Population Outcomes in Primary Central Nervous System Lymphoma: Provincial Experience and National Survey

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Summary:
Introduction: Primary central nervous system lymphoma (PCNSL) is rare and carries a poor prognosis. A retrospective review of Manitoba data for patients diagnosed with PCNSL spanning 1998-2008 was undertaken along with a national survey of PCNSL management. The study's goal was to benchmark provincial metrics for diagnostic work-up and patient outcomes in PCNSL.
Materials and Methods: A retrospective chart review was carried out, and data involving diagnostic workup, treatment, and outcome were collected. A mailed survey regarding PCNSL diagnosis and therapeutic practices was distributed to adult neuro oncology centres in Canada.
Results: The age adjusted rate of PCNSL in Manitoba was 0.8 cases per 100,000. Comparing diagnostic tests obtained by Manitobans with PCNSL between 1998-2003 and 2004-2008, the proportion of patients receiving the appropriate testings increased. Curative intent treatment utilizing high-dose methotrexate was offered to 12/72 (17%) patients, and conferred a median overall survival (OS) of 33 months. Non-curative intent therapy or palliation was offered to 83% of patients, who achieved a median OS of 2 months. No significant survival difference was found between patients receiving non-curative chemotherapy or radiotherapy. National survey results demonstrate significant variation in the management of patients with PCNSL across Canada.
Discussion: The proportion of patients receiving appropriate diagnostic testing has increased over time. Patients considered for non-curative intent therapy have suboptimal responses and may benefit from novel treatment approaches or more aggressive palliation. National variation in PCNSL management offers an opportunity to develop a national consensus.

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Student's Signature **Supervisor's signature**

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare B-cell variant of non-Hodgkin lymphoma (NHL) that is restricted to the brain, cerebrospinal fluid, and eyes. The most common pathological variant is consistent with diffuse large B cell lymphoma. (1) The median age of PCNSL patients at diagnosis falls between 53 to 57 years, with a male-to-female ratio of about 1.7:1. (2) While PCNSL is an uncommon malignancy, its incidence is increasing, particularly amongst immunocompetent individuals. (3)

PCNSL is sensitive to both chemotherapy and radiotherapy and advances to treatment have occurred over the past decades, yet clinical outcomes for patients with PCNSL are inferior to patients with similar stages of systemic NHLs. Surgery provides no significant survival benefit to patients with PCNSL, with average survival following surgical tumour removal of 1 month (4). Whole-brain radiotherapy as a single agent was formerly a mainstay for treatment of PCNSL, however it yields a median survival of around 12 months. (5) Chemotherapeutic approaches used to treat systemic NHLs (such as CHOP chemotherapy) do not adequately penetrate the brain and have failed to show any survival benefit in PCNSL. (6) Use of methotrexate at conventional dosages (less than 100mg/m^2) also results in poor penetration into the CNS, while adequate treatment is achieved by using high dose methotrexate (HDM) at doses ranging from 1 g/m^2 to 8 g/m^2. (7) Combination therapy using HDM together with whole-brain radiotherapy has shown promising results. (8) A more recent study has evaluated multiagent chemotherapy as a treatment option for PCNSL. Combination chemotherapy using HDM and cytarabine versus HDM alone found that patients treated with combination chemotherapy experienced better outcomes. (9)

Chemoradiation is associated with a significant burden of treatment-related neurotoxicity, particularly in those over 60 years at diagnosis. (10) Reducing radiation fractions or withholding radiotherapy altogether reduces the risk of neurotoxicity, however one study found that younger patients experienced a higher relapse rate when they were treated with reduced doses of radiation. (11) Treatment with chemotherapy alone is considered particularly in patients over the age of 60 who are at high risk for treatment-related neurotoxicity. One study assessing the use of methotrexate-based multi-agent chemotherapy found a median overall survival of 50 months. (12) Appropriate treatment for PCNSL remains controversial and at present there is no universally accepted therapeutic management strategy.

