Volume 3 (2013) // Issue 1 // e-ISSN 2224-3453

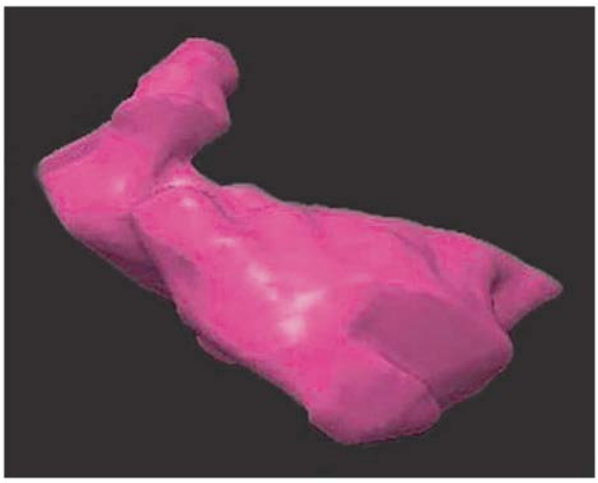
European Association of NeuroOncology Magazine

Neurology · Neurosurgery · Medical Oncology · Radiotherapy · Paediatric Neuro-oncology · Neuropathology · Neuroradiology · Neuroimaging · Nursing · Patient Issues

Prognostic Utility of Neuraxis Imaging in Leptomeningeal Metastasis: A Retrospective Case Series

Chamberlain MC

European Association of NeuroOncology Magazine 2013; 3 (1) 6-10



Homepage:

www.kup.at/journals/eano/index.html

Online Database Featuring Author, Key Word and Full-Text Search

The European Association of NeuroOncology

Member of the DOAJ Directory of Open Access Journals

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · 3003 Gablitz, Austria

Prognostic Utility of Neuraxis Imaging in Leptomeningeal Metastasis: A Retrospective Case Series

Marc C Chamberlain

Abstract: *Objective:* Correlate imaging and survival in a retrospective series of patients with leptomeningeal metastasis (LM).

Methods: 240 patients with LM (125 solid tumour patients with positive CSF cytology; 40 solid tumour patients with negative CSF cytology and MRI consistent with LM; 50 lymphoma and 25 leukaemia patients with positive CSF flow cytometry), all considered for treatment, underwent prior to treatment neuraxis MRI and radio-isotope CSF flow studies.

Results: Survival was significantly shortened in patients with large volume MRI-defined disease and in patients with CSF flow obstruction irrespective of primary tumour histology. Additionally, cause of death differed wherein patients with large volume of disease or obstructed CSF flow more often died of progressive LM disease.

Conclusions: Neuraxis imaging utilizing brain and spine MRI as well as radio-isotope CSF flow studies has prognostic significance and is predictive of median overall survival in this large cohort of patients all considered for treatment with LM. **Eur Assoc NeuroOncol Mag 2012; 3 (1): 6–10.**

Key words: leptomeningeal metastasis (LM), neuraxis imaging, brain and spine contrast MRI, CSF radio-isotope flow study, survival

Introduction

Leptomeningeal metastasis (LM) is the third most common central nervous system (CNS) metastatic complication of cancer occurring in 2–5 % of all patients with solid tumour cancers [1–8]. There is general agreement that in patients considered for LM-directed therapy, CNS staging is indicated as for example articulated in the CNS tumour section of the National Comprehensive Cancer Network guidelines [8]. However, there is limited consensus regarding the extent of CNS imaging required to assess a patient with LM prior to treatment as there have been few studies that correlate CNS imaging abnormalities with survival in patients with LM and consequently the relevance of imaging is unknown. At present, there are no large prospective or retrospective studies that have compared results of pre-treatment imaging with survival in patients with LM [9–23]. This retrospective case series of 240 patients with solid tumours (exclusive of primary brain tumours) and haematological cancer-related LM correlates brain and spine MRI findings as well as radio-isotope CSF flow study findings prior to treatment with overall survival in patients considered eligible for LM-directed therapy.

