Leptomeningeal dissemination of low-grade neuroepithelial CNS tumors in adults: a 15-year experience

Philipp Karschnia, Frank J. Barbiero, Michaela H. Schwaiblmair, Leon D. Kaulen, Joseph M. Piepmeyer, Anita J. Huttner, Kevin P. Becker, Robert K. Fulbright, and Joachim M. Baehring

Department of Neurology, Yale School of Medicine, New Haven, CT, USA (P.K., F.J.B., M.H.S., L.D.K., K.P.B., J.M.B.); Department of Neurosurgery, Yale School of Medicine, New Haven, CT, USA (P.K., J.M.P., J.M.B.); Department of Pathology, Yale School of Medicine, New Haven, CT, USA (A.J.H.); Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, CT, USA (R.K.F.)

Corresponding author: Joachim M. Baehring, MD, DSc, Yale School of Medicine, Department of Neurology, 15 York St, New Haven, CT 06510, USA (joachim.baehring@yale.edu).

Abstract

Background. Leptomeningeal dissemination (LD) in adults is an exceedingly rare complication of low-grade neuroepithelial CNS tumors (LGNs). We aimed to determine relative incidence, clinical presentation, and predictors of outcome.

Methods. We searched the quality control database of the Section of Neuro-Oncology, Yale Cancer Center, for patients with LGN (WHO grade I/II) seen between 2002 and 2017. For cases complicated by LD, we recorded demographics, clinical signs, histopathological diagnosis, and imaging findings. A comprehensive literature review was performed.

Results. Eleven consecutive patients with LD were identified, representing 2.3% of individuals with LGN seen at our institution between 2002 and 2017 ($n = 475$). Ependymoma was the predominant histological entity. Mean time interval from diagnosis of LGN to LD was 38.6 ± 10 months. Symptoms were mostly attributed to communicating hydrocephalus. Tumor deposits of LD were either nodular or linear with variable enhancement (nonenhancing lesions in 4 of 11 patients). Localized (surgery, radiosurgery, involved-field, or craniospinal radiation therapy) or systemic treatments (chemotherapy) were provided. All patients progressed radiographically. Median overall survival after LD was 102 months. Survival was prolonged when a combination of localized and systemic therapies was administered (188.5 vs 25.5 months; $P = .03$). Demographics and tumor spectrum reported in the literature were similar to our cohort.

Conclusions. LD is a rare complication of LGNs. A high level of suspicion is required for timely diagnosis as early symptoms are nonspecific and commonly do not occur until years after initial tumor diagnosis. Repeated aggressive treatment appears to be beneficial in improving survival.

Keywords

incidence | leptomeningeal dissemination | low-grade | primary CNS tumor | therapy.

Low-grade neuroepithelial CNS tumors (LGNs) represent a heterogeneous group of CNS neoplasms corresponding to WHO grade I or II. The group is composed of noninfiltrative

and infiltrative astrocytic tumors, oligodendrogliomas, ependymomas, and mixed neuronal-glial tumors. LGNs account for 15% of all primary CNS tumors.¹ Whereas

infiltrative and noninfiltrative neoplasms display distinctive behavior in their primary parenchymal location, they seem to share common features in the setting of leptomeningeal dissemination (LD). LD is encountered in up to 11% of cases with high-grade gliomas (HGGs),² but it is exceedingly rare in LGNs.³ It appears to be more commonly reported in children.⁴ LD is not captured by prospective tumor registries such as the Central Brain Tumor Registry of the United States or the European Cancer Registry and thus, population-based incidence data are unavailable. Diagnostic imaging criteria and a “standard of care” remain to be defined.

In the present study we describe a group of consecutive adult individuals with LD of LGNs treated at a single institution over a 15-year period. In one of the largest published cohorts, we describe relative incidence, clinical presentation, radiographic findings, treatment, and outcome.