We undertook a retrospective provincial review of diagnostic evaluations and outcomes of consecutive patients with pathologically confirmed PCNSL treated between 1998-2008 in Manitoba. In order to compare local management practices of PCNSL with those of other provinces, a national survey on the diagnosis and management of PCNSL was carried out. This study will act as a benchmark for future provincial comparison, and highlights the need to standardize management approaches for uncommon disorders.

Materials and Methods

Cohort description: To identify the cohort of interest, the Manitoba Cancer Registry was searched using relevant International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) codes for diagnoses made between 1998 and 2008. PCNSL cases were identified as cancers in the primary anatomic sites of the brain, spinal cord, cranial nerves, and other parts of the central nervous system (ICD-O-3 codes C70.0 - C72.9), with specified NHL morphologies (ICD-O-3 codes 9590-9596, 9670-9699, and 9714). The registry database was cross referenced with the Diagnostic Services Manitoba database that identified all cases with a stereotactic brain biopsy consistent with a diagnosis of large cell lymphoma. For patients identified using ICD-O-3 codes but without stereotactic biopsies, charts were reviewed and included if no other diagnosis was apparent. A cohort of 72 patients for the period of 1998-2008 was identified.

Chart review: A retrospective chart review was undertaken for the cohort of interest. Data collection focused on baseline demographics, diagnostic workup, treatment approach and therapeutic outcome. The cohort was separated into those treated with curative intent (receiving doses of methotrexate in excess of 1 gram/m^2/dose) and those not treated with curative intent. To examine trends in diagnostic testing, the proportions of individuals receiving various baseline tests were compared for the periods 1998-2003 and 2004-2008.

Survey: To assess practice variation in Canada in the diagnosis and management of patients with PCNSL, a mailed survey tool (see Appendix 1) was sent to all Canadian adult neuro oncology programs. The survey focused on clinic characteristics, patient volume, and approach to diagnosis and management for patients with PCNSL. Survey data was aggregated.

Analysis: Values are reported with ranges. Univariate analysis using Pearson's chi-square test is used to compare proportions between groups. For the retrospective provincial review, the method of Kaplan and Meier is used to determine the cumulative probabilities of overall survival (OS) for the entire cohort as well as for groups of patients treated with similar protocols. Survival curves are compared using the log-rank test. All results were analyzed using SAS version 9.1.3.

Ethics: Ethics approval was obtained prior to the beginning of this project from the Research Ethics Board at the University of Manitoba.

Results

Between 1998 and 2008, 72 patients were diagnosed with PCNSL in Manitoba, corresponding to an age-adjusted rate of 0.8 cases per 100,000 people. No significant change in the rate of PCNSL was observed comparing the periods of 1998-2003 and 2004-2008, with an incidence rate

ratio of 1.9 (95% CI 0.66, 5.8). The male to female ratio was 1:1. Two thirds of the patients resided in Winnipeg, with the remaining individuals living outside of Winnipeg. The median age of patients at diagnosis was 65 years (20–99 years). Two patients in the cohort were seropositive for HIV.

Within Manitoba, patients receiving curative therapy were more likely to undergo more diagnostic tests as compared to those receiving non-curative therapy (Table 1). Comparing those receiving curative intent therapy versus those receiving non curative intent therapy, there were significant differences noted in the rates of brain MRI, CSF sampling, neuro-ophthalmology assessment, bone marrow assessment, stereotactic biopsy, and serologic testing for HIV, Hepatitis B, and Hepatitis C ($p<0.05$). Rates of viral screening for Hepatitis B, C and HIV were 42% for each test for those patients treated with curative intent, as opposed to 0%, 0%, and 4% respectively for those treated with non-curative intent.

Comparing tests ordered for patients during the period of January 1998-June 2003 with July 2003-December 2008, the proportion of patients receiving recommended staging and screening tests is increasing (Table 2). For patients receiving curative intent therapy, the rate of HIV serology testing was 0% between 1998-2003 and 63% between 2003-2008.

