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Scientific Article

Early Detection of Leptomeningeal Metastases Among Patients Undergoing Spinal Stereotactic Radiosurgery

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Abstract

Purpose: The management of patients with advanced solid malignancies increasingly uses stereotactic body radiation therapy (SBRT). Advanced cancer patients are at risk for developing leptomeningeal metastasis (LM), a fatal complication of metastatic cancer. Cerebrospinal fluid (CSF) is routinely collected during computed tomography (CT) myelography for spinal SBRT planning, offering an opportunity for early LM detection by CSF cytology in the absence of radiographic LM or LM symptoms (subclinical LM). This study tested the hypothesis that early detection of tumor cells in CSF in patients undergoing spine SBRT portends a similarly poor prognosis compared with clinically overt LM.

Methods and Materials: We retrospectively analyzed clinical records for 495 patients with metastatic solid tumors who underwent CT myelography for spinal SBRT planning at a single institution from 2014 to 2019.

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Data sharing statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Results: Among patients planned for SBRT, 51 (10.3%) developed LM. Eight patients (1.6%) had subclinical LM. Median survival with LM was similar between patients with subclinical versus clinically evident LM (3.6 vs 3.0 months, $P = .30$). Patients harboring both parenchymal brain metastases and LM (29/51) demonstrated shorter survival than those with LM alone (2.4 vs 7.1 months, $P = .02$).
Conclusions: LM remains a fatal complication of metastatic cancer. Subclinical LM detected by CSF cytology in spine SBRT patients has a similarly poor prognosis compared with standardly detected LM and warrants consideration of central nervous system-directed therapies. As aggressive local therapies are increasingly used for metastatic patients, more sensitive CSF evaluation may further identify patients with subclinical LM and should be evaluated prospectively.

Introduction

Leptomeningeal metastasis (LM), or the spread of cancer into the cerebrospinal fluid (CSF)-filled spaces surrounding the central nervous system (CNS), carries an extremely poor prognosis and causes rapid neurologic dysfunction and death.[1,2] Approximately 5% to 10% of patients with solid tumors develop LM.[1] With improving therapies for patients with metastatic disease, this incidence is expected to rise.[1,3]

Patients with LM classically present with multifocal neurologic signs and symptoms resulting from involvement of the brain, cranial nerves, or spinal nerves.[4] Diagnosis is typically made after suspicion for LM based on clinical evaluation prompts neuroimaging and/or CSF analysis (Fig. 1A, 1B).[5] However, LM may also be diagnosed incidentally by either magnetic resonance imaging (MRI) or CSF cytology in patients without neurologic symptoms. One such subset of patients includes patients undergoing stereotactic body radiation therapy (SBRT) for spinal bone metastases.[6-9] These patients routinely undergo computed tomography (CT) myelogram for radiation planning (Fig. 1C-F). CT myelography enables opacification of the thecal sac and therefore delineation of the spinal cord as an organ at risk, enabling safer delivery of ablative radiation doses to spinal bone metastases. This procedure involves extraction of CSF, which may undergo cytological evaluation.[10,11] In some patients, tumor cells may be detected in CSF despite the absence of radiographic evidence or symptoms of LM. The clinical significance of such "subclinical LM," including risk for progression to clinically evident LM and survival, remains unknown.

Some have speculated that spinal bony metastases may seed the CSF via retrograde spread of cancer cells along the valveless vertebral venous plexus (Batson's plexus) that surrounds the vertebral column.[13,14] However, this potential route of spread remains hypothetical, and to our knowledge no studies to date have demonstrated increased risk for LM in patients with spinal bony metastases from solid tumors.

We therefore sought to systematically characterize our institution's experience with subclinical LM among patients with solid tumors undergoing spine SBRT. We focused our analyses on histologies accounting for the majority of LM arising from solid malignancies, including breast cancer (BC), non-small cell lung cancer (NSCLC), and malignant melanoma (MM).[15] Our study aimed to reveal rates of subclinical LM among spine SBRT patients, to determine the prognosis of subclinical LM compared with clinically evident LM and to validate previously identified prognostic factors for survival with LM.

Methods and Materials

Patients

We screened 2,371 patients treated with radiation for spinal bone metastases at a single institution between January 1, 2014, and August 1, 2019. Eligibility criteria included spinal bone metastases treated with stereotactic radiosurgery with CT myelography planning. We extracted patient, tumor, treatment, and outcome characteristics from the electronic medical record and electronic obituary databases. If no date of death was identified, patients were censored at the date of last contact, for example, follow-up visit or telephone note. Ethical approval for this research was obtained from the institutional review board under protocol #17-014 on January 6, 2017.

Treatment and planning

For radiation treatment planning, CT myelogram was obtained in a standard fashion for all patients as previously described.[12] For all patients, a minimum volume of 4 mL of CSF was collected before contrast injection. For imaging of 1 or multiple spinal regions (ie, cervical, thoracic, or lumbar), 10 mL of iohexol (Omnipaque) 240 mg iodine/mL was injected into the thecal sac under fluoroscopic guidance. Iohexol was introduced in the lumbar spine for all patients. CT simulation was performed within 1 to 2 hours of myelogram.

