0.59–2.27)	.671	.671
	No	235	-	-	
Immune therapy after initial MBM diagnosis	Yes	215	0.83 (0.42–1.63)	.583	.583
	No	237	-	-	
Radiation	SRS/FSRT	264	0.74 (0.31–1.75)	.489	.663
	WBRT ± SRS	104	1.01 (0.38–2.69)	.983	
	None	84	-	-	
Tumor bordering ventricle w/o surgery	SRS/FSRT	44	1.33 (0.37–4.85)	.662	.358
	WBRT ± SRS	40	0.57 (0.14–2.42)	.447	
	None	20	-	-	
Multivariate					
Covariate	**Level**		**Odds Ratio(95% CI)**	**OR *P*-value**	**Overall *P*-value**
Chemotherapy after initial BM diagnosis	Yes		2.12 (1.02–4.40)	**.044**	**.044**
	No		-	-	
Tumor bordering ventricle/ cistern	Yes		4.38 (2.18–8.77)	**<.001**	**<.001**
	No		-	-	

Discussion

Standard therapy for intracranial metastatic disease has been driven by the Patchell *et al.* study which demonstrated that addition of surgery to WBRT results in improved local control and overall survival compared to WBRT alone.[17] This study has been supplemented over time with additional data supporting the use of SRS as a useful adjunct in various circumstances.[18] RTOG 9508 demonstrated the addition of SRS to WBRT also can result in local control and survival advantages, and now is commonly used as standard practice in place of WBRT for many indications.[18,19]

Controversy exists on the best methods for achieving local control and long-term prevention of LMD, and there is a relative paucity of data examining which factors are predictive of LMD development. Several studies have suggested that surgery for brain metastases confers a higher risk of developing LMD than SRS alone.[12,20,21] Other studies dispute this conclusion, and note that surgery in and of itself is not an independent predictor of LMD development.[22]

Of note, some of the prior studies included LMD resulting from several different types of malignancies.

In regards to surgery as a risk factor for LMD, prior studies have focused on surgical technique of en bloc versus piecemeal resection as a risk factor for developing LMD, indicating that piecemeal resection resulted in higher risk of LMD development compared to en bloc resection or SRS.[9,12] It is important to note that even though these cohorts were not homogenous with regard to the primary malignancy, these studies noted that patients with melanoma had the most pronounced effect with regard to technique of resection. Conversely, a phase 3 trial comparing postoperative SRS to observation did not demonstrate a difference between piecemeal and en bloc resection.[23,24] In our cohort of patients harboring MBM, there was no association between surgical intervention alone and LMD development. Due to the retrospective nature of the data collection over a long period of time and potential inconsistencies in reporting operative techniques, we suggest that one cannot make an accurate assessment on how impactful resection technique is on LMD development.

In the current study, however, amongst patients who underwent craniotomy for resection of a metastatic tumor, entry into the ventricles was strongly associated with LMD development. This finding suggests that LMD may develop through a mechanism of direct CSF seeding of tumor cells at the time of surgery. This hypothesis is further supported by the analysis which demonstrates that entry into the ventricle during removal of a metastasis that borders a ventricle or CSF cistern results in an increased risk of LMD. It would be interesting to understand whether en bloc or piecemeal resection techniques may impact LMD development in this subset of tumors.

A strength of this study is the combined analysis of 2 cohorts of patients with the same pathology (melanoma brain metastasis); one that underwent surgical resection and one that did not. This design element allowed us to separate out the risks of LMD inherent to the disease from those related to surgery. The primary finding in our study was that surgery alone did not increase the risk of LMD development. Instead, in the combined cohort, anatomic factors dominated as the most significant factors that resulted in LMD on multivariate analysis, such as the presence of dural-based and intraventricular metastasis, and metastasis bordering a ventricle or cistern. Within the cohort of patients who had surgery, dural-based and intraventricular metastasis, ventricular entry, and presence of metastasis in the infratentorial space were all found to be predictive of LMD development on multivariate analysis. These findings support that surgical seeding of tumor cells may play an important role in the development of LMD. In the nonsurgical cohort, the only anatomic variable that remained significant on multivariate analysis was metastasis bordering a ventricle or cistern. This supports the hypothesis that seeding relating to proximity to a CSF space is a key element underlying the development of LMD. We speculate that the lack of significance of dural-based or intraventricular metastasis on multivariate analysis of nonsurgical patients may indicated that tumors in those locations are well encapsulated and that seeding occurs secondary to surgical manipulation or local migration of tumor cells within the brain parenchyma.

