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Scientific Article

Revisiting the Concept of Recurrence of Primary Central Nervous System Lymphomas After Complete Response to Methotrexate-Based Therapy: Periventricular Reseeding as the Predominant Mechanism of Recurrence

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Abstract

Purpose: Understanding patterns of relapse for primary central nervous system lymphoma (PCNSL) may inform mechanisms of recurrence and optimal consolidation strategies. In this study, we report patterns of relapse among patients with PCNSL who achieved a complete response to high-dose methotrexate (HD-MTX)-based chemotherapy with or without consolidation radiation therapy (RT).

Methods and Materials: We conducted an institutional retrospective analysis of patients with PCNSL who received HD-MTX-based chemotherapy between November 2001 and May 2019. Relapses were characterized as in-field (within original T1 contrasted lesion), marginal (within T2 fluid-attenuated inversion recovery but not T1), local (in-field or marginal), distant brain (no overlap), or distant (distant brain, cerebrospinal fluid, vitreous or extra-axial) and further characterized with respect to periventricular location (≤10 mm of ventricles).

Results: Seventy-eight patients with PCNSL met inclusion criteria, of whom 29 (37%) underwent consolidation RT. Median progression-free survival and overall survival were 57.0 and 66.7 months, respectively. After a median follow-up of 38.9 months, a total of 32 patients (41%) experienced recurrence. Most patients (21 [65.6%]) had a periventricular failure. Surprisingly, local recurrences (n = 11) were exclusively observed within periventricular lesions, whereas distant recurrences (n = 21) were seen in both periventricular

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and nonperiventricular locations (P = .009). The median time to progression was shorter for locally recurrent lesions compared with distant recurrences (13.8 vs 26.1 months; P = .03).

Conclusions: After complete response to HD-MTX, few failures occurred within initial T1 contrast-enhancing lesions and many of these may have been alternatively classified as periventricular failures. These observations argue against the use of purely focal RT consolidation for patients who achieve a complete response after HD-MTX-based chemotherapy and suggest that periventricular reseeding may have a central role in PCNSL recurrence.

Importance of the Study

After complete response (CR) to first-line methotrexate (MTX), few primary central nervous system lymphoma (PCNSL) radiographic recurrences are observed within initial prechemotherapy T1 contrast-enhancing lesions. In our series, we observed that in addition to being relatively uncommon, local recurrences occurred exclusively within periventricular lesions. This observation raises the question as to whether many, if not all, local failures may be alternatively or more accurately described as periventricular reseeding. Lesion-specific, focal radiation therapy consolidation strategies may not address periventricular reseeding and have been previously reported as ineffective when used with small margins. Further research is warranted into potential consolidation strategies targeting the periventricular compartment and may include low-dose whole-brain radiation therapy, consolidative chemotherapy, autologous stem cell transplant, comprehensive cerebrospinal fluid–targeted radiation therapy, and/or intrathecal chemotherapy. Future studies incorporating emerging immune and cellular therapies may benefit from increased attention to periventricular-directed and CSF-directed analysis and treatment.

Introduction

Primary central nervous system lymphoma (PCNSL) is an aggressive non-Hodgkin lymphoma confined to the central nervous system (CNS), including the brain, cerebrospinal fluid (CSF), and eyes at initial presentation, without evidence of systemic involvement. High-dose methotrexate (HD-MTX) remains the backbone of initial therapy and is associated with a complete response (CR) for the majority (42%-78%) of newly diagnosed patients.[1-5] However, even among those who achieve a CR, approximately half of patients' PCNSLs recur.[6] The response rate for salvage treatment is less favorable (14%-67%), and overall survival (OS) is poor (4-26 months).[7-11] Moreover, recurrent disease often results in new or worsening neurocognitive deficits, both through direct insult by disease and additive neurotoxicity associated with salvage therapy. Owing to the high rates of recurrence and significant

associated morbidity, many patients undergo consolidative therapy to reduce the risk of recurrent disease.[12]

Despite a clear clinical need for consolidation in these patients, the optimal approach remains unclear. Current approaches include adjuvant chemotherapy, autologous stem cell transplant (ASCT), and whole-brain radiation therapy (WBRT).[12-14] For some patients, WBRT is the only treatment option, owing to the patient's comorbidities, inability to tolerate chemotherapy, or other potentially fatal risks associated with ASCT. Although potentially effective, ASCT is typically limited to patients under 70 years of age and carries a 4% to 13% risk of mortality in most reported series,[15] whereas historical high-dose WBRT (40-54 Gy) is associated with a significant risk of moderate to severe neurotoxicity and decreased quality of life.[16-19] As a result, alternative consolidation approaches are needed.