Patients were treated with CT-guided intensity-modulated SBRT using a TrueBeam Linear Accelerator Radiotherapy System (Varian Medical Systems, Palo Alto, CA). All patients received photon beam RT. The treating radiation oncologist determined the radiation dose and

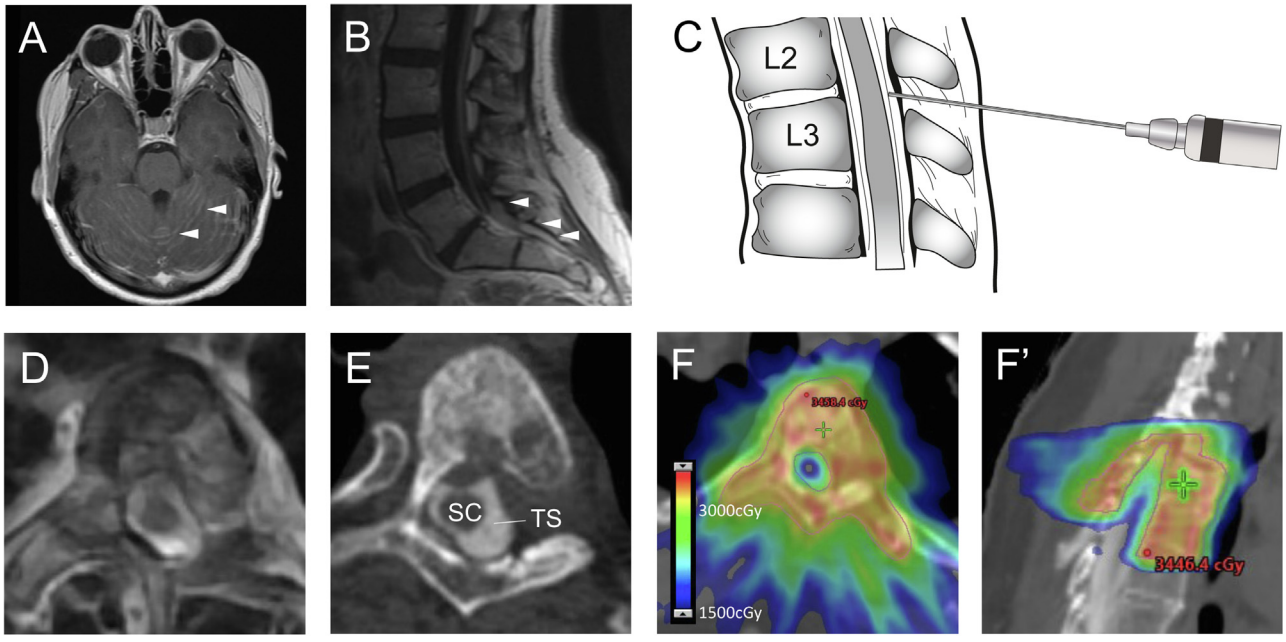

Figure 1 Overview of leptomeningeal disease and computed tomography (CT) myelography for stereotactic body radiation (SBRT) planning for spinal bone metastases. (A, B) Axial and sagittal T1-weighted post-contrast magnetic resonance imaging (MRI) demonstrating leptomeningeal enhancement along the cerebellar folia, surface of the conus, and cauda equina nerve roots (arrowheads) in a 31-year-old woman with metastatic breast cancer. (C) Illustration of myelography procedure for SBRT planning, as previously described.[12] (D) Axial T2-weighted MRI illustrating biventral epidural disease at T3 in a 59-year-old woman with metastatic non-small cell lung cancer (NSCLC). (E) Axial post-myelogram CT at T3 of patient in (D) employed for radiation planning showing spinal cord (SC) and contrast-opacified thecal sac (TS). (F, F') Axial (F) and sagittal (F') images demonstrating radiation plan for SBRT with a total dose of 3000 cGy to T3 and T4 in patient in (D). Red outline denotes planning target volume (PTV). Color wash denotes radiation dose.

fractionation based on the patient's clinical status, prior treatment, and tumor radiosensitivity. Treatment plans were developed using the planning systems Eclipse (Varian Medical Systems) or Top Module (New York, NY) with anisotropic analytical algorithm or pencil beam convolution for dose calculations, respectively. The treating radiation oncologist and a dedicated medical physicist reviewed each plan and performed quality assurance. Patients were immobilized using a custom immobilization system and aligned with cone beam CT as previously described.[6,16] A supervising radiation oncologist verified each patient's setup before radiation delivery.

Follow-up and evaluation

We identified LM based on CSF cytology revealing malignant cells (n = 22) or cells suspicious for malignancy (n = 3) (total n = 25/61, 49%), as determined by morphologic criteria and/or findings consistent with LM on MRI of the brain (n = 33/61, 65%) and/or spine (n = 19/61, 37%) according to clinical practice guidelines.[5,17] Some patients had LM confirmed both on imaging and CSF cytology. Of 61 patients who developed LM at any time during their disease course, 8 had subclinical LM first discovered at the time of SBRT planning. For all patients, cytology and MRI findings were correlated with clinical notes documenting patient symptoms, physical examination findings, and the treating physician's assessment and plan. We defined the date of LM diagnosis as the date of the first positive CSF cytology or the date of the first MRI brain or spine showing LM, whichever occurred first. For our analyses, we defined subclinical LM as positive CSF cytology at the time of myelogram for radiation planning in the absence of radiographic evidence or symptoms consistent with LM. We determined presence or absence of LM symptoms based on examinations performed by the treating neuro-oncologists, neurosurgeons, radiation oncologists, and medical oncologists. CSF cytologic examination performed at the time of CT myelogram did not include routine evaluation of CSF white or red blood cells, protein, or glucose. We defined a "complete" LM workup as CSF cytology examination and gadolinium contrast-enhanced MRI brain and spine within 30 days of LM diagnosis.