We are not aware of a prior study that demonstrates that anatomic factors, such as a metastasis bordering, or residing within, a CSF space results in an increased risk of developing LMD. While it is unsurprising to imagine the contribution of direct access to and dissemination through the cerebrospinal fluid pathways as a pathogenetic driver of LMD, previous work on the issue generally lacks direct data to support this observation. Hence, we have demonstrated that patients with tumors in contact with the CSF space are at higher risk of developing LMD than those who do not have peri-ventricular brain metastases.

Previous reports have demonstrated that posterior fossa metastases results in an increased risk of LMD compared to supratentorial metastases.[11,25,26] Although the presence of infratentorial tumors was not a significant contributor of LMD in the entire cohort of patients, there was a significant difference in LMD rates for the surgical cohort on multivariate analysis. The significance of this finding in the surgical cohort suggests that CSF seeding is more likely to occur when operating in the posterior fossa, a finding that has been documented by others.[9,20] In line with the hypothesis of surgical seeding as a source of LMD, our data also indicates that dural-based tumors are associated with a higher risk of LMD development in surgical patients, which indicate that these malignant cells may spread via direct extension through the subdural space at the time of surgery.

There is recent literature suggesting that the development of postsurgical LMD is higher in patients receiving postoperative SRS as compared to SRS alone, WBRT, or preoperative SRS.[13,16,27,28] Although we did not find that addition of any type of radiation therapy to the first-line treatment of MBM reduced the risk of LMD on univariate or multivariate analysis in any of the cohorts, we did find that radiation reduced the risk of LMD overall. In the entire cohort of patients, univariate analysis demonstrated a decrease risk of LMD in patients with metastasis bordering a CSF space who have received WBRT. We also found in patients with metastases bordering a CSF space who underwent surgical resection (N = 88), the addition of either SRS/FSRT or WBRT resulted in a decreased risk of LMD on univariate analysis. For patients who have peri-ventricular metastases that did not undergo surgery (N = 104), radiation therapy did not affect LMD. These results indicate the importance of adjuvant radiation therapy for patients who underwent surgical resection of a metastasis bordering a CSF space, further supporting the idea that seeding during surgery occurs and radiation may help to reduce the development of LMD. Unfortunately, due to the wide variety in radiation treatments performed over the timeframe (including some treatments performed at outside institutions), a more definitive statement on the impact of specific radiotherapy regimens, timing strategies, or dose/fractionation strategies in this cohort cannot be made at this time.

Two variables that indicated a risk for development of LMD on multivariate analysis that are unexplained are gender and chemotherapy after diagnosis of MBM. Female gender was significantly associated with risk of developing LMD. There is no previously published evidence suggesting that gender impacts on the risk of LMD in melanoma or outcome from brain metastasis/LMD. Recent data from patients with primary malignant brain tumors have shown that there is a difference in peripheral immune responses between males and females with respect to polymorphonuclear myeloid-derived

suppressor cells (PMN-MDSCs).[29] These cells also have been shown to affect tumor cell dissemination and metastases in animal models, but their role in the pathophysiology of brain metastasis or LMD in patients with melanoma remains unknown.[30] The significance of the association between treatment with chemotherapy after initial MBM diagnosis and LMD may be an indication of performance status, in which patients with higher performance status received chemotherapy and had a greater chance to develop LMD.

The limitations of this study include the retrospective nature of the data collection. Due to the time span in which patient records were reviewed, detailed radiation treatment data were not available to assess the impact of specific radiotherapy regimens on the development of LMD. Additionally, surgical reports did not consistently describe the technique used for us to determine use of an en bloc versus piecemeal resection approach. Our analysis also did not distinguish postsurgical nodular versus classic LMD. Although recent literature has established the a nodular characteristic associated with postsurgical LMD,[15] we did not make this determination in our analysis, but since we were able to separate the surgical from the nonsurgical cohort of patients, we can accurately assess surgery itself as a factor in the development of LMD.

Conclusions

The data presented demonstrate a correlation between anatomic location of brain metastases and the risk for development of LMD. Although our data do not demonstrate that surgical resection alone is a risk factor for LMD, we have demonstrated that surgery for dural-based, intraventricular, or infratentorial metastasis, or entry into a ventricle during surgery, did result in an increased risk of developing LMD.

Keywords

brain metastasis | leptomeningeal disease | melanoma | surgery

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