Methods

Patient Population

The retrospective analysis commenced in January 1987 and closed in December 2011. 240 adult patients with a median age of 58 years (range 20–86) with LM defined by CSF positive for cancer (defined as positive or suspicious by cytopathology; atypical was considered negative) with one patient group exception (solid cancers with negative CSF cytology; *vide infra*) were evaluated and considered for LM-directed treatment (Table 1). The intent in all patients was to proceed with intra-CSF chemotherapy and CNS site-specific radiotherapy or systemic chemotherapy when clinically appropriate. Patients with LM defined clinically and with negative CSF cytology or flow cytometry and normal neuraxis imaging and patients with primary brain tumours were not included in this retrospective imaging analysis. Approximately two thirds of the current patients have previously been reported in other contexts not however specifically addressing pre-treatment neuroimaging findings or correlation with survival [24–31]. In addition to excluding patients with negative CSF cytology or flow as well as normal neuraxis MR imaging, patients not considered candidates for LM-directed treatment (defined by a low Karnofsky performance status < 60; expected limited survival, and progressive systemic disease) were not evaluated in this analysis. One category of solid tumour-related LM considered in the analysis was defined by an LM compatible clinical syndrome, negative CSF cytology, and neuraxis imaging demonstrating radiographic abnormalities consistent with LM. All but 25 patients (8 solid tumours, 17 haematologic malignancies) were symptomatic with signs and symptoms of LM.

All patients underwent a similar pre-treatment LM evaluation including CSF assessment (cytology for solid tumours or flow cytometry and cytology for haematological cancers), contrast-enhanced brain and entire spine MR imaging, and radio-isotope ^{111}-Indium CSF flow study as previously reported [9–23]. LM was confirmed in all patients (except for a group of 40 patients with solid cancer and radiographic-only LM) by either positive CSF cytology (in instances of solid tumours and haematologic cancers) or flow cytometry (in haematologic cancers). A majority of patients (85 %) had an Ommaya ventricular access device implanted to facilitate administration of intra-CSF chemotherapy.

The primary tumour histology in patients with solid tumour-related LM (n = 165; 69 % of all patients in the analysis) was breast (45 %) and non-small cell lung cancer (34 %) (Table 1).

Received on November 21, 2012; accepted after revision on December 12, 2012; Pre-Publishing Online on December 18, 2012

From the Division of Neuro-Oncology, Department of Neurology, University of Washington, Seattle, WA, USA

Correspondence to: Marc C. Chamberlain, MD, Division of Neuro-Oncology, Department of Neurology, University of Washington, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, 825 Eastlake Avenue E, MS G4-940, Seattle, WA 98109, USA; e-mail: chambemc@uw.edu

No primary brain tumours were considered in this retrospective study. Haematologic cancers (n = 75; 31 % of all patients in the analysis) were comprised of lymphoma (n = 50; 75 % of all patients with haematologic cancer of which 80 % were diffuse large B-cell lymphoma) and leukaemia (n = 25; 25 % of all patients with haematologic cancer of which 64 % were AML). Karnofsky performance status ranged from 60–100 with a median of 80.

Table 1. Patient characteristics

Characteristics	Solid tumour		Lymphoma	Leukaemia
	Cytology negative	Cytology positive	Flow cytometry positive	Flow cytometry positive
n	40	125	50	25
Age (years)				
Median	56	58	60	62
Range	20–71	32–78	30–86	31–82
Male/female (%)	52/48	60/40	50/50	56/44
Karnofsky Performance Status				
Median	80	70	80	80
Range	50–100	50–100	50–100	50–100
Symptomatic				
No	18 % (7)	0 %	5 % (3)	15 % (4)
Yes	72 % (33)	100 % (125)	95 % (47)	85 % (21)
Tumour histology				
Breast	45 % (18)	45 % (56)		
NSCLC	30 % (11)	35 % (44)		
Melanoma	15 % (6)	10 % (13)		
SCLC	5 % (2)	5 % (6)		
Other	10 % (3)	5 % (6)		
DLBCL			80 % (39)	
Follicular lymphoma			10 % (5)	
Mantle cell lymphoma			5 % (3)	
Burkitt's lymphoma			5 % (3)	
AML				64 % (16)
ALL				20 % (5)
CLL				10 % (2)
CML				10 % (2)

NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer; DLBCL: Diffuse large B-cell lymphoma; AML: Acute myelogenous leukaemia; ALL: Acute lymphoblastic leukaemia; CLL: Chronic lymphocytic leukaemia; CML: Chronic myelogenous leukaemia

Data Collection

Data regarding CNS evaluation (brain and spine MRI; CSF flow studies) obtained before any LM-directed treatment and patient characteristics was prospectively collected and entered into a database. Institutional review board approval was obtained for data collection as well as patient consent for all prospective data collection. No institutional or corporate funding was provided for this analysis.

Imaging

Magnetic Resonance (MR) Imaging

All patients underwent complete neuraxis magnetic resonance imaging (MRI; brain and complete spine) using standard sequences (T1-weighted, T2-weighted, and FLAIR) and pre- and post-contrast imaging as previously described [9–13, 19]. MR imaging was performed on either a 1.5 or 3.0 Tesla MRI machine. Hydrocephalus was noted as present or absent to permit coding of radiographic abnormalities. Contrast enhancing nodules were characterized as subarachnoid (defined as nodules in the CSF containing subarachnoid space), ventricular, or parenchymal (defined as nodules within brain parenchyma) and as present or absent. In addition, nodular disease was characterized as either < or > 5 × 10 mm in orthogonal diameters. Using these parameters, patients with LM and tumour nodules in any location (brain or spine parenchyma or subarachnoid space or ventricular) were subdivided into small or large volume LM disease. Pial enhancement was defined as focal, diffuse, or none. Other abnormalities characterized and tabulated were ependymal, sulci, folia, cranial nerve, or spinal root enhancement as either present or absent.

Radio-Isotope CSF Flow Studies

All patients underwent either lumbar or ventricular administered ^{111}-Indium DTPA CSF flow studies prior to treatment and as previously described [9, 14–18, 20–23]. Failure of radio-isotope movement was defined as complete obstruction or blockage of CSF flow. The site of CSF flow interruption was identified as either in brain (ventricular, skull base, or convexity) or spine (cervical, thoracic, or lumbar). Partial CSF flow obstruction was not considered as constituting a CSF flow block. In the event CSF flow obstruction was identified, site of obstruction directed radiotherapy (30 Gy in 10 fractions) was administered. Patients were categorized as normal (no obstruction) or abnormal (obstruction present) with respect to CSF flow obstruction. In patients with obstruction, a repeat CSF flow study was performed following site-directed radiotherapy and patients were categorized as normal (termed re-established) or abnormal (obstruction persists) with respect to CSF flow obstruction.

Therapy

Intra-CSF chemotherapy using a variety of agents but predominantly liposomal cytarabine and administered by the intraventricular route was given to > 85 % of all patients as previously described [23–31]. Site-specific radiotherapy (to sites of symptomatic disease, to MRI defined large volume disease and to sites of CSF flow obstruction) was administered to

45 % of patients. Systemic chemotherapy was used in the majority (90 %) of patients with haematological cancers and in approximately 27 % of solid tumour-related LM patients.

Survival Analysis

Overall survival (OS) was defined as the time from LM diagnosis to death or last follow-up when patients were still alive. Survival rates were determined using the Kaplan Meier method and survival curves were compared using the log-rank test. Statistical analysis were performed using the SAS Software (USA, Cary, NC) V9.2.