Patients who received therapy with curative intent (12/72) experienced a median OS of 33 months with 50% of the cohort being long-term survivors (Fig.1). Of those treated with curative intent, 9 out of 12 (75%) were able to complete initially planned treatment. Non-curative treatment or palliation was offered to 60/72 (83%) patients. For those treated with non-curative intent or palliated, median OS was 2 months, with an overall survival at 1 year of 6%. Within the cohort of patients receiving non-curative treatment, 31 out of 60 individuals received either chemotherapy or radiation, where 50% were able to complete their planned therapy, with the remainder passing away prior to planned completion.

For the cohort of patients who received non-curative therapy or palliation, treatment was categorized as follows: those receiving chemotherapy, those receiving radiation, and those palliated. Patients receiving non-curative chemotherapy (procarbazine, lomustine, vincristine or temozolamide) had a median OS of 2.5 months, those receiving radiotherapy had a median OS of 1.5 months, and those receiving palliation had a median OS of 0.5 months. Survival curves for the three groups were compared using the log-rank test (Fig. 2). Patients who received some form of non-curative treatment experienced a statistically significant increase in OS as compared to patients who were palliated ($p<0.05$). No statistically significant difference was found between patients receiving non-curative chemotherapy compared with those receiving radiotherapy alone.

A mailed survey of Canadian practice was distributed to 14 adult neuro oncology centers with a response from 11 centers (79%). The majority of responses indicated that centres treat fewer than 5 patients per year. Half of the surveyed clinics provide care through a single-physician clinic,

while the remaining clinics involve several different physicians. Tests used in the diagnostic work-up of patients with PCNSL vary significantly across the country (Table 3). While all clinics across the country screen PCNSL patients for HIV, fewer than half of all clinics give patients a lumbar puncture before commencing therapy. Regarding curative intent treatment, 7 out of 11 clinics (64%) treat patients with chemotherapy alone while the remaining 4 clinics use a combination of chemotherapy and radiation for younger patients, with chemotherapy alone being reserved for older patients. Rituximab therapy was administered in 4 out of 11 clinics (36%).

Discussion

Certain epidemiological parameters of PCNSL in Manitoba differ from those published in the literature. Most studies find that male PCNSL patients outnumber female patients, but Manitoba had an equal number of males and females diagnosed with PCNSL. Manitoba's age-adjusted rate of 0.8 cases per 100,000 is similar to the observed rate in the United States of 0.5 cases per 100,000. (13) The median age of 65 at diagnosis in Manitoba is comparable to that described in the literature.

Analysis of the initial diagnostic evaluation of patients with PCNSL in Manitoba varied significantly with treatment intent and with time. It is not surprising that patients receiving curative intent therapy were more likely to receive a more thorough diagnostic work-up. Patients treated with curative intent had an expectation of prolonged survival and this played a role in the intensity of investigations undertaken. Within the non-curative cohort, 6 individuals (10%) did not survive beyond one week of their diagnosis, passing away before an appropriate diagnostic work-up could have been administered. Fifty percent of patients in the non-curative cohort were palliated, in which case limited diagnostic testing would have been appropriate.

Both the National Comprehensive Cancer Network (NCCN) and the British Committee for Standards in Hematology (BCSH) guidelines recommend that patients being treated curatively undergo systemic CT scans and receive HIV serology testing. (14, 15) In the Manitoba cohort, rates of systemic CT scans and HIV serology testing in those treated curatively were 50% and 0% between 1998 and 2003 and 100% and 63% between 2004-2008. Rates of serological testing for Hepatitis B virus (HBV) also remained low in both time periods despite recommendations supporting testing (NCCN guidelines recommend HBV testing in patients with diffuse large B cell lymphomas). With increasing use of rituximab in PCNSL therapy, increasing immunosuppression may in turn lead to reactivation of latent HBV infections, emphasizing the importance of HBV testing.

Variability in diagnostic testing rates in Manitoba is likely multifactorial. Investigation of patients with PCNSL requires the integration of many specialties including oncology, neurology and neurosurgery. Lack of care maps or algorithms of care may lead to patients receiving

inadequate diagnostic testing. The multi-disciplinary nature of this disease emphasizes the need for team-based care, and the establishment of diagnostic pathways to ensure that tests are not missed when transferring patients between physicians. Introduction of a local guideline on diagnostic testing in 2009 should improve adherence with recommended diagnostic testing in Manitoba.

