Leptomeningeal metastases in the MRI era

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ABSTRACT

Background: Diagnosis of leptomeningeal metastasis (LM) has become increasingly frequent. The diagnostic gold standard has been CSF cytology, but MRI is now used routinely for diagnosis. Diagnosis and prognosis of LM has not been studied in the MRI era.

Methods: Patients with LM from 2002 through 2004 were identified through a neurology database, as well as by reviewing all abnormal CSF cytologies from a pathology database. Diagnosis was made by malignant cytology or imaging; suspicious cases treated as LM were also included.

Results: A total of 187 patients with LM were analyzed in this retrospective review. Of these, 150 had solid and 37 had hematopoietic malignancies. Median age was 56.4 years, and median Karnofsky performance status (KPS) was 70. The most common types of solid tumor were breast (65 patients), lung (47), gastrointestinal (11), and melanoma (9). Of the hematopoietic tumors, 21 were lymphoma and 15 were leukemia. Fifty-three percent of patients were diagnosed by imaging, 23% by cytology, and 24% by both. Treatment included radiation therapy in 55%, intrathecal chemotherapy in 29%, and systemic chemotherapy in 18%; 21% received supportive care alone. Median overall survival was 2.4 (95% confidence interval 1.9–3.1) months. Median survival for patients with hematopoietic tumors was 4.7 months and for solid tumors was 2.3 months ($p = 0.0006$). In multivariate analysis, initial KPS and tumor type (solid vs hematopoietic) were significant predictors of survival.

Conclusions: Despite enhanced diagnosis with MRI, prognosis remains poor in leptomeningeal metastasis. Those with hematopoietic tumors continue to fare better than those with solid tumors. *Neurology*® 2010;74:1449–1454

GLOSSARY

CI = confidence interval; ICP = intracranial pressure; KPS = Karnofsky performance status; LM = leptomeningeal metastasis; VP = ventriculoperitoneal.

Leptomeningeal metastasis (LM) from cancer was first described in 1870.¹ Previously rare, it has become an increasingly common diagnosis as better treatments lengthen survival of patients with cancer. Many otherwise-effective chemotherapies for cancer have relatively poor CNS penetration, which may allow malignant cells to persist in the CNS and develop into LM. This was well-documented in acute lymphocytic leukemia, where curative treatment now includes CNS prophylaxis.²

Identification of malignant cells by CSF cytology has been the diagnostic gold standard, although the sensitivity of cytology is limited.³ With improved visualization of the subarachnoid space by MRI, imaging has become the initial, and often sole, diagnostic tool.⁴ Large case series of LM have been reported,^{4–15} but few were conducted in the era of high-quality MRI.

We collected data from patients with LM diagnosed over 3 years, during which time MRI was used routinely in the evaluation of neurologic symptoms. We sought to determine whether MRI affected diagnosis or outcome of patients with LM. We also sought to validate if the previously described positive prognostic factors of breast cancer histology,^{9,11} female gender,¹⁰

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performance status,¹² and intrathecal^{9,10} or systemic chemotherapy¹¹ remained important in the modern era.

METHODS **Case ascertainment.** This is a retrospective study of patients newly diagnosed with LM between January 1, 2002, and December 31, 2004. All potential patients were identified through 2 databases at our institution, a neurology patient database, and a pathology database of all collected CSF cytologic specimens.

The diagnosis was made in 1 of 3 ways: 1) a CSF cytology positive for malignant cells, 2) MRI scans showing LM, or 3) by clinical judgment of the treating physician, defined as initiation of treatment for LM in the setting of suspicious cytology or imaging findings. Eligibility criteria also included age ≥ 18 , primary cancer source outside the CNS (i.e., not a primary brain or

spinal cord tumor), and adequate information to provide follow-up (i.e., not an isolated consultation or second opinion at initial diagnosis).

Standard protocol approvals, registrations, and patient consents. This study was approved by the Memorial Sloan-Kettering Cancer Center Institutional Review Board; because of its retrospective nature, the Institutional Review Board waived the need for informed consent.

Data collection. Data collected for each patient included date of birth, date of initial cancer diagnosis, date of LM diagnosis, Karnofsky performance status (KPS) score at LM diagnosis (which was estimated by the investigator if not recorded), primary cancer histology, extent of systemic disease at diagnosis of LM, the presence of prior or current brain metastases, history of prior radiation to brain or spine, neurologic signs and symptoms at diagnosis, MRI results, CSF results, initial and subsequent treatment, outcome, and date of death or last follow-up. For patients whose date of death was not recorded, the social security death index and a Web-based obituary search service were used in an attempt to determine date of death. If none was identified, patients were censored at date of last follow-up.