The use of low-dose WBRT consolidation (23.4 Gy) is one alternative treatment strategy that does not appear to confer risk of the clinically significant neurotoxicity that has been reported with higher doses (≥30 Gy).[1,2,4,20] Early results of Radiation Therapy Oncology Group (RTOG) 1114, which used 23.4 Gy WBRT consolidation, suggest a significant, approximately 2-fold decrease in failures with 2-year progression-free-survival (PFS) (54% [chemotherapy] vs 78% [chemoradiation therapy]) without evidence of clinically observable neurocognitive toxicity.[21] Despite the promise of this approach, long-term outcomes are not yet available for low-dose WBRT consolidation, and doses of 30 to 40 Gy have been historically thought necessary for long-term consolidation of high-risk non-CNS large-cell lymphomas.[12] As a result, there have been many attempts to use focal radiation therapy (RT) alone or as a boost in conjunction with low- to moderate-dose WBRT. However, there is no consensus as to the appropriate local RT target volume.[22] Furthermore, retrospective studies of patients treated with focal (ie, lesion-only) RT have shown a high failure rate and decreased survival rates, suggesting that simple targeting of enhancing lesions alone may not be adequate.[23,24] As a result, the optimal dose and design of consolidation radiation fields for patients who have attained a CR after HD-MTX remain unclear.

PCNSL generally involves the supratentorial brain, and lesions are most typically in contact with ventricular surfaces. The most commonly involved sites include periventricular white matter, deep gray nuclei, the corpus callosum, and areas adjacent to CSF spaces. It has been

hypothesized that the CSF compartment might serve as a reservoir for lymphoma precursor cells that may serve as the origin of lymphoma reseeding or relapse.[25] Previous studies have classified relapses based on brain lobes or whether the relapse was local or distant but have not examined the relationship between local failures and periventricular location.[1,23,26-30] Understanding the pattern of relapse is critical to characterizing the true extent of disease and may help inform physicians regarding underlying disease biology, mechanisms of resistance and recurrence, multimodal treatment strategies, and optimal consolidative radiation fields and boost design. In this study, we report the patterns of relapse of patients with PCNSL, with a focus on periventricular failures and their relationship to previously examined in-field, marginal, or distant brain failures as defined by prechemotherapy-based contrast-enhancing lesions.

Methods and Materials

Overview and data source

We conducted a retrospective review of consecutive patients with histologically confirmed PCNSL without extra-axial disease who achieved a CR or unconfirmed CR according to International PCNSL Collaborative Group (IPCG) criteria[31] after treatment with systemic HD-MTX−based chemotherapy regimens with or without consolidative RT. Complete response is defined as complete disappearance of contrast enhancement on magnetic resonance images (MRIs), no evidence of ocular lymphoma, negative CSF cytology, and discontinuation of corticosteroid use for at least 2 weeks before the evaluation of response. Unconfirmed CR is defined to characterize MRI that continues to show small but persistent enhancing abnormalities possibly related to biopsy or surgery. Although the formal IPCG criteria provide the ideal assessment of treatment response, we found that in the routine treatment of these patients, unconfirmed CR was most often used in routine practice and therefore was likely most relevant in the general management of these patients. Consolidation WBRT was at the discretion of the treating physicians but was often refused by the patient even when recommended. Patients were treated at our institution between November 2001 and May 2019. Pretreatment evaluation included history review; physical examination; routine blood workup; HIV screening; ophthalmologic testing; contrast-enhanced MRI of the brain; computed tomography scans of the neck, chest, and abdomen; lumbar puncture to assess leptomeningeal involvement and CSF protein levels; and bone marrow aspirate and biopsy to rule out systemic lymphoma. Patients were excluded from the primary analysis if they had secondary CNS lymphoma, primary refractory disease, underlying immunodeficiency syndromes such as AIDS or only vitreous or CSF involvement at diagnosis, if they had MRI under corticosteroid treatment, or if they were lost to follow-up. We excluded 120 out of 198 CNS lymphoma cases according to the inclusion criteria.

Primary endpoints

Anatomic sites of disease were categorized as involving the brain parenchyma (lesion on T1 contrast-enhanced or T2-weighted fluid-attenuated inversion recovery [T2-FLAIR] MRI), vitreous humor (positive slit-lamp examination or new-onset visual field deficit that resolved with chemotherapy), CSF (lumbar puncture), or extra-axial disease (computed tomography scan) at the time of initial disease presentation and disease recurrence. Lesions on contrast-enhanced T1 or T2-FLAIR MRI were categorized with respect to periventricular versus nonperiventricular location (within ≤10 mm of ventricles).[32] The location of T1 contrast-enhanced and T2-FLAIR lesions were compared between images from the initial diagnosis and first relapse.

Relapses were further characterized as in-field (within T1 contrast-enhanced lesion; Fig 1), marginal (within T2-FLAIR enhancement but not T1 contrast-enhanced region; Fig 2), or distant brain (within the brain, but not overlapping with initial T2-FLAIR enhancement; Fig 3). We defined local recurrence as either an in-field or a marginal recurrence. All nonlocal relapses were categorized as distant relapses. Recurrences within the CSF, extra-axial, and intraocular (vitreous, retina, choroid) compartments were also recorded, and these were considered distant relapses. If a patient had relapses at more than one site in their disease course, we recorded the site where the first relapse was detected.

Image analysis

Axial, coronal, and sagittal T1 contrast-enhanced and T2-FLAIR MRI images from initial diagnosis and relapse were imported into Mirada, version 1.8 (RTx; Mirada Medical, Oxford, United Kingdom) for analysis. The MRIs were fused, the lesion was delineated on T1 postcontrast and T2-FLAIR MRI images, and lesion locations were compared.