Materials and Methods

Study Population

We retrospectively searched the quality control database of the Section of Neuro-Oncology, Yale Cancer Center, for adult patients with LGNs (WHO grade I or II) seen between 2002 and 2017. For cases complicated by LGNs, we recorded demographic data including sex and age, clinical presentation, date of initial diagnosis with LGN, tumor histology and grade, interval between primary tumor diagnosis and LD, radiographic findings, treatment addressing the primary tumor and LD, and overall survival. Study design and methods were approved by the Human Research Protection Program of Yale School of Medicine.

Imaging Review

LD was defined as presence of tumor dissemination along the meninges distant from the primary tumor (absence of imaging abnormalities bridging both lesions) in serial imaging studies. Imaging characteristics were established through review of the neuraxis MRI chronologically closest to the date of diagnosis of LD, and of the last available MRI. Particular attention was paid to presence of hydrocephalus, metastatic growth pattern according to Harisiadis and Chang,⁵ contrast enhancement, and disease progression as defined by appearance of new lesions or increase of the LD lesion over 25%.⁶

Statistical Analysis

Data were tested for normal distribution and equal variance. Differences between 2 groups were analyzed by the unpaired Student *t*-test. In case of nonparametric data, we used the Mann-Whitney *U*-test to assess differences between the groups. All values are expressed as mean $\pm$ SE of the mean if not indicated otherwise, and range is given. Categorical variables are described in absolute numbers and percentage. For survival analyses, patients were followed until death or the day of database closure (August

30, 2017). Patients lost to follow-up were censored at the day of last follow-up. Survival and predictors of outcome were calculated using Kaplan–Meier survival analysis and log-rank test. All statistical analyses were performed using Prism statistical software (Prism 7.0a; GraphPad Software Inc, San Diego, CA, USA). The significance level was set at $P \leq .05$.

Literature Review

We performed a comprehensive review of the PubMed database of the US National Library of Medicine. Articles were identified using the terms “leptomeningeal,” “meningeal,” “disseminated,” “dissemination,” “ganglioglioma,” “choroid plexus papilloma,” “neurocytoma,” “low-grade glioma,” “ependymoma,” “neuroepithelial,” “pilocytic,” “ganglioneurocytoma,” “gangliocytoma,” “low-grade astrocytoma,” “glioneuronal,” and “pilomyxoid astrocytoma” in various combinations. We searched for cases published in the English literature after revision of the WHO classification system in 1993.⁷ Only cases with WHO grading and clinical information were included. Individuals with low-grade gliomas later upgraded to HGGs prior to LD were excluded. Papers were searched for cross-references.

Results

Study Population

Primary tumor and treatment

LD was diagnosed in 11 cases out of a cohort of 475 LGN patients seen at our institution between 2002 and 2017. Histopathologic tumor categories and relative LD incidence are listed in Table 1. Patient characteristics at diagnosis of the primary tumor are summarized in Table 2. Male-to-female ratio was 4:7 and median age at diagnosis of the primary LGN was 35.6 ± 5 years (range, 8–56 years). Three patients included in our cohort were diagnosed with their primary LGN during adolescence. The following histologies were encountered at diagnosis of the primary tumor: ependymoma (5/11 patients, 46%), low-grade astrocytomas (2/11, 18%), choroid plexus papilloma (1/11, 9%), ganglioneurocytoma (1/11, 9%), gangliocytoma (1/11, 9%), and ganglioglioma (1/11, 9%). The primary tumor was located within the posterior cranial fossa in 5 cases (5/11, 46%), in the thoracic spine in 2 cases (2/11, 18%), and in the cervical spine, the lumbosacral spine, the thalamus, and the frontal lobe in 1 case each (1/11, 9%). Five patients had undergone gross total resection (GTR) of their primary tumor and 5 a partial resection. In 1 case, only a biopsy was performed. Five patients received adjuvant radiation or radiosurgery and 1 of the 5 patients received additional chemotherapy.