Results

Four categories of patients with LM were retrospectively analyzed; solid tumour-related LM with (n = 125) or without (n = 40) positive CSF cytology, lymphoma (n = 50), and leukaemia (n = 25; Table 2). Both categories of haematologic cancers (lymphoma and leukaemia) were positive by CSF flow cytometry and in 40 % positive as well by CSF cytology. In 4 patients (5 % of all patients with haematologic cancers) with haematologic malignancies CSF flow cytometry was negative and LM was determined by CSF cytology.

Patient categories were further divided into normal or abnormal MRI findings (Table 2). Abnormal MRI findings were then divided into small or large volume disease as defined by measurable tumour nodules < or > 5 × 10 mm in orthogonal diameter. Solid tumour-related LM had a higher incidence of patients with abnormal MRI findings as well as patients with large volume disease as compared to haematological cancer-related LM. Patients were also characterized by having normal or abnormal (ie, obstructed) radio-isotope CSF flow studies. One further category included patients with initial obstructed CSF flow that following radiotherapy converted to normal CSF flow (re-established) as determined by post-radiotherapy CSF flow study (Table 2).

Median overall survival (mOS) was similar (p = 0.3) in both categories (CSF positive and CSF cytology negative) of patients with solid tumour-related LM (Table 3). However, survival in patients with solid tumour-related LM with large volume disease was significantly less than in patients with either normal MRI findings or small volume disease (p = 0.03). Similarly, mOS was not significantly different in solid tumour patients with normal or re-established CSF flow studies (p = 0.2). There was a significant difference in patients with ob-

Table 2. CNS imaging

Pre-treatment imaging	Solid tumour		Lymphoma	Leukaemia
	Cytology negative	Cytology positive		
n	40	125	50	25
MRI (brain + spine)				
Abnormal	40 (100 %)	50 (40 %)	10 (20 %)	4 (16 %)
Small volume disease	10 (25 %)	25 (50 %)	8 (80 %)	3 (75 %)
Large volume disease	30 (75 %)	25 (50 %)	2 (20 %)	1 (25 %)
Normal	0 (0 %)	75 (60 %)	40 (80 %)	21 (84 %)
CSF flow study				
Abnormal	10 (25 %)	35 (28 %)	5 (10 %)	2 (8 %)
Re-established	4 (40 %)	12 (34 %)	2 (40 %)	1 (50 %)
Normal	30 (75 %)	90 (72 %)	45 (90 %)	23 (92 %)

Small volume disease: number of patients (percent) with MRI abnormalities and without tumour nodules or nodules < 10 mm in diameter; Large volume disease: number of patients (percent) with MRI abnormalities and tumour nodules > 5 × 10 mm in diameter; Abnormal: number of patients (percent) with obstructed CSF flow study; Re-established: number of patients (percent of total obstructed) post-radiotherapy with normal CSF flow study

Table 3. Median overall survival with respect to CNS imaging

Pre-treatment imaging	Solid tumour		Lymphoma	Leukaemia
	Cytology negative	Cytology positive		
n	40	125	50	25
MRI (brain + spine)				
Abnormal				
Small volume disease	3 months	3.5 months	5 months	6 months
Large volume disease	2 months	2 months	3 months	2 months
Normal	3 months	3.5 months	5 months	6 months
CSF flow study				
Abnormal	2 months	2 months	2 months	2 months
Re-established	3 months	3.5 months	5 months	6 months
Normal	3 months	3.5 months	5 months	6 months

structed (abnormal) CSF flow that could not be corrected by radiotherapy compared to the other 2 categories (normal or re-established; p = 0.04).

Comparable findings were seen with haematological cancer-related LM wherein normal or small volume MRI abnormalities defined a longer surviving cohort of patients relative to patients with large volume disease (p = 0.018). In addition, CSF obstruction not corrected by radiotherapy characterized a haematological cancer patient category with worse outcome than those with normal or re-established CSF flow studies (p = 0.015).