The median OS for PCNSL patients in Manitoba treated with curative intent are similar to those reported in the literature. Survival rates are inferior in Manitoba for patients treated non-curatively compared to outcomes published in the literature. Patients treated with curative intent in Manitoba had a median OS of 33 months, compared to a reported median OS of 37 months. (16) Patients treated non-curatively with radiation alone achieved a median OS of 1.5 months, compared to a reported median OS of 12 months. (17) Differences between patient populations in age and comorbidities may partially explain this discrepancy. The median age of patients treated with radiotherapy in Manitoba was 74, compared to a median age of 57 in the study. It is also possible that patients treated according to a research protocol as in the cited study experience better survival outcomes than patients treated off protocol such as those in Manitoba. Research protocols involve strict adherence to treatment algorithms and remove decision-making power from the physician, which may result in fewer mistakes or omissions.

It is possible that some patients receiving radiotherapy in Manitoba were treated more aggressively than necessary. The median age of patients receiving radiotherapy was 74, with 13/17 (76%) being over the age of 60. Older patients are more likely to have co-morbidities, develop treatment toxicities, and experience poorer survival. As the median OS for patients treated with radiotherapy was 1.5 months, older patients might better be treated supportively with palliation rather than more aggressively with radiotherapy. Further research is necessary to determine whether Manitoba needs to become more selective in treating PCNSL patients with radiotherapy.

The national survey of adult neuro oncology centres indicates that there is significant practise variation in the treatment of PCNSL across Canada. Guideline-recommended diagnostic tests such as bone marrow assessment and CSF sampling are only performed at 55% and 45% of Canadian centres respectively, indicating significant practise variation across Canada for a rare disorder. Every centre reported that HIV testing was provided to PCNSL patients. Data collected regarding treatment of patients with PCNSL also demonstrate widespread variation between centres offering various combinations of chemotherapy with and without rituximab, and radiotherapy. These results emphasize the need to develop a national practise document for the treatment of PCNSL or a research consortium.

The major limitation to this study was the limited number of patients diagnosed with PCNSL in Manitoba. During the study period treatments varied for this patient population. As such, it was difficult to find meaningful differences between treatment types. Development of a national

registry of PCNSL outcomes may allow better delineation of outcomes. The survey response rate of 79% was adequate but could be improved in order to yield more accurate results.

PCNSL is a rare form of large cell lymphoma. Baseline diagnostic testing in Manitoba is becoming more homogenous. Patients treated with non-curative therapy represent an opportunity for improved outcomes. Treaters in Manitoba may need to develop more selective guidelines regarding the use of radiotherapy or chemotherapy, and consider the merits of palliative care for older patients. Widespread national variation exists in PCNSL diagnosis and management, offering an opportunity to develop national practice guidelines.

Tables, Figures, and Appendices

Table 1. Percentage of patients with PCNSL receiving diagnostic tests based on treatment intent. Tests recommended by the National Comprehensive Cancer Network (NCCN) and the British Committee for Standards in Hematology (BCSH) guidelines for PCNSL are noted.

	Curative (N=12)	**Non-Curative (N=60)**	**P**	**NCCN**	**BCSH**
Tests Done at Baseline					
CT Brain	100%	88%	0.099		
MRI Brain	100%	54%	<0.001	Yes	
CSF sampling	100%	41%	<0.001	Yes	Yes
Neuro-ophthalmology assessment	100%	50%	<0.001	Yes	Yes
Bone MarrowAssessment	75%	24%	<0.001	Yes	
Systemic CT scan	83%	59%	0.102	Yes	Yes
Stereotactic Biopsy	100%	63%	0.002	Yes	Yes
HIV serology	42%	4%	<0.001	Yes	Yes
Hepatitis B serology	42%	0%	<0.001		
Hepatitis C serology	42%	0%	<0.001		
EBV Serology	17%	4%	0.066		

Table 2. Percentage of patients receiving diagnostic tests in subsequent 5-year time periods.