Time Interval and Symptoms of LD

Mean time interval from diagnosis of the primary tumor to LD was 38.6 ± 10 months (range, 0–100 months). One patient was diagnosed with LD concomitant with

Table 1 Low-grade neuroepithelial neoplasms (LGNs) seen between 2002 and 2017. Shown are absolute numbers of all tumors seen by WHO classification category, absolute numbers of tumors with leptomeningeal dissemination (LD), and relative incidence of LD.

	N (all LGNs)	N (LD)	Relative Incidence of LD
Astrocytic and Oligodendroglial Tumors	346		
Oligodendrogliomas	133		
Oligoastrocytomas	64		
Astrocytomas	149		
Other Astrocytic Tumors	30		
Pilomyxoid astrocytoma	3	1	0.333
Pilocytic astrocytoma	23	1	0.043
PXA	4		
Ependymal tumors	57		
Ependymoma	41	4	0.098
Myxopapillary ependymoma	16	1	0.063
Choroid plexus tumors	3		
Choroid plexus papilloma	3	1	0.333
Neuronal and mixed neuronal glial tumors	39		
DNET	6		
Ganglioneurocytoma	1	1	1.000
Gangliocytoma	4	1	0.250
Ganglioglioma	28	1	0.036
Total	475	11	0.023

Abbreviations: DNET, dysembryoplastic neuroepithelial tumor; PXA, pleomorphic xanthoastrocytoma.

primary tumor diagnosis. Interval to LD diagnosis was 56.1 ± 16 months in patients who had a GTR of the primary neoplasm, and 23.9 ± 12 months in individuals with subtotal resection or biopsy ($P = .13$). An association between adjuvant therapy and a prolonged time to dissemination could not be demonstrated because of the small case numbers (36.6 ± 13 months with adjuvant therapy vs 46.2 ± 18 months without adjuvant therapy; $P = .74$). Ten patients were symptomatic at the time of LD diagnosis (10/11, 91%). In 1 individual, LD was merely a radiographic finding on a surveillance MRI (1/11, 9%). The most frequently reported symptoms were attributed to communicating hydrocephalus: headache (5/11, 46%), nausea and vomiting, gait abnormalities, cognitive impairment, limb weakness, localized pain, or cranial nerve deficit (4/11 each, 36%). Fig. 1 summarizes the clinical features of LD.

Imaging features of LD

Six patients had LD intracranial lesions and concomitant spinal lesions (6/11, 55%). Isolated intracranial LD was found in 4 individuals (4/11, 36%) and isolated spinal LD in 1 (1/11, 9%) (Fig. 1).

MRI was available in most patients to evaluate the growth pattern of the lesions: Positive MRI brain obtained at the time of LD diagnosis was available for our review in 8 cases; additional positive MRI spine was available in 5 cases. Three different types of lesions related to LD were

distinguished: tumor deposits were either nodular, linear or showed a mixed growth pattern (Fig. 2A-C). The 8 available MRIs of the brain showed that hydrocephalus was noted in 6 patients (6/8, 75%). Mixed growth pattern was the most frequent phenotype of cerebral lesions (4/8, 50%), followed by exclusive linear thickening of the pia mater representing diffuse growth within the subarachnoid space (3/8, 38%). Exclusive nodular lesions were visualized in 1 patient (1/8, 13%). LD of the brain was largely gadolinium enhancing (7/8, 88%). In 1 patient (1/8, 13%), cerebellar LD lesions did not enhance, but were hyperintense on fluid-attenuated inversion recovery (FLAIR) sequences and hypointense on T1-weighted images, likely representing the combined result of tumor cell coating and secondary ischemia (Fig. 2D and E). The 5 available spine MRIs showed isolated nodular or linear lesions in 2 cases each and a mixed growth pattern in 1 case. All spinal lesions were gadolinium enhancing.

Therapy of LD

Of our cohort of 11 patients, 2 were offered supportive care and 1 refused therapy. Eight patients underwent treatment after diagnosis of LD (8/11, 73%). Therapeutic approaches included surgical resection, radiosurgery, radiation (craniospinal radiation or spinal radiation therapy), systemic chemotherapy, or a combination of these options. Intrathecal chemotherapy was not administered. Median overall survival was 102 months (range, 4-189 months) in

Table 2 Patient cohort.