Cause of death, an arguably subjective analysis, showed similar trends across all categories of patients wherein patients with either large volume disease defined by MRI or non-corrected CSF flow obstruction by radio-isotope imaging more often died of LM (2-fold increase) compared to patients with normal or small volume MRI disease and normal or re-established CSF flow (Table 4). By contrast, patients with normal or small volume MRI disease and normal or re-established CSF flow more often (3-fold increase) died of systemic disease progression.

Discussion

It has previously been suggested that there are categories of patients with LM that are not candidates for LM-directed therapy [8]. As outlined in the NCCN CNS tumour guidelines *vide supra*, these include patients with poor performance, likely short life expectancy, carcinomatous encephalopathy, uncorrected CSF flow obstruction, and large CNS tumour burden [8]. These recommendations are primarily based upon expert opinion with a paucity of literature-based evidence. The current retrospective study selected patients considered eligible for LM-directed therapy based upon these recommendations and excluded patients *a priori* not considered by clinical criteria to warrant intra-CSF chemotherapy. What remains problematic in treating patients with LM is deciding whom to treat and the current large retrospective study provides some illumination in this regard.

Previous work has suggested CSF flow studies are informative with respect to outcome and the current study corroborates these findings in a considerably larger patient data set [14–18, 20–23]. CSF flow obstruction as defined by radioisotope studies appears prognostic as patients with non-corrected CSF flow obstruction survive a significantly shorter time than patients with normal or re-established CSF flow irrespective of tumour histology (solid tumour or haematological cancer-related LM). In part the impoverished survival seen in patients with CSF flow obstruction is reflective of tumour burden as well as the pharmacologic barrier posed by interrupted CSF flow dynamics that mitigates intra-CSF chemotherapy administration. Whether intra-CSF chemotherapy alters survival in patients with LM is as yet undetermined and controversial as there has never been a large prospective randomized trial that shows a survival benefit for the receipt of intra-CSF chemotherapy [32, 33]. In that CSF flow obstruction was not predicted by MRI aside from the finding of hydrocephalus (nor by patients presenting symptoms) in the current study (data not shown), radio-isotope CSF flow studies appear complimentary to MRI in determining outcome in patients otherwise considered for LM-directed therapy. The current study supports the paradigm of utilizing CSF flow studies in patients with LM considered for treatment regardless if intra-CSF chemotherapy is used as survival is negatively impacted with evidence of interrupted CSF flow. Importantly, the current findings, ie that CSF flow obstruction is prognostic, require validation in a prospective study of LM wherein radio-isotope CSF flow studies are incorporated into pre-treatment evaluation. It was also noted that patients with non-correctable CSF flow obstruction more often succumb to LM as a cause of death than patients with normal or re-established CSF flow. Though the current study represents the largest data set of patients with haematological cancer-related LM (n = 75), the total number of patients, particularly with obstructed CSF flow, is comparatively small (n = 7) and therefore may not be generalizable.

MRI-based imaging in patients with LM has primarily been utilized to define brain involvement and when spine MRI is used, its use is mostly to define clinically site-relevant disease involvement [10–13]. The current study is unique in defining

Table 4. Cause of death with respect to CNS imaging

Pre-treatment imaging	Solid tumour						Lymphoma			Leukaemia		
	Cytology negative			Cytology positive								
n	40			125			50			25		
Cause of death (%)	LM	SD	LM + SD	LM	SD	LM + SD	LM	SD	LM + SD	LM	SD	LM + SD
MRI (brain + spine)												
Abnormal												
Small volume disease	23	53	25	25	48	27	26	51	25	24	52	23
Large volume disease	48	15	37	53	12	35	47	16	37	51	14	35
Normal	25	51	24	23	55	22	24	52	24	25	50	25
CSF flow study												
Abnormal	51	14	35	47	16	37	53	12	35	48	15	37
Re-established	25	50	25	25	50	25	25	50	25	25	50	25
Normal	25	50	25	25	50	25	25	50	25	25	50	25