Statistical analysis

The primary study endpoint was survival with LM, defined as time from LM diagnosis to the date of death

from any cause. We calculated overall survival (OS) as the time from the start of first course of spine SBRT to the date of death from any cause. We used Kaplan-Meier analysis to estimate rates of survival. Age, histology, and Karnofsky performance scale (KPS) at either SBRT or LM diagnosis and the presence of parenchymal metastases at LM diagnosis were considered. Univariate associations with time to death from SBRT and time to death from LM diagnosis were performed using a log-rank test with the median survival reported. Variables found to be significant in univariate models were entered into a Cox proportional hazards model with assumptions of proportional hazards verified, and the independent hazard ratios (HRs) and 95% confidence intervals are reported. We analyzed categorical data using the Fisher exact test. For all clinical factors, medians and range are reported. Survival estimates are reported as a median survival with a 95% confidence interval. Significance was reported using an $\alpha = 0.05$ for all tests.

Results

Patient characteristics

We identified 495 patients who satisfied eligibility criteria (Table 1). The median age at SBRT was 65 years (29-90 years), and the median KPS was 80 (40-100). The majority of patients had NSCLC (n = 319, 64%), followed by BC (n = 132, 27%) and MM (n = 44, 9%). The most common fractionation regimens were 27 Gray (Gy) in 3 fractions (n = 302, 61%) and 24 Gy in 1 fraction (n = 123, 25%). Median KPS, radiation dose, and fractionation were similar across histologies.

Of 495 patients, 162 (33%) were alive at last follow-up. The median OS for all patients was 12.5 months (10.9-14.4 months). The median OS for patients with BC was 32.8 months (25.2 months-not estimated), significantly longer than that of patients with NSCLC (9.7 months [8.1-11.2 months]) or MM (7.8 months [5.6-13.8 months]) ($P < .001$). Patients with a KPS ≥80% (n = 370/478) survived longer (median OS 15.9 vs 6.0 months, $P < .001$). In a multivariate model, KPS <80 (HR, 2.0; 1.6-2.6), melanoma relative to BC (HR, 2.4; 1.5-3.7), and NSCLC relative to BC (HR, 2.7; 2.0-3.7) were independently associated with worse OS ($P < .001$).

Among all evaluated patients, 51 (10.3%) developed LM (Table 2). In patients who underwent complete LM workup within 30 days of diagnosis (n = 22), LM accompanied by a positive CSF cytology (n = 18) had a median OS of 3.5 months (1.0-6.1 months) compared to a median OS of 5.4 months (2.7-8.2 months) in MRI-positive/CSF-negative LM (n = 4). There was no difference in rates of LM by histology; LM occurred in 10% of patients with BC (n = 13/132) and NSCLC (n = 33/319) and 11% of patients with MM (n = 5/44). Patients who received postoperative RT (n = 151/495, 31%) had similar rates of LM compared with patients with other indications for RT (8% vs 11%, respectively).

Table 1 Baseline SBRT patient and treatment characteristics by histology

Characteristic	BC (n = 132) n (%)	NSCLC (n = 319) n (%)	MM (n = 44) n (%)	All patients (n = 495) n (%)
Sex				
Female	129 (98%)	190 (60%)	17 (39%)	336 (68%)
Male	3 (2%)	129 (40%)	27 (61%)	159 (32.%)
KPS*				
≥80%	108 (85%)	234 (76%)	27 (63%)	370 (77%)
<80%	19 (15%)	72 (24%)	16 (37%)	108 (23%)
Median age at diagnosis (y) (range)	49.6 (26.8-73.1)	65.5 (28.9-89.0)	51.1 (24.6-82.7)	60.0 (24.6-89.0)
Median age at SBRT (y) (range)	57.5 (29.7-83.9)	67.9 (32.1-90.0)	55.7 (29.1-83.2)	64.9 (29.1-90.0)
Fractionation				
24 Gy in 1 fraction	40 (30%)	72 (23%)	11 (25%)	123 (25%)
27 Gy in 3 fractions	72 (55%)	208 (65%)	22 (50%)	302 (61%)
Other	20 (15%)	39 (12%)	11 (25%)	70 (14%)
Postoperative radiation	29 (22%)	104 (33%)	18 (41%)	151 (31%)

Abbreviations: BC = breast cancer; KPS = Karnofsky performance scale; MM = malignant melanoma; NSCLC = non-small cell lung cancer; SBRT = stereotactic body radiation therapy.

* KPS not available for 17 patients.

Table 2 Baseline characteristics of SBRT patients with LM

Characteristic	n (%)
Histology	
BC	13 (25%)
NSCLC	33 (65%)
MM	5 (10%)
KPS*	
≥80	39 (80%)
<80	10 (20%)
Sex	
Female	40 (78%)
Male	11 (22%)
Age at LM diagnosis	
≤60	23 (45%)
>60	28 (55%)
Parenchymal brain metastases at time of LM diagnosis	
Yes	30 (59%)
No	21 (41%)
Postoperative radiation	
Yes	12 (24%)
No	39 (76%)
Subclinical LM	
Yes	8 (16%)
No	43 (84%)
CSF cytology	
Positive	25 (49%)
Negative	8 (16%)
Not performed†	18 (35%)
MRI brain	
Positive	33 (65%)
Negative	16 (31%)
Not performed‡	2 (4%)
MRI spine	
Positive	19 (37%)
Negative	27 (53%)
Not performed‡	5 (10%)

Abbreviations: BC = breast cancer; CSF = cerebrospinal fluid; KPS = Karnofsky performance scale; LM = leptomeningeal metastasis; MM = malignant melanoma; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; SBRT = stereotactic body radiation therapy.

* KPS not available for 2 patients.

† For patients with MRI-detected LM, "not performed" indicates no CSF cytology within 2 months preceding or any time after positive MRI.