Patient	Age (Years)	Sex	Pathology	Location	Treatment	Time to LD (months)	LD Biopsy Confirmation	LD Location	Growth Pattern	LD Treatment	Outcome (Years)
1	34	F	Ependymoma	Thoracic spine	STR; XRT	24.5	B	Cranial and spinal	N/A	STR; XRT; TMZ	9.4
2	39	F	Ependymoma	Temporal lobe/posterior fossa	STR; XRT; RS	28	B ^a , C ^b	Cranial	Mixed	STR; RS	0.5 ^c
3	42	F	Choroid plexus papilloma	Posterior fossa	GTR	68.5	–	Cranial and spinal	Cranial; mixed; spinal; nodular	None	0.2 ^c
4	37	F	Ependymoma	Posterior fossa	GTR; XRT	59.5	B ^a	Spinal	N/A	STR; XRT; RS; TMZ; CTX	15.3
5	49	F	Ganglioglioma	Posterior fossa	BX; XRT	77	–	Cranial	Cranial; nodular	RS	2.1 ^c
6	56	F	Ependymoma	Posterior fossa	GTR; VP shunt	1.5	–	Cranial and spinal	Cranial; mixed; spinal; nodular	XRT	0.3 ^c
7	13	M	Ganglioglioma	Thoracic spine	GTR	51	B	Cranial and spinal	Cranial; linear; spinal; linear	VP shunt	8.3
8	17	M	Piloxyoid astrocytoma	R thalamus	STR; XRT; TMZ	4	C	Cranial and spinal	Cranial; linear; spinal; linear	VP shunt	0.2 ^c
9	8	M	Pilocytic astrocytoma	R frontal lobe	STR; VP shunt	10	B ^a	Cranial	N/A	STR; TMZ; CTX	15.7 ^c
10	42	M	MPE	Lumbosacral spine	–	0	B	Cranial and spinal	Cranial; linear; spinal; mixed	STR; XRT	8.5 ^c
11	54	F	Ganglioglioma	Cervical spine	GTR	100	B	Cranial	Mixed	TMZ; VP shunt	3.8

Abbreviations: B, tissue confirmation of LD prior to LD-treatment initiation; B^a, tissue confirmation of LD after LD-treatment initiation; BX, biopsy; C, cytopathology confirmation of LD based on cerebrospinal fluid prior to LD-treatment initiation; C^b, cytopathology confirmation of LD based on cerebrospinal fluid after LD-treatment initiation; CTX, chemotherapy other than temozolomide (letoposide, vincristine, carboplatin, PCV [procarbazine, lomustine, and vincristine]); F, female; GTR, gross-total resection; LD, leptomeningeal dissemination; M, male; MPE, myxopapillary ependymoma; N/A, not available; R, right; RS, radiosurgery; STR, subtotal resection; TMZ, temozolomide; VP, ventriculoperitoneal; XRT, radiotherapy.

^cDeath.

Demographic data of patients with low-grade neuroepithelial CNS tumors; histopathological characteristics: treatment prior to LD; time interval to LD in months; LD location, growth pattern, and treatment; as well as outcome data included in the present study.

patients who underwent treatment and 2.5 months (range, 2.5-100 months) in the 3 individuals who did not (hazard ratio [HR] 2.6, $P = .19$).

Four of 8 treated patients had symptomatic nodular lesions and were treated with localized therapeutic modalities: radiosurgery (1), a combination of radiosurgery and surgery (1), a combination of surgery and craniospinal radiation (1), or craniospinal radiation (1). One of 8 treated patients was found to be symptomatic because of diffuse LD and received systemic chemotherapy (temozolomide) alone. Three of 8 treated patients (38%) had symptomatic nodular lesions and concomitant symptomatic diffuse linear lesions. They were treated both with localized therapeutic modalities and systemic chemotherapy: a combination of chemotherapy (temozolomide), surgery and craniospinal radiation (1); a combination of chemotherapy (etoposide, temozolomide), surgery, radiosurgery, and spinal radiation (1); or a combination of chemotherapy (etoposide; vincristine; carboplatin; PCV [procarbazine, lomustine, and vincristine]; temozolomide) and surgery (1).