Statistical analyses

The PFS and OS were estimated with the Kaplan-Meier method and compared using the log-rank test. Comparisons of categorical variable distribution were performed using the χ^2 or Fisher exact test. Comparisons of continuous variable distribution were performed using
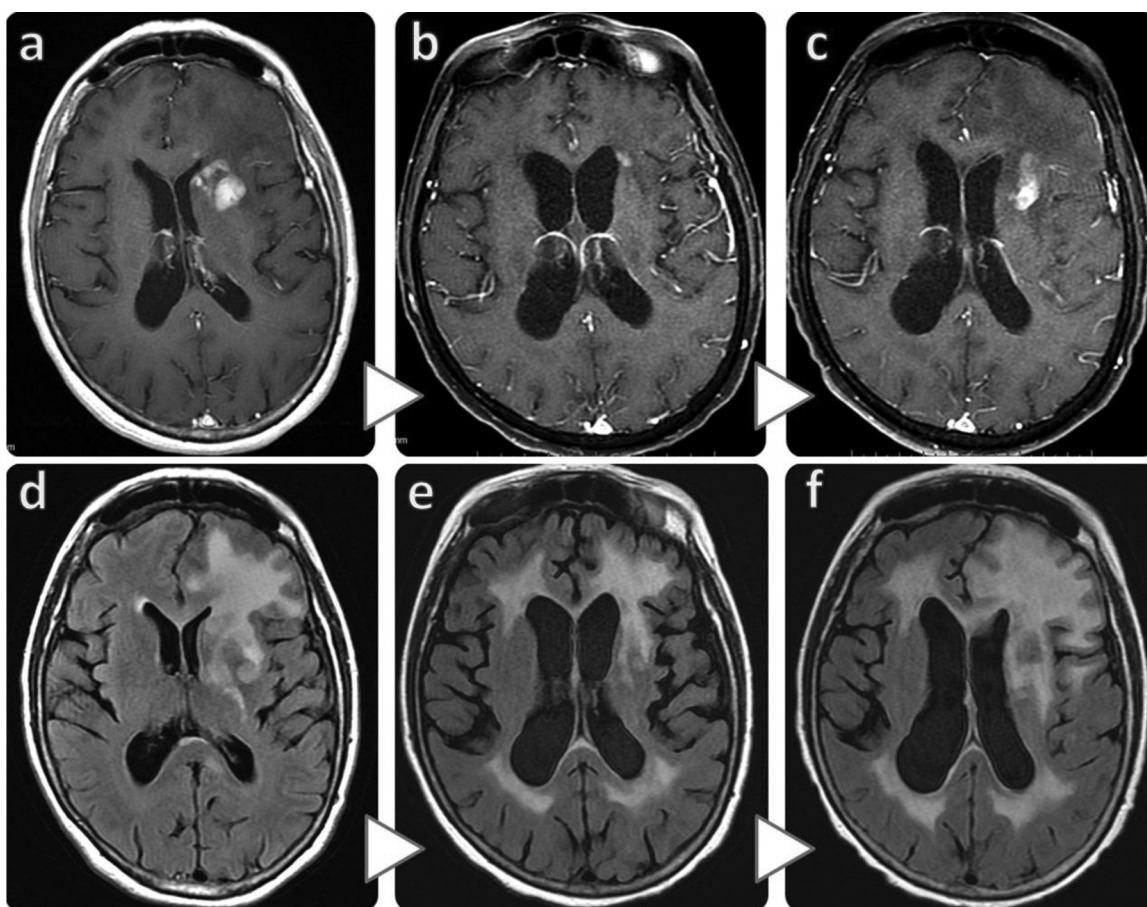
Figure 1   Example of in-field relapse. (A-C) Axial T1-weighted postcontrast imaging. (D-F) T2-weighted fluid-attenuated inversion recovery (T2 FLAIR) imaging. (A) The contrast-enhanced axial T1-weighted image showed the initial disease as an enhancing parenchymal lesion in the left periventricular area. (D) The T2 FLAIR image showed mixed hypointense and isointense lesions surrounded by extended hyperintense white-matter changes. (B, E) Contrast-enhanced axial T1-weighted image and T2 FLAIR images show an unconfirmed complete response after the DeAngelis protocol.[1] (C, F) Four months after finishing the treatment, in-field relapse was noted in the left periventricular area.

the nonparametric Mann-Whitney test. General descriptive statistics were summarized as counts and percentages for categorical variables and as median and range for continuous variables. Values with $P < .05$ were considered significant. Statistical analysis was performed using SPSS, version 22 (SPSS Inc, Chicago, Illinois). The study was approved by our institutional review board.

Results

Patient characteristics at diagnosis

A total of 78 patients met inclusion criteria, of whom 29 (37.2%) underwent consolidation RT (Table 1). The majority of patients (50 [64.1%]) had initial disease involving the periventricular region on T2-FLAIR MRI, and most patients had a single lesion at diagnosis (57 [73.1%]). No significant differences in patient

characteristics were found between the chemotherapy-only and consolidation RT treatment arms ($P > .05$). The median WBRT dose for patients receiving consolidation RT was 23.4 Gy (range, 18-44.4 Gy), and the median total dose, including the tumor bed boost for patients who received the boost treatment with WBRT, was 36 Gy (range, 36-45.0 Gy), with fraction sizes ranging from 1.5 to 1.8 Gy/d.