Statistical analysis. Overall survival was defined as the time from LM diagnosis to time of death or last follow-up. Survival rates were determined using the Kaplan-Meier method, and survival curves were compared using the log-rank test. The Cox proportional hazards model was used to determine prognostic factors associated with improved survival. All factors tested on univariate analysis were included in a multivariable Cox model. A *p* value less than 0.05 was considered significant for all analyses. All statistical analyses were performed in SAS 9.1 (SAS Institute Inc., Cary, NC).

RESULTS **Patient characteristics.** A total of 187 patients satisfying the eligibility criteria were diagnosed with LM at Memorial Sloan-Kettering Cancer Center over these 3 years of 564 patients screened for this study; only 6 (3%) were included on the basis of the physician's clinical judgment. Of these 187 patients, 150 had solid tumors and 37 had hematologic cancers (table 1). The median age was 56 years (range, 19–87 years) and the median KPS was 70 (range, 10–100). There were more women (*n* = 137, 73%); the largest number of patients had breast cancer (*n* = 65, 35%) followed by lung cancer, lymphoma, leukemia, and melanoma. The median time from diagnosis of the primary tumor to diagnosis of LM was 1.6 years (range, 0–22.6 years) in the entire population. However, patients with solid tumors had a median time interval of 2.0 years (range, 0–22.6 years), in contrast to 11 months (range, 0–7.7 years) for those with hematologic primaries (*p* = 0.004). At LM diagnosis, 121 (81%) patients with solid tumors had known metastatic disease and 30 (81%) with hematopoietic tumors had active disease. Only 14 (9%) patients with solid tumors and 6 (16%) with hematopoietic tumors were considered free of disease prior to their LM diagnosis. A total of 109 patients (58%) had previous or current brain metastases, 105

Table 1 Patient and tumor characteristics

	All patients (n = 187)	Primary tumor	
		Solid (n = 150)	Hematopoietic (n = 37)
Gender, n (%)			
Female	137 (73)	117 (78)	20 (54)
Male	50 (27)	33 (22)	17 (46)
Age, y, median (range)	56 (19–87)	56 (19–87)	54 (23–79)
KPS, %, median (range)	70 (10–100)	70 (20–100)	70 (10–100)
Cancer diagnosis to LM diagnosis, y, median (95% CI)	1.6 (1.3–2.2)	2.0 (1.4–2.7)	0.9 (0.6–1.5)
Primary tumor, n (%)			
Breast	65 (35)	65 (43)	—
Lung	47 (25)	47 (31)	—
NSCLC	43 (23)	43 (29)	—
SCLC	4 (2)	4 (3)	—
Gastrointestinal	11 (6)	11 (7)	—
Esophageal	5 (3)	5 (3)	—
Gastric	5 (3)	5 (3)	—
Colon	1 (1)	1 (1)	—
Melanoma	9 (5)	9 (6)	—
Other solid	13 (7)	13 (9)	—
Head and neck	4 (2)	4 (3)	—
Bladder	2 (1)	2 (1)	—
Ovarian	2 (1)	2 (1)	—
Endometrial	1 (1)	1 (1)	—
Prostate	1 (1)	1 (1)	—
Sarcoma	1 (1)	1 (1)	—
Germ cell	1 (1)	1 (1)	—
Neuroendocrine	1 (1)	1 (1)	—
Unknown	5 (3)	5 (3)	—
Lymphoma	21 (11)	—	21 (57)
Leukemia	15 (8)	—	15 (41)
Multiple myeloma	1 (1)	—	1 (3)

Abbreviations: CI = confidence interval; KPS = Karnofsky performance status; LM = leptomeningeal metastasis; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

(70%) with solid tumors and 4 (11%) with hematopoietic tumors.

The clinical picture of LM classically involves symptoms and signs referable to multiple levels of the neuraxis. Only 2% of the cohort had no clinical features at diagnosis; 2 patients had leukemia, 1 was found to have LM during prophylactic intrathecal chemotherapy and 1 to have LM on a screening MRI, and 2 patients had non-small cell lung cancer with incidentally found LM on MRI done for known brain metastases. Thirty-four percent of patients had symptoms or signs referable to one compartment of the CNS (cerebral, posterior fossa, or spine), 39% to 2 compartments, and 25% to all 3. Headache, confusion, nausea/vomiting, diplopia, cerebellar dysfunction, back pain, and leg weakness were the most common findings.