LM: leptomeningeal metastasis; SD: systemic disease; LM + SD: combined LM and systemic disease

the total burden of CNS disease in patients with LM as all patients underwent both brain and whole spine MRI. Although the data is not shown, there was limited concordance between symptoms and MRI findings whether in brain or spine. Consequently, CNS disease burden is not predicted by LM-related symptoms and therefore neuraxis imaging is required to adequately stage the CNS. More important, however, is the correlation between survival and MRI-defined disease burden. In patients with large volume disease defined in this study as patients with tumour nodule(s) > 5 × 10 mm in size, survival is significantly shortened relative to patients with normal or small volume MRI disease. Whether tumour nodules > 5 × 10 mm in diameter define all categories of large tumour burden is unknown as there has never been a study attempting to quantify LM disease burden. Five by 10 millimetre diameters were selected as nodules of this size or larger were easily and reproducibly measured by MRI. Other common radiologic findings by MRI of LM for example leptomeningeal, cranial nerve, or spinal nerve root enhancement do not lend themselves to quantification. An improved radiographic method to quantify LM disease burden would be a welcome tool in assessing LM disease. Also noted in patients with large volume disease burden, cause of death was more often a result of LM as compared to patients with normal or small volume MRI disease that more frequently died due to systemic disease progression.

In conclusion, neuraxis imaging utilizing brain and spine MRI as well as radio-isotope CSF flow studies may have prognostic significance and appears predictive of median overall survival in this large cohort of patients with LM. The study is limited by the retrospective design, the novel definition of MRI large volume disease, and multiple small categories of patients upon which these conclusions are based. However, pending a larger prospective trial the current retrospective data set is the most robust data available regarding the utility of CNS imaging in predicting survival in patients with LM.

Conflict of Interest

The author has no financial disclosures.

References:

1. Chamberlain MC. Leptomeningeal metastasis. Curr Opin Oncol 2010; 22: 627–35.

2. Shapiro WR, Johanson CE, Boogerd W. Treatment modalities for leptomeningeal metastases. Semin Oncol 2009; 36: S46–S54.

3. Mammoser AG, Groves MD. Biology and therapy of neoplastic meningitis. Curr Oncol Rep 2010; 12: 41–9.

4. Glantz MJ, Jaeckle KA, Chamberlain MC, et al. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. Clin Cancer Res 1999; 5: 3394–402.

5. Glantz MJ, LaFollette S, Jaeckle KA, et al. Randomized trial of a slow release vs. a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. J Clin Oncol 1999; 17: 3110–6.

6. Strik H, Prommel P. Diagnosis and individualized therapy of neoplastic meningitis. Expert Rev Anticancer Ther 2010; 10: 1137–48.

7. Jaeckle KA. Neoplastic meningitis from systemic malignancies: diagnosis, prognosis, and treatment. Semin Oncol 2006; 33: 312–23.

8. Brem SS, Bierman PJ, Black P, et al. Central nervous system cancers: clinical practice guidelines in oncology. J Natl Compr Canc Netw 2008; 6: 456–504.

9. Chamberlain MC, Glantz M, Groves MD, et al. Diagnostic tools for neoplastic meningitis: detecting disease, identifying patient risk, and determining benefit of treatment. Semin Oncol 2009; 36 (Suppl 2): S35–S45.

10. Clarke JL, Perez HR, Jacks LM, et al. Leptomeningeal metastases in the MRI era. Neurology 2010; 74: 1449–54.

11. Collie DA, Brush JP, Lammie GA, et al. Imaging features of leptomeningeal metastases. Clin Radiol 1999; 54: 765–71.

12. Straathof CS, de Bruin HG, Dippel DW, et al. The diagnostic accuracy of magnetic resonance imaging and cerebrospinal fluid cytology in leptomeningeal metastasis. J Neurol 1999; 246: 810–4.