Patterns of failure and survival

After a median follow-up of 38.9 months (interquartile range [IQR], 14.8-75.2 months), 32 patients (41%) experienced recurrence. The median follow-up time was 55.4 months (IQR, 15.9-81.8 months) for the chemotherapy-only group and 30.3 months (IQR, 13.8-44.2 months) for the consolidation RT group owing to a shift in institutional practice toward the increased incorporation of low-dose (23.4 Gy) WBRT consolidation within recent
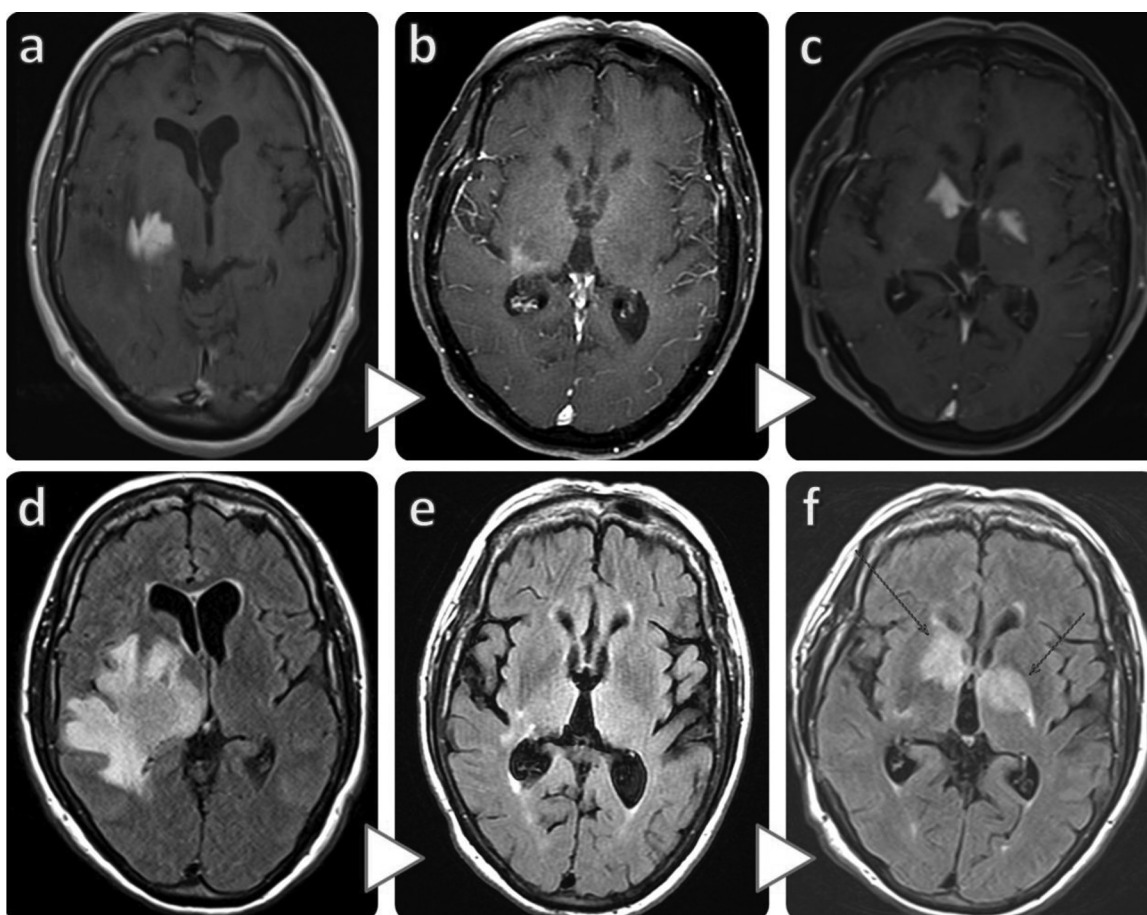
Figure 2 Example of marginal relapse. (A-C) Axial T1-weighted postcontrast imaging. (D-F) T2-weighted fluid-attenuated inversion recovery (T2 FLAIR) imaging. (A) Contrast-enhanced axial T1-weighted image shows an enhancing parenchymal lesion in the right basal ganglia. (D) T2 FLAIR image shows mixed hypointense and isointense lesions surrounded by extended hyperintense white-matter changes compressing the right lateral ventricle with associated midline shift owing to vasogenic edema. (B, E) Contrast-enhanced axial T1-weighted image and T2 FLAIR images show an unconfirmed complete response after the DeAngelis protocol.[1] (C, F) Three months after finishing the treatment, marginal relapse was noted in the bilateral periventricular area. The recurrent lesion was in the prior T2 FLAIR area but not in the T1 postcontrast enhancement area.

years. Twenty-five recurrences (51.0%) were seen among the patients who received chemotherapy only versus 7 (24.1%) among the patients who had consolidation RT (P = .03; Table 1); however, the lower absolute incidence of recurrences in the consolidation RT group may have been owed to the shorter median follow-up.