Diagnostic procedures. Of the 187 patients, the diagnosis of LM was established by imaging in 53%, by CSF cytology in 23%, and by both methods in 24%. Not every patient had all tests performed. A total of 177 (95%) had MRI of at least 1 segment of the CNS, while 102 (55%) underwent cytologic analysis; 1 patient with solid tumor was diagnosed solely by cranial CT (figure e-1 and table e-1 on the *Neurology*[®] Web site at www.neurology.org). The proportion of patients undergoing CSF analysis was higher in those with hematopoietic tumors than solid tumors (100% vs 43%). The proportion of patients undergoing MRI was high in both groups, 96% in solid tumors and 89% in hematologic cancers. Imaging was diagnostic for LM in 143 of 177 patients (81%) who had an MRI; 88 of 102 patients (86%) had a positive CSF cytology. For patients with solid tumors, neuroimaging was positive for LM in 88% and CSF was positive in 85% of those tested. In contrast, only 48% of patients with hematopoietic tumors had positive neuroimaging for LM, while 89% had a positive CSF cytologic analysis.

Cytology vs MRI. Ninety-three patients had both MRI of at least 1 segment and CSF analysis (table 2).

LM was confirmed by both positive cytology and MRI results in 45 patients (48%). In 34 of 93 patients (37%), the diagnosis was established only by the demonstration of malignant cells in the CSF, while the diagnosis was made by neuroimaging alone in 14 of 93 patients (15%). The distribution of diagnostic tools used to confirm LM was marginally different between primary tumor types ($p = 0.08$). Both diagnostic tests were positive for LM in 55% of solid tumor patients compared with only 36% of hematopoietic patients. Cytology alone was positive more frequently in patients with hematopoietic tumors compared to solid tumors (52% vs 28%). In contrast, positive neuroimaging alone was uncommon in both solid and hematopoietic tumor patients (17% vs 12%).

Of the 48 patients who underwent both cytologic evaluation and MRI of the entire neuraxis (brain and total spine) at diagnosis, 35 had solid tumors and 13 had hematopoietic tumors. Of these patients, only 54% had concordant positive results on both diagnostic tests (table 2). Twenty-one percent of patients had positive MRI results but negative CSF cytology, while 25% had a negative MRI but positive CSF cytology. In patients with solid tumors, the rate of positive MRI scans was incrementally higher, whereas in patients with hematopoietic tumors the rate of positive CSF cytology results was slightly higher ($p = 0.42$). True sensitivity and specificity could not be calculated, as all patients had a positive result on at least one of the studies.

CSF findings. A total of 102 patients underwent some degree of CSF analysis, of which cytology was malignant in 76 and suspicious in 12. Only 5 patients had completely normal CSF (defined as negative cytology, leukocytes ≤ 5 per mm^3 , protein ≤ 50 mg/dL, glucose ≥ 40 mg/dL, and opening pressure ≤ 20 cm water); of these, 4 had breast cancer and one had leukemia. Four other patients had cytology samples taken from ventricular rather than lumbar fluid; other CSF characteristics in these patients were not analyzed due to differing normal values in ventricular vs lumbar fluid.² Overall, cytology was abnormal in 86% of patients, while leukocytes were elevated in 64%, protein was elevated in 59%, and glucose was decreased in 31% (table e-2). Opening pressure was measured in only 32 patients, but was elevated in 50%. Leukocytosis was seen more often in hematopoietic tumors, while elevated protein, low glucose, and elevated opening pressure were seen more often in solid tumors.

Treatment. Of the 187 LM patients, 28 (15%) received supportive care alone, all but one of whom had solid tumors. There were 67 patients (36%) who

Table 2 Comparison of diagnostic tools

	Diagnostic tool		Overall, count (%)	Hematopoietic, count (%)	Solid, count (%)	p Value
	Cytology	MRI				
Cytology and MRI (seg ≥ 1 , n = 93)	+	+	45 (48)	12 (36)	33 (55)	0.08
	–	+	14 (15)	4 (12)	10 (17)	
	+	–	34 (37)	17 (52)	17 (28)	
Cytology and full MRI n, =48	+	+	26 (54)	6 (46)	20 (57)	0.42
	–	+	10 (21)	2 (15)	8 (23)	
	+	–	12 (25)	5 (38)	7 (20)	