‡ For patients with LM initially detected by positive CSF cytology, "not performed" indicates no MRI within 2 months preceding or any time after positive CSF cytology.

Subclinical LM

CSF cytologic evaluation at the time of myelography for SBRT planning identified subclinical LM in 8 patients (2%). Of these, 6 had positive cytology, and 2 had suspicious cells on cytology. Notably, the 2 patients with suspicious cells on cytology (Table 3, ID 7-8) had the shortest survival in this cohort. Among patients with subclinical LM, 2 had BC (25%, ID 1-2), 5 had NSCLC (63%, ID 3-7), and 1 had MM (13%, ID 8). Indications for spine SBRT comprised postoperative RT (n = 2, 25%), epidural disease/spinal cord compression without prior surgical intervention (n = 4, 50%), and symptom palliation (n = 2, 25%). Three patients (38%, ID 5, 7-8) had preexisting parenchymal brain metastases. All 8 patients completed their planned SBRT courses. All but 2 of the 8 patients with subclinical LM were under the care of a neurologist/neuro-oncologist (n = 4) and/or neurosurgeon (n = 2) at the time of positive cytology. Indications for prior neurology/neuro-oncology care included back pain in the setting of spinal epidural disease, meningioma, intraparenchymal/subdural hematoma, and unilateral peroneal neuropathy. A treating neuro-oncologist and/or neurosurgeon examined 5 of the 8 patients within 2 weeks of positive cytology. Six of 8 patients had prior normal complete neuraxis imaging; an additional patient had a prior normal spinal MRI.

We sought to determine the prognosis of subclinical LM by evaluating survival and rates of progression to clinically evident LM. Patients with subclinical LM had similarly poor survival from time of LM diagnosis compared to patients with clinically evident LM (median LM survival 3.6 vs 3.0 months, respectively, $P = .30$) (Fig. 2A). Five of 8 patients (63%) with subclinical LM developed subsequent clinical symptoms or radiographic evidence of LM (Fig. 2B, Table 3). One of these patients (ID 8) was asymptomatic at the time of CT myelogram; however, they presented to our hospital's urgent care center with symptoms consistent with LM that began approximately 4 days after incidentally positive myelogram cytology. Among patients who developed symptomatic LM, the median time to symptoms was 1.4 months (0.1-17.1 months). Of these 5 patients, 3 (60%) also developed radiographic evidence of LM. Two patients (ID 5 and 7) had radiographic LM detected within a week of positive myelogram cytology; in both cases, complete neuraxis imaging was obtained to complete a workup for LM in response to their CSF cytology result. Notably, 3 patients never showed clinical symptoms or MRI evidence of LM, although 1 of these patients (ID 3) had multiple CSF cytologic evaluations positive for tumor cells.

We next evaluated whether a diagnosis of subclinical LM resulted in the use of CNS-directed and/or change in systemic therapy. Of the 5 patients with NSCLC (ID 3-7), 4 were receiving epidural growth factor receptor tyrosine kinase inhibitors therapy with erlotinib (n = 1), afatinib

Table 3 Subclinical and treatment characteristics of patients with LM

Case No.	Diagnosis	KPS	Sex	Age at SBRT (y)	Site	Dose (Gy)	Fractions	Indication	Parenchymal brain metastases	Number of prior RT courses	Time to symptomatic LM (mo)	Status	LM survival (mo)
ID 1	BC	90	F	60	T4	27	3	Postoperative	N	5	17.1	Dead	18.0
ID 2	BC	90	F	61	C7	27	3	Epidural disease/spinal cord compression	N	0	1.4	Alive	13.6*
ID 3	NSCLC (*EGFR* mut)	90	F	56	C3 L1	24 24	1 1	Symptom palliation	N	0	-	Dead	9.5
ID 4	NSCLC (*EGFR* mut)	70	F	69	T7	27	3	Postoperative	N	1	-	Alive	9.0*
ID 5	NSCLC (*EGFR* mut)	70	F	69	T7-T8 T11	27 24	3 1	Epidural disease/spinal cord compression	Y	2	2.3	Dead	3.6
ID 6	NSCLC (*EGFR* mut)	90	F	67	T12-L1	27	3	Epidural disease/spinal cord compression	N	1	-	Dead	1.9
ID 7	NSCLC (*EGFR* mut)	80	F	75	L5-S3	30	5	Symptom palliation	Y	2	1.1	Dead	1.3
ID 8	MM	70	M	61	T12	24	1	Epidural disease/spinal cord compression	Y	0	<1	Dead	1.0

Abbreviations: BC = breast cancer; F = female; KPS = Karnofsky performance scale; LM = leptomeningeal metastasis; M = male; MM = malignant melanoma; mut = mutation; N = no; NSCLC = non-small cell lung cancer; RT = radiation therapy; SBRT = stereotactic body radiation therapy; Y = yes.

* Patient living at time of analysis.