The median time to progression was significantly shorter for locally recurrent lesions than for distant recurrences (13.8 vs 26.1 months, P = .03). Among patients whose disease recurred, the median time to progression was 23.4 months (range, 4.6-76.6 months) for patients in the chemotherapy-only group and 21.9 months (range, 7.5-36.6 months) for patients in the consolidation RT group (P = .65). At the time of analysis, 42 (53.8%) of 78 patients were alive at the time of last follow-up. For the entire cohort, the median PFS was 57.0 months (95% CI, 30.9-83.1) and the median OS was 66.7 months (95% CI,

52.4-80.9). The PFS and OS rates did not significantly differ by receipt of consolidation RT (P > .05; Figure E1).

Most patients (21 [65.6%]) had a periventricular failure (Table 2). To examine whether periventricular failures were particularly enriched for any specific periventricular location, we further categorized periventricular regions into 7 classifications according to anatomic localization: 19 (90.5%) were located or involved in a ventricle; 7 (33.3%) were within the corpus callosum; 6 (28.6%) were within the hippocampus; 5 (23.8%) were within the subventricular stem cell zones; 5 (23.8%) were within the thalamus; 4 (19%) were within the caudate nuclei; and 3 (14.3%) were within the lentiform nuclei. We did not observe any evidence of enrichment for recurrences within any specific region. Periventricular versus nonperiventricular recurrence location did not significantly differ by receipt of consolidation RT (P > .05). However, local
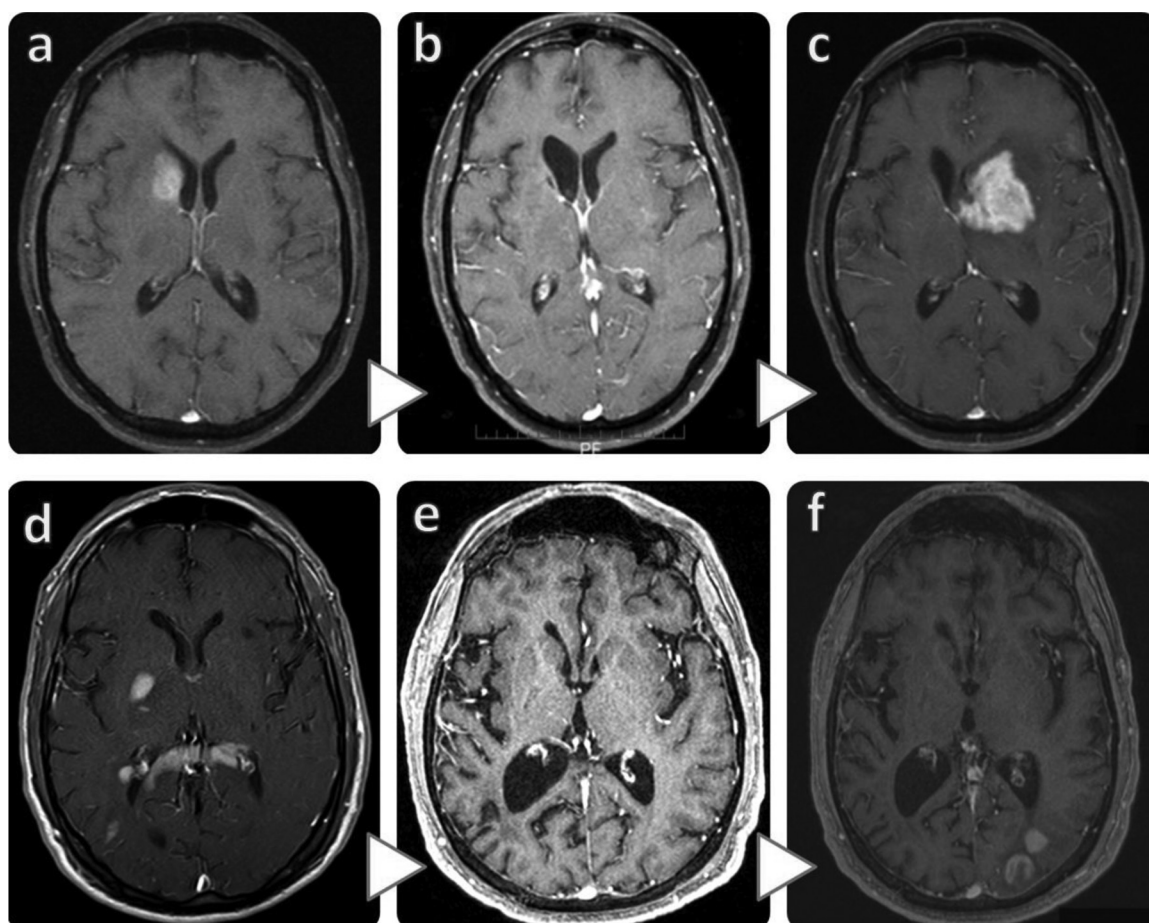
Figure 3   Examples of distant brain relapse in the (A-C) periventricular area and (D-F) nonperiventricular area by axial T1 postcontrast imaging. In the first patient (top panel), the initial disease was composed of an enhancing parenchymal lesion in the right periventricular area (A) that exhibited complete response after high-dose methotrexate therapy and rituximab (B). Fifteen months after finishing the complete response, distant brain relapse was seen in the opposite site periventricular area (C). In the second patient (bottom panel), the initial disease was characterized by a few enhancing lesions in the right parietotemporal lobe and periventricular area crossing the midline and involving both sides of the corpus callosum. After high-dose methotrexate, no parenchymal enhancement was visible (E) and the patient went on to undergo consolidation with autologous hematopoietic stem cell transplantation. One year later at relapse, a distant brain recurrence was observed in the left occipital lobe nonperiventricular area (F).