	January 1998 – June 2003 (N=25)	**July 2003 – December 2008 (N=47)**	**P**
Tests Done at Baseline			
CT Brain	52%	91%	<0.001
MRI Brain	36%	66%	0.011
CSF sampling	50%	53%	0.854
Neuro-ophthalmology assessment	57%	60%	0.909
Bone Marrow assessment	7%	40%	0.003
Systemic CT scan	43%	68%	0.034
Stereotactic Biopsy	40%	70%	0.009
HIV serology	0%	19%	0.004
Hepatitis B serology	0%	13%	0.013
Hepatitis C serology	0%	11%	0.025
EBV serology	0%	13%	0.013

Table 3. Percentage of adult neuro oncology clinics in Canada using established treatment practices in the management of patients with PCNSL. (N=11)

Treatment Practice	**Yes (%)**
Steroids deferred until after biopsy	91
Initial workup includes HIV testing	100
Initial workup includes HBV testing	82
Initial workup includes HCV testing	55
PET scan before therapy	9

CT chest, abdomen and pelvis before therapy	73
Bone marrow assessment before therapy	55
LP before therapy	45
Slit lamp eye exam before therapy	73

Fig. 1. Overall survival of patients stratified by treatment intent. (1 = curative, 2 = non-curative)

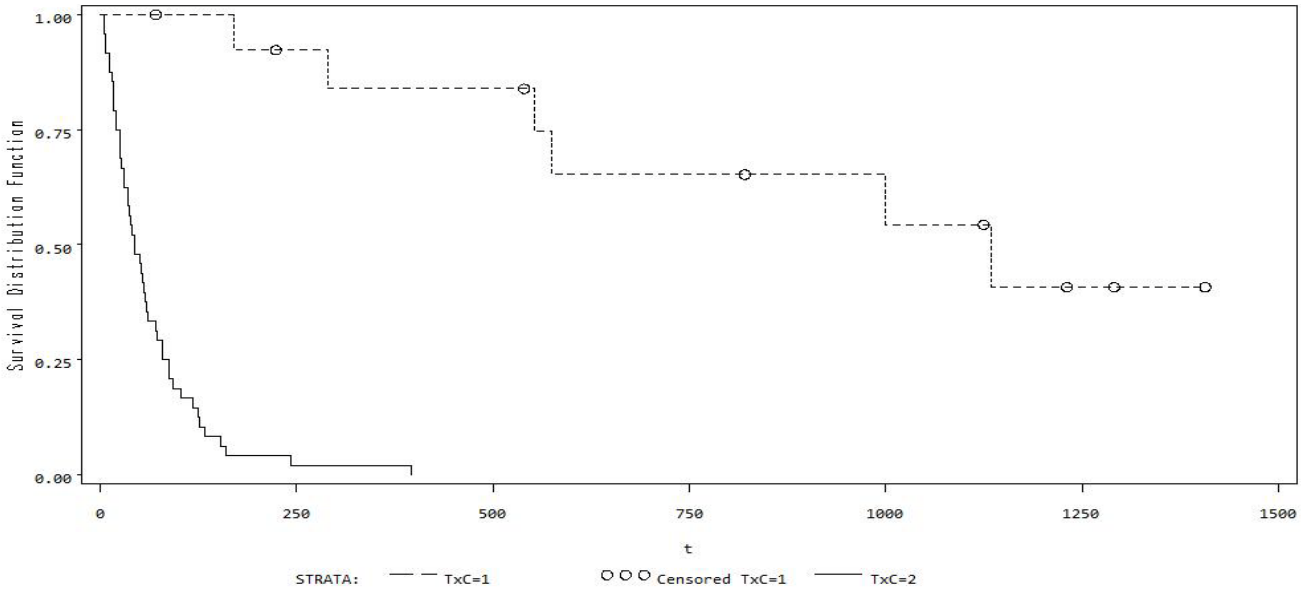
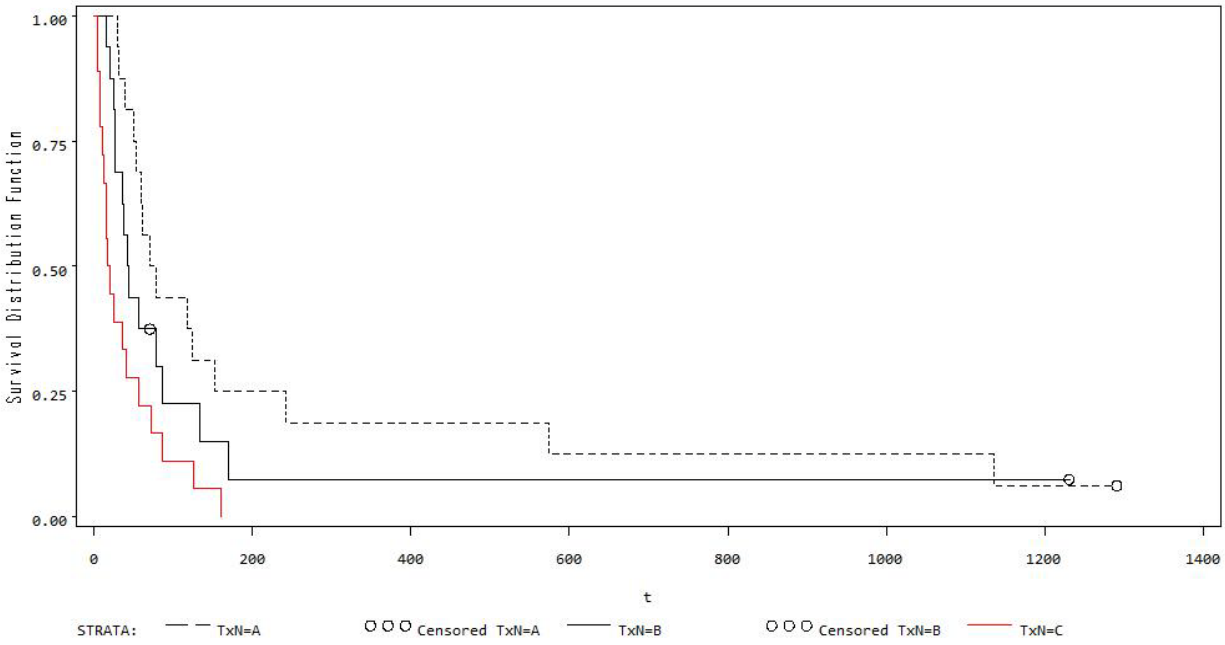