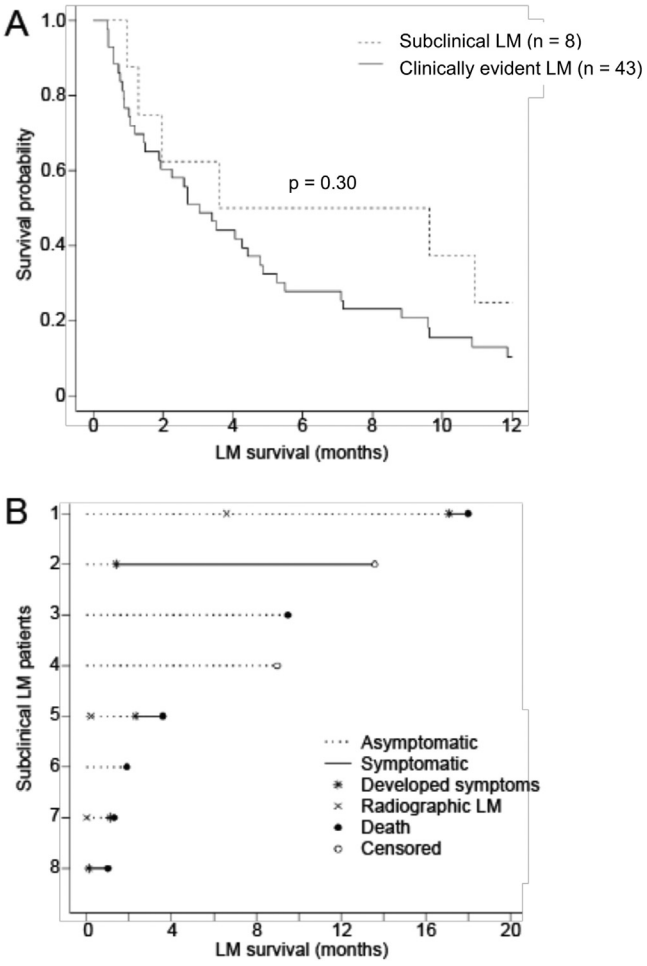

Figure 2 Survival in patients with subclinical and clinically evident leptomeningeal metastasis (LM). (A) Kaplan-Meier curves of patients with subclinical LM diagnosed on myelogram cytology (n = 8) and patients with clinically evident LM (n = 43). Median LM survival 3.6 versus 3.0 months, respectively (P = .30). (B) Swimmer plot of patients with subclinical LM showing time to symptomatic and radiographic LM progression. Two patients with breast cancer (BC) (ID 1-2), 4 patients with non-small cell lung cancer (NSCLC) (ID 3-7), and 1 patient with melanoma (MM) (ID 8) had subclinical LM detected in CSF collected at the time of CT myelogram.

(n = 2), or osimertinib (n = 1) at the time of subclinical LM diagnosis. Subsequently, all 5 patients received tyrosine kinase inhibitors therapy, with the majority continuing on or switching to osimertinib (n = 4, 80%). Of the 2 patients with BC (ID 1,2), both changed systemic therapies at the time of subclinical LM diagnosis, including to oral capecitabine (ID 2). By contrast, the patient with MM (ID 8) died soon after his subclinical LM diagnosis and did not change systemic regimens, possibly owing to this short interval. No patients with subclinical LM received intrathecal therapy. Only 1 patient (ID 1) received LM-directed RT. She underwent whole brain RT (WBRT) with 30 Gy in 10 fractions after neuroimaging confirmed new brain metastases and LM approximately 7 months after positive CSF cytology. She was neurologically asymptomatic and had a negative CSF cytology at the time of WBRT. Follow-up imaging showed isolated radiographic disease progression in the brain 4 months later based on the Response Assessment in Neuro-Oncology criteria.[17] She had continuous radiographic progression of spinal LM as early as 6 weeks after WBRT. Of the 6 patients with subclinical LM who succumbed to disease at last follow-up, 2 patients (33%, IDs 7 and 8) died of LM alone, 1 (17%, ID 1) of progressive brain disease (LM and/or brain metastases), 2 (33%, IDs 3 and 6) of systemic disease progression, and 1 (17%, ID 5) of unknown causes, in line with data from patients with standardly detected LM.[18,19]

Clinicopathologic factors associated with survival with LM

The median survival from LM diagnosis for all 51 patients who developed LM was 3.4 months (2.0-5.3

months). On univariate analysis, age at LM diagnosis and histology were not associated with different survival. LM patients with a KPS <80 had worse survival relative to those with a KPS ≥80 (median LM survival 1.5 months [0.9-7.1 months] vs 4.3 months [2.7-10.9 months], $P = .02$) (Fig. 3A). Patients with concomitant parenchymal brain metastases (n = 30, 59%) at the time of LM diagnosis succumbed to disease sooner than patients without brain metastases (2.4 months [1.5-4.8 months] vs 7.1 months [2.7-17.5 months], $P = .02$) (Fig. 3B). A multivariate model with KPS <80 (HR, 2.3; 1.2-4.7) and parenchymal brain metastases (HR, 4.2; 1.8-9.8) showed independent associations with worse outcome ($P < .001$).

Discussion

LM is a devastating and fatal complication of advanced cancer. Historically, LM was diagnosed after patients developed neurologic symptoms, prompting CSF evaluation and neuroaxis imaging. With the increasing use of local interventions, including spine SBRT in the