recurrences were less common among patients who received consolidation RT (1 of 7 [14.3%]) compared with patients who received chemotherapy alone (10 of 25 [40.0%]; P = .03). Local recurrence was observed among 11 patients (34.4%). Surprisingly, all 11 local recurrences were exclusively observed within the periventricular region, whereas distant recurrences (n = 21; Table 3) were seen in both periventricular (15 of 21 [71.4%]) and non-periventricular locations (6 of 21 [28.6%]; P = .009).

Discussion

To our knowledge, this study is the first to report on the relationship between local and periventricular recurrence patterns for PCNSL. We observed that all local recurrences occurred exclusively within periventricular lesions. This observation raises the question as to whether many, if not all, local failures may be alternatively or more accurately described as periventricular failures or reseeding. These periventricular local failures occurred rapidly, in approximately half the time as it took for patients to have distant progression, suggesting that this pattern of failure is rapid and may be enriched for patients with primary refractory disease. In support of this, we observed that local failures were significantly less common in patients who received consolidation WBRT. Recent preliminary reports of prospective randomized low-dose WBRT consolidation (RTOG 1114)[21] have also demonstrated improved disease control, with an approximately doubled median progression-free survival in patients who received WBRT, but the study has not yet

Table 1   Cohort characteristics

Characteristic	Patients, No. (%)			P value
	All (N = 78)	Receiving chemotherapy (n = 49)	Receiving chemoradiation therapy (n = 29)	
Age at diagnosis; range, y	64; 16-83	64; 16-81	64; 32-83	.86
Age category, y				
< 60	28 (35.9)	18 (36.7)	10 (34.5)	.84
≥60	50 (64.1)	31 (63.3)	19 (65.5)	
Sex				
Female	46 (59.0)	27 (55.1)	19 (65.5)	.48
Male	32 (41.0)	22 (44.9)	10 (34.5)	
Pathology				
DLBCL	76 (97.4)	47 (95.9)	29 (100)	.53
Lymphoma unknown	2 (2.6)	2 (4.1)	0 (0)	
Prior solid tumors				
Yes	9 (11.5)	7 (14.3)	2 (7.0)	.47
No	69 (88.5)	42 (85.7)	27 (93.0)	
Initial lesion location				
Periventricular	50 (64.1)	31 (63.3)	19 (65.5)	1.0
Nonperiventricular	28 (35.9)	18 (36.7)	10 (34.5)	
Lesion count				
Single	57 (73.1)	36 (73.5)	21 (72.4)	1.0
Multiple	21 (26.9)	13 (26.5)	8 (27.6)	
HIV status				
Positive	4 (5.1)	3 (6.1)	1 (3.4)	.62
Negative	57 (73.1)	34 (69.4)	23 (79.3)	
Unknown	17 (21.8)	12 (24.5)	5 (17.3)	
Recurrence				
Yes	32 (41.0)	25 (51.0)	7 (24.1)	.03
No	46 (59.0)	24 (49.0)	22 (75.9)	

Abbreviations: DLBCL = diffuse large B cell lymphoma.

reported on patterns of failure. Further research is warranted into potential consolidation strategies targeting the periventricular compartment and may include low-dose whole-ventricle RT, comprehensive CSF-targeted (ie, craniospinal) RT, intrathecal chemotherapy, or other approaches aimed at potentiating CSF-directed therapy (ie, intrathecal chemo- or immunotherapy). Future studies incorporating emerging cellular therapies may benefit from increased attention to periventricular- and CSF-directed analysis and treatment.

Previous reports of PCNSL failure patterns support a minor role for local recurrence after CR to MTX-based chemotherapy consistent with the present study. In our study, we observed a local recurrence rate of 34% after CR and unconfirmed to MTX-based chemotherapy. Previous

reported local recurrence rates have varied between 19% and 57% (prior studies are reviewed in Table E1).[1,27,28,30,33] However, studies reporting higher rates of local recurrences (1) included patients who received non-MTX-based chemotherapy and (2) included a significant proportion of patients who failed to achieve a CR to systemic therapy.