Figure 1 Overall survival of the entire cohort of 187 patients

received initial treatment with radiotherapy alone, 46 (25%) chemotherapy alone, and 36 (19%) combined radiation and chemotherapy. Treatment was unknown in 10 patients (5%). Chemotherapy was intrathecal in 26% of patients, combined intrathecal and systemic in 4%, and systemic only in 14%. Just over 40% of all patients received whole brain radiotherapy, while 19% received radiotherapy to the spine. Of note, 42% of patients with solid tumors had previously received cranial radiotherapy for brain metastases, of whom 97% received whole brain radiotherapy, and 3% received stereotactic radiosurgery. Intrathecal chemotherapy was used more often in patients with hematopoietic tumors than in those with solid tumors; 46% of patients with hematopoietic tumors received intrathecal methotrexate while

Figure 2 Survival of patients following diagnosis of leptomeningeal metastasis by tumor type

32% received cytarabine in either regular or liposomal form. Of patients with solid tumors, only 11% received intrathecal methotrexate and 4% received some form of intrathecal cytarabine. Approximately 20% of patients in each group received systemic chemotherapy.

Survival and prognostic factors. Of the 187 patients with LM, 177 (95%) had died at last follow-up. Median overall survival for the entire cohort was 2.4 months (95% confidence interval [CI] 1.9–3.1) (figure 1). Median overall survival for patients with solid tumors was 2.3 months (95% CI 1.7–2.6) compared with 4.7 months (95% CI 2.7–6.8) for patients with hematopoietic tumors ($p = 0.0006$; figure 2). Median survival of patients with breast cancer was 2.8 months, comparable to those with lung cancer at 2.2 months. Patients with other solid tumors fared worse. Leukemia patients survived a median of 5.8 months, and lymphoma patients 4.6 months. There were no differences in overall survival seen within the solid ($p = 0.09$) or hematopoietic ($p = 0.32$) patient populations. Twenty patients had no active disease prior to their diagnosis of LM; these patients survived a median of 3.8 months vs a median survival of 2.4 months in patients known to have active disease ($p = 0.18$). We were unable to confirm their systemic disease status, as staging was often not completed once LM was diagnosed.

Twenty patients survived longer than 12 months (range 12.6 to 66.3 months); of these, 10 had hematopoietic tumors (6 leukemia and 4 lymphoma) and 10 had solid tumors (4 breast, 4 lung, 1 bladder, and 1 carcinoma of unknown primary). Of the 6 leukemia patients, none died of progressive LM: 3 were alive, 2 died of systemic disease, and 1 died of methotrexate leukoencephalopathy. No clear difference could be found between these 20 patients and the remainder of the cohort with regard to extent of disease at LM diagnosis, the presence of previous or concurrent brain metastases, symptoms at diagnosis, or treatment provided.

Elevated intracranial pressure (ICP) was present in 48 patients (26%), as determined by an elevated opening pressure (>20 cm water) on lumbar puncture (16 patients), diagnosis of hydrocephalus,³ placement of or recommendation for a ventriculoperitoneal (VP) shunt,⁷ or other symptoms or signs consistent with elevated ICP.²² The median overall survival of patients with a diagnosis of elevated ICP was 1.7 months, while it was 2.9 months for those without the diagnosis ($p = 0.02$). All but 3 of the patients with elevated ICP had solid tumors.

After univariate Cox regression analysis, 20 patients were removed from the multivariate analysis because they were missing variable information, re-

Table 3 Univariate and multivariate Cox regression analysis

Variable	Univariate (n = 187)		Multivariate (n = 167)	
	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Age at LM diagnosis (10-year increase)	1.06 (0.93-1.213)	0.21		
Gender				
Female	1.00			
Male	1.20 (0.86-1.67)	0.27		
Primary tumor type				
Hematopoietic	1.00		1.00	
Solid	1.97 (1.33-2.93)	0.0008	2.00 (1.28-3.11)	0.002
Initial KPS (n = 167)	0.72 (0.66-0.80)	<0.0001	0.72 (0.66-0.80)	<0.0001
Time: cancer diagnosis to LM diagnosis				
>3 mo	1.00			
≤3 mo	1.26 (0.92-1.72)	0.15		
Elevated ICP				
No	1.00	1.00		
Yes	1.49 (1.07-2.08)	0.02	1.28 (0.89-1.84)	0.12

Abbreviations: CI = confidence interval; HR = hazard ratio; ICP = intracranial pressure; KPS = Karnofsky performance status; LM = leptomeningeal metastasis.

sulting in 167 patients included in the final analysis (table 3). Univariate analysis demonstrated an association between initial KPS, primary tumor type, and elevated ICP with overall survival. Initial KPS and primary tumor type continued to be significant in the multivariate analysis. Gender became significant in multivariate analysis, but was not in univariate analysis; there was an interaction seen between gender and tumor type. When comparing women with hematopoietic tumors to men with hematopoietic tumors, men had a higher risk of death (hazard ratio 3.1 [95% CI 1.4–6.9], $p = 0.005$). When comparing women with solid tumors to men with solid tumors, men had a higher risk of death (hazard ratio 1.5 [95% CI 1.0–2.3], $p = 0.04$), perhaps related to the different tumor types in each group.