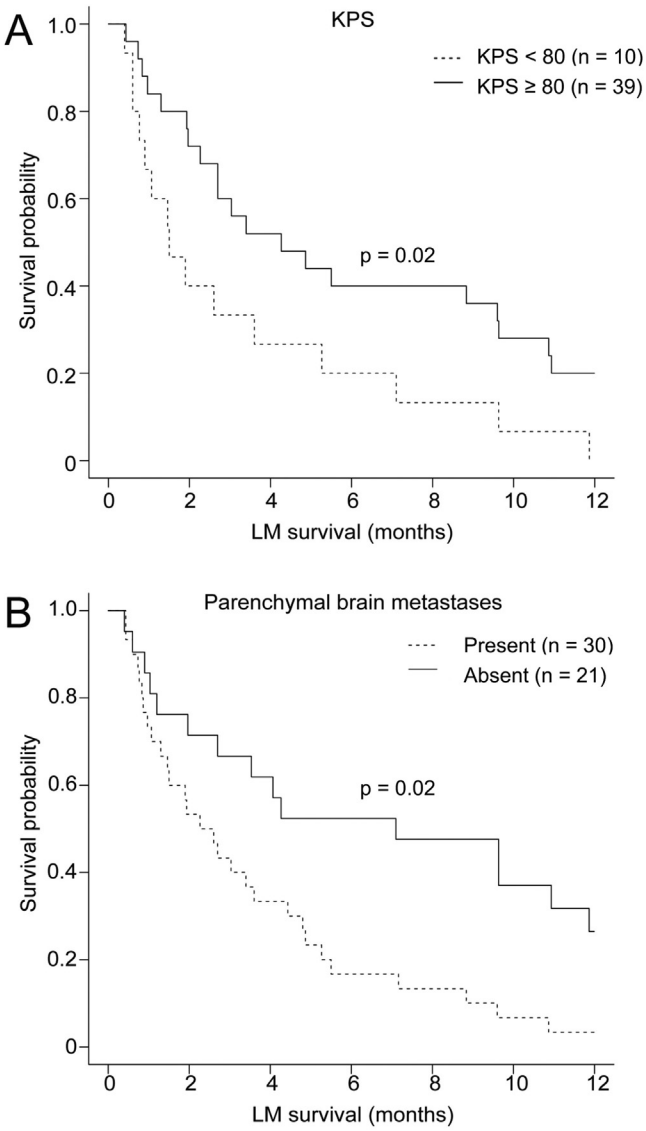

Figure 3 Clinicopathologic factors associated with leptomeningeal metastasis (LM) survival. (A) Kaplan-Meier curves of all patients with LM with Karnofsky performance scale (KPS) ≥80 (n = 39) and KPS <80 (n = 10). Median LM survival 4.3 versus 1.5 months, respectively ($P = .02$). (B) Kaplan-Meier curves of patients with LM with (n = 30) and without (n = 21) preexisting and/or concurrent parenchymal brain metastases. Median LM survival 2.4 versus 7.1 months, respectively ($P = .02$).

metastatic setting, there are opportunities to detect malignant cytology in the absence of symptoms or radiographic evidence of LM. The clinical relevance of such incidental findings has not been systematically studied. As a result, there is considerable uncertainty about the prognosis and optimal management of patients with subclinical LM.

We present a single-institution retrospective analysis of patients treated with spine SBRT and evaluate progression to LM, including subclinical LM. Consistent with earlier studies, approximately 10% of patients developed LM.[1,3] Our analyses reveal an incidence of subclinical LM of 2% among patients undergoing CT myelography for spine SBRT planning. It might be expected that such a malignant cytology would reflect a false positive result or indicate an earlier manifestation of disease, for which potentially earlier detection would result in lead time bias and prolonged apparent survival. However, contrary to expectations, survival in patients with subclinical LM was not superior to that of patients with clinically overt LM. Rather, the grim prognosis of patients with subclinical LM suggests that these patients merit consideration of CNS-directed therapy even in the absence of symptoms or MRI evidence of LM. Notably, the patient who survived the longest with subclinical LM in this cohort was the only patient to receive LM-directed RT.

An alternative hypothesis is that subclinical LM, like other forms of type I LM, that is, confirmed LM with positive CSF cytology, portends worse prognosis compared with patients who present with a constellation of typical MRI features and clinical signs but negative CSF cytology (type II LM).[5,20] Supporting the notion that positive CSF cytology is associated with a more aggressive LM phenotype, a recent retrospective analysis of 35 patients with breast and/or lung cancer LM found that patients with CSF-only LM succumbed to their disease sooner than patients with LM diagnosed by MRI alone or by both modalities (ie, CSF- and MRI-positive LM).[21]

To further understand the clinical outcomes associated with cancer cell tropism, we examined the effect of concomitant parenchymal brain metastases on LM survival. Consistent with prior studies,[1,22,23] approximately two-thirds of patients in this cohort had coexisting parenchymal brain metastases and LM. Here, we report that a history of parenchymal brain metastasis is associated with decreased LM survival, in line with data showing that brain metastases, as well as increasing brain metastatic burden, portend worse outcomes in the metastatic setting.[24] Notably, the literature on LM survival and parenchymal brain metastasis is less clear. A retrospective study of 49 patients with LM secondary to breast cancer did not find that presence of parenchymal brain metastases affected survival outcomes; however, one-third of patients in this study did not receive neuroaxis imaging at the time of LM diagnosis.[25] A study of 110 patients from the UT—MD Anderson Cancer Center with metastatic melanoma and LM similarly found no association between presence of parenchymal brain metastases and LM survival.[26] In this cohort, all patients with preexisting CNS parenchymal disease had been previously treated with surgery, RT, or chemotherapy, which might theoretically suppress cancer progression in the leptomeninges. As well, there may have been increased CNS surveillance in patients with known brain metastases, potentially artificially inflating LM survival assessment. Our data, collected in a cohort of patients undergoing spine SBRT, indicate that concurrent CNS parenchymal disease predicts worse LM outcomes.

This study has several limitations, many of which are related to its retrospective nature. First, aspects of data collection are necessarily incomplete. For example, performance status was not available for all patients and, when available, may have been influenced by existing provider biases and interobserver variability. Second, medical details were not available for all patients at the end of life, for example in patients who sought care closer to home or were unable to travel as their status worsened, which may have resulted in underestimation of the overall incidence of LM in this cohort. Third, because all patients in this study had a history of bony metastases and particularly because oligometastatic disease was likely overrepresented in this cohort compared with the general metastatic population, our observations may not be generalizable to the overall population of patients with LM.