In our study, all local recurrences observed were within periventricular lesions. The small sample sizes in our study limit the ability to claim that all local recurrences are truly periventricular, and this specific relationship has not been previously investigated within the literature. However, others who have investigated local failures have found results that also support this notion. For example, Ambady and colleagues reported only 19% local relapses,

Table 2   Site of relapse among patients with recurrence overall and by treatment modality

	Patients, No. (%)			P value
	Total (N = 32)	Receiving chemotherapy (n = 25)	Receiving chemoradiation therapy (n = 7)	
Ventricular location				
Periventricular area	21 (65.6)	16 (64.0)	5 (71.4)	1.0
Nonperiventricular area	11 (34.4)	9 (36.0)	2 (28.6)	
Location with respect to initial lesion				
In-field recurrence*	5 (15.6)	4 (16.0)	1 (14.3)	.27
Marginal recurrence†	6 (18.8)	6 (24.0)	0 (0)	
Distant brain recurrence	12 (37.5)	9 (36.0)	3 (42.8)	
Vitreous	6 (18.8)	5 (20.0)	1 (14.3)	
CSF	2 (6.3)	1 (4.0)	1 (14.3)	
Extra-axial recurrence	1 (3.1)	0 (0)	1 (14.3)	
Local vs distant				
Local‡	11 (34.4)	10 (40.0)	1 (14.3)	.03
Distant	21 (65.6)	15 (60.0)	6 (85.7)	

Abbreviation: CSF = cerebrospinal fluid.

* In-field recurrence is defined as a recurrence that overlaps the original T1 enhancing lesion.

† Marginal recurrence is defined as a recurrence that overlaps the initial T2 lesion but not the T1 enhancement.

‡ Local recurrence is defined as either in-field (T1 contrast) or marginal (T2 fluid-attenuated inversion recovery) recurrence.

defined as recurring within 2 cm of initial T2 lesions, and noted that local relapses were more common when the initial lesion involved the corpus callosum, posterior fossa, leptomeninges, or subependymal disease—all periventricular regions.[33] Shibamoto and colleagues reported a series of patients who received focal RT, in which they observed that 4-cm minimum margins were associated with improved disease control.[23] Although they did not report periventricular versus nonperiventricular initial lesion locations, a 4-cm margin would be expected to cover most or all of the ventricular system for periventricular lesions. Taken together, we thought that many local recurrences may be prompted by subependymal, CSF, or other ventricular sanctuary sites as opposed to the persistence of treatment-resistant clones within the initial enhancing parenchymal lesion. These observations support previous conclusions that MRI-based staging does not accurately depict all active disease. Detection of tumor-cell and cell-free DNA in CSF might be useful to confirm and better understand the role of CSF-based recurrence patterns in the future,[34] which may be particularly important given the lack of sensitivity of conventional histology-based or flow-based whole-cell CSF detection of malignancy.

The primary site of disease in PCNSL has historically been thought to be represented by contrast-enhancing lesions, which enhance owing to disruption of the blood-brain barrier (BBB). However, microscopic tumor infiltration may lead to hyperintensity on a T2 scan, may be entirely radiographically occult, and may cause symptomatic disease within the CSF in the presence of a completely stable brain MRI, particularly at recurrence. This is consistent with the present study, in which we observed that the majority of failures did not overlap the initial site of disease. Several additional lines of evidence suggest that the contrast-enhancing lesions do not accurately reflect the full extent of PCNSL disease burden. First, autopsy studies by Lai and colleagues have demonstrated the diffuse presence of disease in the brain without corresponding MRI abnormalities in patients who succumb to PCNSL, confirming that disease is likely present throughout much of normal-appearing brain parenchyma at the time of staging.[35] Second, Tabouret and colleagues observed frequent (approximately 50%) recurrences within T2 abnormalities at diagnosis that exhibited no contrast enhancement.[27] Lastly, observation of contrast enhancement indicates increased permeability of the BBB, which may increase the ability of chemotherapy, particularly MTX, to penetrate the initial enhancing lesions up to 10-fold. The increased permeability and exposure to chemotherapy within contrast-enhancing lesions may offer an explanation as to why PCNSL is not prompted by local failures, which is in contrast to all non-CNS lymphomas for which initial dominant or bulky lesions are the most common site of recurrence.

Table 3   Patient characteristics according to relapse pattern (PCNSL cohort, N = 78)

	Local recurrence, No. (%) (n = 11)	Distant recurrence, No. (%) (n = 21)	No recurrence, No. (%) (n = 46)	P value
Age at diagnosis; range, y	60; 37-80	60; 34-81	68; 16-83	.19
Patient age, y				
<60 years	5 (45.5)	10 (47.6)	13 (28.3)	.24
≥60 years	6 (54.5)	11 (52.4)	33 (71.7)	
Treatment				
Chemotherapy	10 (90.9)	15 (71.4)	24 (52.2)	.04
Chemoradiation therapy	1 (9.1)	6 (28.6)	22 (47.8)	
Sex				
Female	6 (54.5)	13 (61.9)	27 (58.7)	.92
Male	5 (45.5)	8 (38.1)	19 (41.3)	
Pathology				
DLBCL	10 (90.9)	20 (95.2)	46 (100)	.17
Lymphoma unknown	1 (9.1)	1 (4.8)	0 (0)	
Prior malignancy				
Yes	2 (18.2)	2 (9.5)	5 (10.9)	.75
No	9 (81.8)	19 (90.5)	41 (89.1)	
HIV status				
Positive	1 (9.1)	0 (0)	3 (6.5)	.47
Negative	8 (72.7)	14 (66.7)	35 (76.1)	
Unknown	2 (18.2)	7 (33.3)	8 (17.4)	
Lesion count				
Single	9 (81.8)	17 (80.9)	31 (67.4)	.40
Multiple	2 (18.2)	4 (29.1)	15 (32.6)	
Initial lesion location				
Periventricular	11 (100)	15 (71.4)	24 (52.2)	.009
Nonperiventricular	0 (0)	6 (28.6)	22 (47.8)	

Abbreviations: DLBCL = diffuse large B cell lymphoma.