Fig. 2. Overall survival for patients treated with non-curative therapy stratified by treatment. (A = chemotherapy, B = radiation, C = palliation)



Appendix 1. PCNSL National Survey.

Primary CNS Lymphoma Canadian Management Survey

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CancerCare Manitoba Neuro Oncology Disease Site Group

Thank you for agreeing to participate in this national mailed survey. The survey should take no longer than 15 minutes. Once you have completed the survey we would ask that you return it in the stamped self addressed envelope enclosed.

(1) In your center, the number of patients diagnosed with primary central nervous system lymphoma (PCNSL) per year on average ranges from:
a. 0-5 patients
b. 6-10 patients
c. ≥ 11 patients

(2) For patients with a diagnosis of PCNSL, managed at your center, care is provided through:
a. a multi disciplinary clinic with participation of relevant care providers
□ b. a single physician practice with referral to appropriate clinical services

(3) Where a diagnosis of PCNSL is suspected at your center, steroid administration is routinely deferred until after a stereo tactic biopsy.
□ Yes □No

(4) At your center, an initial patient workup for PCNSL includes testing for
(i) HIV status □ Yes □No
(ii) Hepatitis B status □ Yes □No
(iii) Hepatitis C status □ Yes □No

(5) At your center, all patients with PCNSL who are immunocompetent
(i) routinely undergo positron emission tomography before commencing therapy
□ Yes □No
(ii) routinely undergo computed tomography of the chest, abdomen and pelvis before commencing therapy
□ Yes □No
(iii) routinely undergo bone marrow assessment before commencing therapy
□ Yes □No
(iv) routinely undergo lumbar puncture before commencing therapy
□ Yes □No
(v) routinely undergo slit lamp examination of the anterior chamber, vitreous and fundus before commencing therapy
□ Yes □No
(6) At your center, the initial management strategy for immunocompetent patient with PCNSL involves
□ a. chemotherapy alone
b. chemotherapy in combination with radiation therapy for all age groups

 c. chemotherapy in combination with radiation therapy for younger patients with chemotherapy alone reserved for older patients
 d. treated on a research protocol

(7) For patients being treated with chemotherapy, rituximab is routinely administered as part of the regimen
 Yes No

(8) Once treatment has been completed, and complete remission has been documented, routine scheduled follow up imaging at your center is
 a. not performed
 b. undertaken with computed tomography
 c. undertaken with magnetic resonance imaging

(9) At your center, routine comprehensive neuro cognitive assessment is performed for patients with PCNSL at baseline and follow up
 Yes No

(10) In the setting of an AIDS related PCNSL, your center's therapeutic strategy routinely involves
 a. radiation therapy alone
 b. chemotherapy alone
 c. combined modality treatment

(11) Please note any comments or suggestions:

References

1. The Non-Hodgkin's Lymphoma Classification Project: A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997; 89:3909-3918.

2. Schabet M. Epidemiology of primary CNS lymphoma. J Neurooncol 1999; 43:199-201.

3. Olsen JE, Janney CA, Rao RD et al. The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: A surveillance, epidemiology, and end results analysis. Cancer 2002; 95:1504-1510.

4. Murray K, Kun L, Cox J. Primary malignant lymphoma of the central nervous system. J Neurosurg 1986; 65:600-607.

5. Nelson DF. Radiotherapy in treatment of primary cerebral lymphoma. J Neurooncol 1999; 43:241–247.

6. Mead GM, Bleehen MN, Gregor A et al. A Medical Research Council randomized trial in patients with primary cerebral non-Hodgkin lymphoma: cerebral radiotherapy with and without cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. Cancer 2000; 89:1359–1370.

7. Shapiro WR, Young DF, Mehta BM. Methotrexate: Distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. N Engl J Med 1975; 293:161-166.

8. Morris PG, Abrey LE. Therapeutic challenges in primary CNS lymphoma. Lancet Neurol 2009 Jun; 8(6):581-92.

9. Ferreri AJ, Reni M, Foppoli M et al. High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. Lancet Neurol 2009 Oct 31; 374(9700):1512-20.

10. Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. J Clin Oncol 1998; 16:859-63.

11. Bessell EM, Lopez-Guillermo A, Villa S et al. Importance of radiotherapy in the outcome of patients with primary CNS lymphoma: an analysis of the CHOD/BVAM regimen followed by two different radiotherapy treatments. J Clin Oncol 2002; 20:231–236.

12. Pels H, Schmidt-Wolf IG, Glasmacher A et al. Primary central nervous system lymphoma: Results of a pilot and phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. J Clin Oncol 2003; 21:4489-4495.

13. Gerstner ER, Batchelor TT. Primary central nervous system lymphoma. Arch Neurol 2010 Mar; 67(3):291-7.

14. NCCN Guidelines [Internet]. Fort Washington: NCCN Guidelines Version 2.2011, Primary CNS lymphoma c2011 [cited 2011 July 31]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

15. BCSH Guidelines [Internet]. London: Guidelines on the diagnosis and management of adult patients with primary CNS lymphoma (PCNSL) and primary intra-ocular lymphoma (PIOL); c2007 [cited 2011 July 31]. Available from: http://www.bcshguidelines.com/documents/PCNSL__bcsh_2007.pdf

16. DeAngelis LM, Seiferheld W, Schold SC et al. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group 93-100. J Clin Oncol 2002; 20:4643-4648.

17. Nelson DF, Martz KL, Bonner H et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radiat Oncol Biol Phys 1992; 23(1):9-17.