13. Freilich RJ, Krol G, DeAngelis LM. Neuroimaging and cerebrospinal fluid cytology in the diagnosis of leptomeningeal metastasis. Ann Neurol 1995; 38: 51–7.

14. Grossman SA, Trump CL, Chen DCP, et al. Cerebrospinal flow abnormalities in patients with neoplastic meningitis. Am J Med 1982; 73: 641–7.

15. Glantz MJ, Hall WA, Cole BF, et al. Diagnosis, management, and survival of patients with leptomeningeal cancer based on cerebrospinal fluid-flow status. Cancer 1995; 75: 2919–31.

16. Chamberlain MC, Corey-Bloom J. Leptomeningeal metastasis: Indium-DTPA CSF flow studies. Neurology 1991; 41: 1765–9.

17. Mason WP, Yeh SD, DeAngelis LM. ^{111}Indium-diethylenetriamine pentaacetic acid cerebrospinal fluid flow studies predict distribution of intrathecally administered chemotherapy and outcome in patients with leptomeningeal metastases. Neurology 1998; 50: 438–44.

18. Chamberlain MC. Spinal ^{111}Indium-DTPA CSF flow studies in leptomeningeal metastasis. J Neurooncol 1995; 25: 135–41.

19. Chamberlain MC. Comparative spine imaging in leptomeningeal metastases. J Neurooncol 1995; 23: 233–8.

20. Chamberlain MC. Radioisotope CSF flow studies in leptomeningeal metastases. J Neurooncol 1998; 38: 135–40.

21. Chamberlain MC, Glantz M. Utility of CSF radioisotope flow studies in leptomeningeal metastases: A review. J Nucl Med 2002; 5: 2101–12.

22. Chamberlain MC, Sandy A, Press GA. Leptomeningeal metastasis: A comparison of gadolinium-enhanced MR and contrast-enhanced CT of the brain. Neurology 1990; 40: 435–8.

23. Chamberlain MC, Kormanik P. Prognostic significance of ^{111}Indium-DTPA CSF flow studies. Neurology 1996; 46: 1674–7.

24. Chamberlain MC, Kormanik P. Leptomeningeal metastases due to melanoma: Combined modality therapy. Int J Oncol 1996; 9: 505–10.

25. Chamberlain MC, Kormanik PA. Carcinomatous meningitis secondary to non-small cell lung cancer: Combined modality therapy. Arch Neurol 1998; 55: 506–12.

26. Chamberlain MC, Kormanik PA. Non-AIDS related lymphomatous meningitis: Combined modality therapy. Neurology 1997; 49: 1728–31.

27. Chamberlain MC, Kormanik P, Glantz M. Recurrent primary central nervous system lymphoma complicated by lymphomatous meningitis. Oncol Rep 1998; 5: 521–3.

28. Chamberlain MC. Combined modality treatment of leptomeningeal gliomatosis. Neurosurgery 2003; 52: 324–30.

29. Chamberlain MC, Chalmers L. Acute binocular blindness. Cancer 2007; 109: 1851–4.

30. Chamberlain M, Glantz MJ. Myelomatous meningitis: multimodal therapy. Cancer 2008; 112: 1562–7.

31. Chamberlain MC, Johnston S, Van Horn A, et al. Recurrent lymphomatous meningitis treated with intra-CSF rituximab and liposomal ara-C. J Neurooncol 2009; 91: 271–7.

32. Siegal T. Leptomeningeal metastases: rationale for systemic chemotherapy or what is the role of intra-CF chemotherapy? J Neurooncol 1998; 38: 151–7.

33. Boogerd W, van den Bent MJ, Koehler PJ, et al. The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomized study. Eur J Cancer 2004; 40: 2726–33.