A primary goal of better understanding the patterns of PCNSL relapse is to help inform the minimum target volume needed to provide effective consolidation RT. Given uncertainty in the optimal target volume, WBRT is the most frequently used approach because it does not have the potential for out-of-field failures.[22] Shibamoto and colleagues showed that margins smaller than 4 cm around the lesion were associated with a higher failure rate and decreased survival rate.[23] In our study, most patients' disease demonstrated involvement of the ventricular system at relapse, supporting the increased risk of ventricular relapse in PCNSL and suggesting the need to enlarge the radiation field to include the ventricles. Whole-ventricular RT is used for intracranial germ cell tumors owing to their tendency for subependymal and CSF spread and might

represent a rational consolidation approach after a CR to modern chemotherapy. However, the efficacy and integral reduction in toxic effects of such an approach would first need to be prospectively studied before being adopted into practice. This is particularly important in light of recent data suggesting that low-dose WBRT consolidation (23.4 Gy) is not associated with an increased risk of neurocognitive toxic effects, unlike moderate- or high-dose *WBRT* (≥30 Gy).[1,2,4,20] A small prospective study of 52 patients suggested that low-dose WBRT consolidation given to patients with a CR after HD-MTX−based chemotherapy was associated with reasonable tumor control: the 2-year PFS rate was 77%, and the median PFS was 7.7 years.[2,4] The RTOG 1114 has preliminarily reported a 2-year PFS rate of 54% for patients receiving chemotherapy versus

78% for patients receiving chemotherapy and low-dose WBRT. Although no evidence of subjective neurocognitive toxic effects was observed with the addition of low-dose WBRT, more detailed neuropsychological testing and neuroimaging analyses are ongoing.[21] Early reports of prospective randomized data from the Japan Clinical Oncology Group 1114C trial suggest that the addition of temozolomide to moderate- to high-dose WBRT (30 Gy $\pm$ 10 Gy focal boost) does not provide any additional benefit and results in higher risk of cytopenias.[36] The addition of intravenous rituximab to MTX-based chemotherapy does not appear to improve patient outcomes;[37,38] however, intraventricular delivery may present an alternative CSF-directed approach to help reduce the risk of periventricular recurrence,[39,40] and the benefit of intraventricular therapy may be modulated by WBRT-based BBB disruption.

Limitations

Our study has several limitations including a single-institution retrospective study design and a small sample size. There is no single definition for the periventricular area and local relapse in the literature, and most definitions are used to define white-matter changes, not tumor location. We used 1 cm as a cutoff point for defining the periventricular area, as reported previously by DeCarli and colleagues,[32] for anatomic mapping of white-matter hyperintensities. However, other distances (3-13 mm) have been reported to describe periventricular lesions.[41] In previous studies, Ambady and colleagues[33] accepted the recurrences in a 2-cm margin of the T2 intensity as a local relapse, but Tabouret et al[27] and Schulte-Altedorneburg et al[28] defined the recurrences in the initial enhancing site as local recurrences. Sheu and colleagues[29] defined T2 FLAIR contrasted area as the RT boost area in their study. Thus, we accepted all the recurrences in the T2 FLAIR−contrasted area as local relapses, because these would have all been included in the treatment volume from a focal radiation perspective. Detailed CSF analysis results were not found for all patients in our study; however, CSF results at a minimum were reported in clinical notes for all patients. Neurocognitive toxic effects could not be reliably extracted from the medical record and were not included in this study. Anecdotally, we have not seen any evidence of clinically evident neurocognitive toxic effects in patients treated with low-dose (23.4 Gy) WBRT, but we have seen toxic effects with higher doses of WBRT (30 + Gy), consistent with other emerging reports. The median follow-up time for the consolidation RT group was shorter than for the chemotherapy-only group owing to changes in practice over time. This implies more immature data on outcomes for the consolidation RT group, and we may have observed more recurrences in the consolidation RT group if the follow-up time were longer.

Conclusions

Understanding patterns of relapse for PCNSL may inform mechanisms of recurrence and optimal consolidation strategies. Although sites of initial enhancing disease have been historically considered the at-risk lesions, findings from our study and others suggest that in patients who achieve a CR to MTX-based regimens, few failures occur within initial T1 contrast-enhancing lesions. Of these, many may be more accurately classified as periventricular failures. These observations argue against the use of focal (ie, lesion-only) RT consolidation for patients who achieve a complete response after HD-MTX-based chemotherapy and suggest that periventricular reseeding may play a central role in PCNSL recurrence. Future studies of optimal consolidation strategies, including the incorporation of emerging immune and cellular therapies, may benefit from increased attention to periventricular and CSF-directed treatment and patterns of failure analysis.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.100940.

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