Increased intracranial pressure was addressed in 3 patients by ventriculoperitoneal shunting in a supportive care (2) or a curative setting (1).

Follow-up and outcome

A follow-up MRI of the brain and spine was available for 9 patients. All patients progressed radiographically. At last follow-up, 7 patients had concomitant disease of the brain and of the spine (7/9, 78%). Isolated intracranial or spinal disease was noted in 1 case (1/9, 11%) each. A mixed

growth pattern was the predominant phenotype of intracranial (6/8, 75%) and spinal lesions (5/8, 63%) at last follow-up MRI. Interestingly, 3 more patients developed nonenhancing FLAIR lesions suspicious for LD in the cerebellum (Fig. 2D and E). Biopsy documented the metastatic nature of these lesions in 2 cases (Fig. 2F-H).

Clinically, most individuals suffered from progressive psychomotor decline. Median overall survival of patients with LD was 102 months. Seven individuals died 3.9 ± 5.6 years after LD diagnosis (range, 2.5-25.5 months). Four patients were alive at database closure for this study. They survived 9.2 ± 4.1 years (range, 45-184 months) after LD diagnosis (Fig. 3A). Median overall survival of individuals treated with a combination of systemic and localized therapeutic modalities compared favorably to that of patients who underwent exclusive systemic or localized therapy only (188.5 vs 25.5 months; HR 6.3, $P = .03$) (Fig. 3B). Age <45 years at diagnosis of LD (HR 2.5, $P = .21$), WHO grade I of the initial neoplasm (HR 1.8, $P = .360$), and extent of initial resection (GTR vs non-GTR; HR 1.4, $P = .69$) did not have a significant impact on overall survival after diagnosis of LD.

Comparison with previously reported cases

A literature review revealed 86 cases of LD from LGNs in adults since 1993. The cases are summarized together with our patients in Supplementary Table 3. LD was most frequent in the setting of low-grade ependymoma (37 patients), choroid plexus papilloma (14 patients), and low-grade astrocytoma (12 patients). Among the 86 patients in the literature, primary histology (ependymoma; 43% in the literature vs 46% in our cohort), mean age (34 ± 2 vs 36 ± 5 years), interval from initial diagnosis of LGN to LD (3 ± 1 vs 3 ± 1 years), and median survival (8.7 vs 8.5 years) were similar when compared to our cohort. Contrary to the pertinent literature, most of our patients were women (male-to-female ratio 1:0.5 in the literature vs 0.6:1 in our cohort) and our median follow-up period was longer (1.5 vs 9.4 years; $P = .004$).

Discussion

LD of primary CNS tumors is a well-known complication of pediatric low-grade gliomas⁴ and of adult HGGs.³ However, LD in adults is a rare event in LGNs. A thorough literature search identified 86 cases published within the last 25 years. With the present study we add 11 consecutive cases from a single institution to the medical literature.

Incidence and Demographics

In this study, we found an incidence of 2.3% for LD in LGN patients seen at our institution between 2002 and 2017. This number is markedly lower compared with the 7% incidence that has been reported for pediatric low-grade gliomas.⁸ We included 3 adult patients with LD who were diagnosed during childhood. Our calculated incidence may