DISCUSSION This series represents the largest cohort of patients with LM in the MRI era. Consistent with results seen in older studies, most of our patients presented with LM at a late stage of their disease, usually in the setting of widespread metastases. Sixty-four percent of our patients had multifocal symptoms and signs, but it can be difficult to attribute all clinical findings to LM as opposed to brain metastases, which frequently coexist. For this reason alone, MRI is important in these patients to localize the cause of symptoms accurately and direct palliative therapy to the appropriate sites of disease.

Contrary to expectations, survival in this modern patient cohort (median of 2.4 months) was no better

than that described in the past. Possible earlier detection by MRI did not even cause lead time bias and longer apparent survival. By comparison, one previous cohort included 105 patients with LM from systemic primary tumors with a median survival of 4.7 months for the entire cohort and 3.3 months for the 88 patients with solid tumors.¹¹ A second study of 85 patients with LM from systemic solid tumors demonstrated a median survival of only 51 days (1.7 months).¹⁶ There was no clear correlation between histology and survival within our solid tumor group, although there was a trend toward better survival in patients with breast cancer ($p = 0.09$). Interestingly, there was also an interaction between gender and tumor type, with women having longer survival in both the solid and hematopoietic tumor groups. Female gender has been reported to be a positive prognostic factor in other studies¹⁰; the explanation remains unclear.

MRI was an important component of diagnosis in all patient groups, but particularly in the solid tumor population, whereas CSF cytology was relatively more important in hematopoietic tumor patients, as described previously.⁴ Presumably, this relates to the propensity of solid tumors to adhere to neural structures and form nodules, which become visible on MRI. While we included only patients with LM, it is clear that neither MRI nor CSF analysis is sensitive enough to stand alone as a diagnostic method for LM in patients with either solid or hematopoietic tumors. Diagnosis often requires vigorous pursuit with MRI of the entire neuraxis as well as CSF cytologic evaluation if imaging is negative in patients suspected to have LM clinically. The rate of diagnosis by imaging alone was high in our study; 45% of patients never had CSF analysis. This may differ from standard clinical practice at other institutions. However, while CSF cytology has often been held as the gold standard for the diagnosis of LM, it is accurate only 54% of the time with a single specimen and can remain falsely negative in 14% of patients even after 3 samples.⁹

Cytologic examination is not the only reason to perform a lumbar puncture in a patient with suspected or diagnosed LM. Elevated ICP remains a significant concern in patients, particularly in those with solid tumors. The 26% incidence of elevated ICP in our cohort is similar to a prior report of 37% in patients diagnosed with radiographic evidence of hydrocephalus.⁹ Elevated ICP was likely underestimated in our cohort as most patients did not have pressure measured even when a lumbar puncture was performed. VP shunt placement can improve symptoms in patients with LM with elevated ICP with a low rate of procedure-related complications.¹⁷ While

a VP shunt precludes delivery of intrathecal chemotherapy via an Ommaya reservoir, elevated ICP is a relative contraindication to intrathecal therapy depending upon the patient's clinical condition and the pressure measurement. On-off valves do not restore normal CSF flow, and should not be used to facilitate intrathecal chemotherapy in shunted patients. Management of elevated ICP is the priority, and subsequent treatment of LM must be accomplished through alternative approaches.

Our study has several weaknesses, most of which relate to its retrospective nature. Data collection was fairly complete, but performance status was inconsistently recorded by the treating physicians and was estimated by the investigators from available information. Estimation likely adds potential bias to this prognostic variable, as a patient's survival was known when KPS was assigned, which may have colored interpretation of the descriptive information available. Performance status and treating physicians' existing prejudices may have affected treatment decisions, leading to more aggressive therapy offered to those with better performance status or histologies perceived as having better outcomes. However, it seems clinically appropriate to reserve aggressive treatment for patients in relatively good condition, and in this manner our series reflects standard clinical practice accurately. In addition, we could not determine the benefit of specific therapeutic interventions due to patient selection for treatment or palliative care. Regardless, therapy rarely prolonged survival. Improved treatment of LM and possible prevention with agents that penetrate the CNS are sorely needed.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Lindsay Jacks, MSc, and Dr. Katherine S. Panageas.

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DISCLOSURE

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