Conclusion

Our findings indicate that subclinical LM, similar to clinically overt LM, has a dismal prognosis and warrants an early referral to neuro-oncology to generate multidisciplinary therapeutic strategies with radiation and medical oncology in these patients. Furthermore, addressing goals of care with patients and their families is crucial, as is early involvement of palliative care specialists, which leads to better quality of life and improved survival in the metastatic setting.[27] Taken together with the high specificity of malignant cytology for LM,[28] our findings indicate that a diagnosis of subclinical LM warrants consideration of CNS-directed therapy. In addition to standard therapies for LM, recent findings from early-phase clinical trials in patients with solid tumor LM showed favorable outcomes with hypofractionated proton craniospinal irradiation, a technique that has been successfully combined with spinal SBRT.[29,30] Given the poor prognosis of LM even with maximal therapy, patients with subclinical LM detected at the time of CT myelography may benefit from standard 3-dimensional conformal RT, rather than SBRT, for management of spinal bony metastases, as such an approach provides comparable symptomatic benefit and enables less labor-intensive planning and therefore earlier delivery of therapy.

With improving therapies for patients with advanced malignancies and more sensitive CSF evaluation,[31] including rare cell capture-based technologies,[32–36] tumor cell-specific marker-based flow cytometry approaches,[37–39] and cell-free strategies examining the CSF genome, transcriptome, and proteome,[40–45] the incidence of subclinical LM will increase. The expanding population of metastatic patients undergoing local therapies for advanced disease provides opportunities for earlier interventions and prospective studies. LM remains a devastating metastatic manifestation of cancer for which improved therapies, including targeted and/or combinatorial treatment approaches, are desperately needed. Earlier identification of patients who may benefit from such approaches is warranted and merits attention in future studies.

References

1. Clarke JL, Perez HR, Jacks LM, Panageas KS, Deangelis LM. Leptomeningeal metastases in the MRI era. *Neurology*. 2010;74:1449-1454.
2. Dankner M, Lam S, Degenhard T, et al. The underlying biology and therapeutic vulnerabilities of leptomeningeal metastases in adult solid cancers. *Cancers*. 2021;13:732.
3. Brower JV, Saha S, Rosenberg SA, Hullett CR. Ian Robins H. Management of leptomeningeal metastases: Prognostic factors and associated outcomes. *J Clin Neurosci*. 2016;27:130-137.
4. Nayar G, Ejikeme T, Chongsathidkiet P, et al. Leptomeningeal disease: Current diagnostic and therapeutic strategies. *Oncotarget*. 2017;8:73312-73328.
5. Le Rhun E, Weller M, Brandsma D, et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours. *Ann Oncol*. 2017;28(suppl 4):iv84-iv99.
6. Yamada Y, Bilsky MH, Lovelock DM, et al. High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. *Int J Radiat Oncol Biol Phys*. 2008;71:484-490.
7. Gerszten PC, Mendel E, Yamada Y. Radiotherapy and radiosurgery for metastatic spine disease: What are the options, indications, and outcomes? *Spine*. 2009;34(22 suppl):S78-S92.
8. Gerszten PC, Burton SA, Ozhasoglu C, Welch WC. Radiosurgery for spinal metastases: Clinical experience in 500 cases from a single institution. *Spine*. 2007;32:193-199.
9. Chang EL, Shiu AS, Mendel E, et al. Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. *J Neurosurg Spine*. 2007;7:151-160.
10. Ozdoba C, Gralla J, Rieke A, Binggeli R, Schroth G. Myelography in the age of MRI: Why we do it, and how we do it. *Radiol Res Pract*. 2011;2011: 329017.
11. American College of Radiology. ACR–ASNR–SPR practice parameter for the performance of myelography and cisternography. Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/myelog-cisternog.pdf. Accessed July 28, 2021.
12. Cox BW, Spratt DE, Lovelock M, et al. International Spine Radiosurgery Consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys*. 2012;83:e597-e605.
13. Bubendorf L, Schöpfer A, Wagner U, et al. Metastatic patterns of prostate cancer: An autopsy study of 1,589 patients. *Hum Pathol*. 2000;31:578-583.
14. Geldof AA. Models for cancer skeletal metastasis: A reappraisal of Batson's plexus. *Anticancer Res*. 1997;17:1535-1539.
15. Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: Experience with 90 patients. *Cancer*. 1982;49:759-772.
16. Yamada Y, Lovelock DM, Bilsky MH. A review of image-guided intensity-modulated radiotherapy for spinal tumors. *Neurosurgery*. 2007;61:226-235. discussion 235.
17. Chamberlain M, Junck L, Brandsma D, et al. Leptomeningeal metastases: A RANO proposal for response criteria. *Neuro-Oncol*. 2017;19:484-492.
18. Jaeckle KA, Phuphanich S, Bent MJ, et al. Intrathecal treatment of neoplastic meningitis due to breast cancer with a slow-release formulation of cytarabine. *Br J Cancer*. 2001;84:157-163.
19. Gleissner B, Chamberlain MC. Neoplastic meningitis. *Lancet Neurol*. 2006;5:443-452.
20. Le Rhun E, Devos P, Weller J, et al. Prognostic validation and clinical implications of the EANO ESMO classification of leptomeningeal metastasis from solid tumors. *Neuro-Oncol*. 2021;23:1100-1112.
21. Remsik J, Chi Y, Tong X, et al. Leptomeningeal metastatic cells adopt two phenotypic states. *Cancer Rep (Hoboken)*. 2020;5:e1236.
22. Umemura S, Tsubouchi K, Yoshioka H, et al. Clinical outcome in patients with leptomeningeal metastasis from non-small cell lung cancer: Okayama Lung Cancer Study Group. *Lung Cancer*. 2012;77:134-139.
23. Morris PG, Reiner AS, Szenberg OR, et al. Leptomeningeal metastasis from non-small cell lung cancer: Survival and the impact of whole brain radiotherapy. *J Thorac Oncol*. 2012;7:382-385.
24. Raizer JJ, Hwu WJ, Panageas KS, et al. Brain and leptomeningeal metastases from cutaneous melanoma: Survival outcomes based on clinical features. *Neuro-Oncol*. 2008;10:199-207.
25. Lara-Medina F, Crismatt A, Villarreal-Garza C, et al. Clinical features and prognostic factors in patients with carcinomatous meningitis secondary to breast cancer. *Breast J*. 2012;18:233-241.
26. Harstad L, Hess KR, Groves MD. Prognostic factors and outcomes in patients with leptomeningeal melanomatosis. *Neuro-Oncol*. 2008;10:1010-1018.
27. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363:733-742.
28. Glass JP, Melamed M, Chernik NL, Posner JB. Malignant cells in cerebrospinal fluid (CSF): The meaning of a positive CSF cytology. *Neurology*. 1979;29:1369-1375.
29. Yang TJ, Wijetunga NA, Yamada J, et al. Clinical trial of proton craniospinal irradiation for leptomeningeal metastases. *Neuro-Oncol*. 2021;23:134-143.
30. Yang JT, Wijetunga NA, Pentsova E, Wolden S, Young RJ, et al. Randomized Phase II Trial of Proton Craniospinal Irradiation Versus Photon Involved-Field Radiotherapy for Patients With Solid Tumor Leptomeningeal Metastasis. *J Clin Oncol*. 2022;40:3858-3867.
31. Nevel KS, Wilcox JA, Robell LJ, Umemura Y. The utility of liquid biopsy in central nervous system malignancies. *Curr Oncol Rep*. 2018;20:60.
32. van Bussel MTJ, Pluim D, Milojkovic Kerklaan B, et al. Circulating epithelial tumor cell analysis in CSF in patients with leptomeningeal metastases. *Neurology*. 2020;94:e521-e528.
33. Malani R, Fleisher M, Kumthekar P, et al. Cerebrospinal fluid circulating tumor cells as a quantifiable measurement of leptomeningeal metastases in patients with HER2 positive cancer. *J Neurooncol*. 2020;148:599-606.