Fig. 2 A, Coronal T1-weighted gadolinium-enhanced brain MRI shows an ependymoma within the fourth ventricle. B, Axial brain and C, sagittal thoracic spine T1-weighted gadolinium-enhanced MRI identified enhancing B, linear and C, nodular lesions (arrows) suggestive of leptomeningeal dissemination. Coronal T1-weighted D, gadolinium-enhanced and E, fluid-attenuated inversion recovery brain MRI shows atrophy and extensive signal abnormalities involving cerebellar folia. F, Hematoxylin and eosin (HE), G, epithelial membrane antigen, and H, synaptophysin stains of a biopsy specimen taken from the cerebellar lesion in E reveals leptomeningeal dissemination from a gangliocytoma (original magnification $\times 20$). HE demonstrates a monomorphic population of cells with oligodendrocyte-like morphology and focal perinuclear clearing. Mitotic activity is low; necrosis and vascular proliferation are absent. Immunohistochemical staining for epithelial membrane antigen is negative, and synaptophysin is positive. Scale bars: F, 30 μm ; G, H, 60 μm .

therefore still represent an overestimation. However, the number of LD diagnoses in patients with LGN may have increased over recent years. Medical and surgical therapeutic advances in the field of primary CNS tumors have resulted in prolonged survival, and sophisticated imaging techniques improved yield in the diagnosis of LD.^{9,10} Our literature review revealed that an average LGN patient with

LD is in his mid-30s when diagnosed with the primary CNS tumor and develops LD after a median of 3 years. The time interval between diagnosis of the primary tumor and LD is similar to what has been found in LD from childhood low-grade gliomas.⁸ Adult LGN patients appear to be younger and develop LD later when compared with adults with LD from HGGs.^{11,12}

Fig. 3 A, Time interval to leptomeningeal dissemination (LD) (black lanes) and to last follow-up (green lanes) or death (red lanes) in individual patients from our cohort. Exact number of years is given behind every lane (first number: years to LD + second number: years to last follow-up or death). Asterisks represent patients treated with a combination of localized therapeutic modalities and chemotherapy. B, Kaplan–Meier survival curve for patients treated with a combination of localized therapeutic modalities (surgery, radiosurgery, radiation) and chemotherapy (brown, $n = 3$), localized therapeutic modalities or chemotherapy alone (blue, $n = 5$), or best supportive care (orange, $n = 3$). Median overall survival for each group is given (in parentheses). CTX indicates chemotherapy; RS, radiosurgery; XRT, radiation.

We studied the association of demographic and clinical characteristics with the development of LD. The male-to-female ratio was 0.6:1 in our cohort. However, male sex is overall predominant in LGN patients with LD because the male-to-female ratio was 1:0.5 among the 86 cases described in the literature. This discrepancy may reflect our limited number of cases. Therefore, male sex may predispose to LD in LGNs as previously postulated by others.¹³ Proximity to a ventricular surface or the arachnoid space likely plays a major role in the pathogenesis of LD in LGNs. This is suggested by the high incidence of ependymomas we and others have encountered while studying the tumor spectrum of LD in LGNs.^{14,15} A high level of suspicion is therefore required in patients with ependymoma as these individuals appear to harbor a substantial risk for LD. The posterior cranial fossa was the most frequent localization of the primary tumor in our cohort: an anatomical space harboring the fourth ventricle, a chamber with multidirectional cerebrospinal fluid (CSF) flow, delivering fluid to cerebral as well spinal meninges.^{8,16} Accordingly, LD from tumors at this site was found intracranially and in the spinal canal. Neoplasms with a ventricular or arachnoid surface may release metastatic cells into the ventricular system after reaching a critical mass and subsequently seed along CSF pathways. This assumption is also supported

by the observation that patients with tumors after near-complete resection had a longer interval between primary LGN diagnosis and LD than individuals with less-complete resections.^{15,17} However, we failed to demonstrate a significant association with the grade of resection in our cohort, likely because of the small sample size.