34. Torre M, Lee EQ, Chukwueke UN, Nayak L, Cibas ES, Lowe AC. Integration of rare cell capture technology into cytologic evaluation of cerebrospinal fluid specimens from patients with solid tumors and suspected leptomeningeal metastasis. *J Am Soc Cytopathol*. 2020;9:45-54.
35. Lin X, Fleisher M, Rosenblum M, et al. Cerebrospinal fluid circulating tumor cells: A novel tool to diagnose leptomeningeal metastases from epithelial tumors. *Neuro-Oncol*. 2017;19:1248-1254.
36. Nevel KS, DiStefano N, Lin X, et al. A retrospective, quantitative assessment of disease burden in patients with leptomeningeal metastases from non-small-cell lung cancer. *Neuro-Oncol*. 2020;22:675-683.
37. van Bussel MTJ, Pluim D, Bol M, Beijnen JH, Schellens JHM, Brandsma D. EpCAM-based assays for epithelial tumor cell detection in cerebrospinal fluid. *J Neurooncol*. 2018; 137:1-10.
38. Cordone I, Masi S, Summa V, et al. Overexpression of syndecan-1, MUC-1, and putative stem cell markers in breast cancer leptomeningeal metastasis: A cerebrospinal fluid flow cytometry study. *Breast Cancer Res*. 2017;19:46.
39. Le Rhun E, Tu Q, De Carvalho, Bittencourt M, et al. Detection and quantification of CSF malignant cells by the CellSearch technology in patients with melanoma leptomeningeal metastasis. *Med Oncol*. 2013;30:538.
40. Pentsova EI, Shah RH, Tang J, et al. Evaluating cancer of the central nervous system through next-generation sequencing of cerebrospinal fluid. *J Clin Oncol*. 2016;34:2404-2415.
41. Smalley I, Law V, Wyatt C, et al. Proteomic analysis of CSF from patients with leptomeningeal melanoma metastases identifies signatures associated with disease progression and therapeutic resistance. *Clin Cancer Res*. 2020;26:2163-2175.
42. Ying S, Ke H, Ding Y, et al. Unique genomic profiles obtained from cerebrospinal fluid cell-free DNA of non-small cell lung cancer patients with leptomeningeal metastases. *Cancer Biol Ther*. 2019;20: 562-570.
43. Pan Z, Yang G, He H, et al. Identification of cerebrospinal fluid microRNAs associated with leptomeningeal metastasis from lung adenocarcinoma. *Front Oncol*. 2020;10:387.
44. Suryavanshi M, Jaipuria J, Panigrahi MK, et al. CSF cell-free DNA EGFR testing using DdPCR holds promise over conventional modalities for diagnosing leptomeningeal involvement in patients with non-small cell lung cancer. *Lung Cancer*. 2020;148:33-39.
45. Boire A, Brandsma D, Brastianos PK, et al. Liquid biopsy in central nervous system metastases: A RANO review and proposals for clinical applications. *Neuro-Oncol*. 2019;21:571-584.