Subarachnoid dissemination of tumor cells can be detected by MRI or CSF testing. Although cytological CSF analysis represents the diagnostic gold standard with high specificity, MRI has been proposed as the method of choice in the evaluation of dissemination from primary CNS tumors because of its greater sensitivity.¹⁸ Using postcontrast T1-weighted imaging, we were able to detect enhancement along the CSF space as a sign of LD. However, postcontrast T1-weighted sequences failed to detect growing metastases, which were visible only on FLAIR sequences in 4 patients. We were able to determine the nature of these FLAIR-hyperintense pial and arachnoid abnormalities through biopsy in 2 cases. Nonenhancing LD has been described in low-grade brain tumors recently.¹⁹ The cerebellum was the clear predilection site for nonenhancing lesions in our study, with a high surface of leptomeninges covering the cerebellar folia. This finding may reflect the fact that cerebellar folia are densely packed and the subarachnoid space between the folia

is tight. This may have resulted in a higher sensitivity of FLAIR sequences in posterior fossa disease compared with supratentorial disease. Taken together, a high level of suspicion is required for timely diagnosis as imaging findings may be nonspecific and enhancement is variable.

We identified 3 different growth patterns of LD using postcontrast T1-weighted imaging: nodular, linear, and mixed enhancement. Distinction among these growth patterns is consistent with the growth patterns that have been described in various case reports of LD from LGNs.^{20,21} In line with the findings of Passarin et al²¹ in a patient with LD from low-grade oligoastrocytoma, mixed nodular and linear growth patterns were also found in our cohort. Most patients developed LD with a mixed growth pattern during follow-up, accompanied by progressive clinical decline. Although no comprehensive data for LD of LGNs exist so far, Onda and colleagues³ previously reported that linear LD from HGGs was more likely to be symptomatic. Differential diagnosis for LD-suspicious lesions includes meningitis or slow flow in meningeal vessels. The correct diagnosis requires interpretation of imaging findings within the clinical context and tissue analysis in equivocal cases.

Median survival in our cohort was 102 months and thus similar to survival in children with LD from LGNs.⁸ This is substantially longer than the average survival of <1 year in patients with LD from HGGs.² Large symptomatic lesions in our patients were treated with localized therapy (surgery, radiosurgery, involved-field, or craniospinal radiation), and systemic chemotherapy was administered for linear and diffuse lesions. Survival was retrospectively prolonged in our patients when a combination of localized therapeutic modalities and chemotherapy was provided. Numerous LGN patients have been reported to have persistent remission of LD after aggressive treatment. Anderson et al²² achieved disease stability for 10 years in a patient with LD from a choroid plexus papilloma using radiation, chemotherapy (CCNU and 6-thioguanine), and bevacizumab. A patient with disseminated ependymoma from our cohort survived 15 years with sequential use of chemotherapy (etoposide and temozolomide), surgery, radiosurgery, and radiation. Although repeated aggressive treatment appears to be beneficial in improving survival, no definitive treatment recommendations can be made based on our findings. None of our patients received intrathecal chemotherapy; however, this might be promising in patients with widely disseminated disease.²³ The potential for long-term survival underlines the importance of carefully weighing treatment-related morbidity against the impact of the natural course of the disease on quality of life.²⁴ As many LD-related symptoms appear to be related to hydrocephalus, ventriculoperitoneal shunting might provide clinical improvement both in the curative and palliative setting.

Our study limitations include those inherent to its retrospective design such as selection and ascertainment bias. In addition, we aggregated patients with different histologies and WHO grades under the term “low-grade neuroepithelial CNS tumors.” Although survival did not differ between WHO grades in our cohort, different histologies such as low-grade gliomas and glioneuronal tumors are known to be heterogeneous with respect to genomic alterations, optimal treatment, and outcome.²⁵ Small sample size from

this single-institution series did not allow us to perform subgroup analyses. Given that diagnosis of the primary neoplasms dated back up to 25 years, detailed molecular characteristics were not available. We did not include diffuse leptomeningeal glioneuronal tumors or primary leptomeningeal oligodendrogliomatosis as these tumors primarily arise from the subarachnoid space and therefore leptomeningeal involvement in these tumors is a characteristic feature rather than a rare complication.

Considering the rarity of the disease, randomized prospective studies of treatment algorithms will not be available any time soon. Molecular characterization of factors determining dissemination and serving as therapeutic targets may be a promising approach.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (<http://neuro-oncology.oxfordjournals.org/>).

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