Saudi Journal of Biological Sciences 26 (2019) 595–599

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Original article

Comparative study on different therapies on patients with primary central nervous system lymphoma

Xuchu Yang [a], Xinfeng Zhang [a], Huaizhang Wang [a], Shuochuan Liu [b], Wenwen Jin [c], Yingyue Li [c], Huaimin Liu [a,*]

[a] Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou 450000, China
[b] Nanchang University Queen Mary School, Nanchang 330000, China
[c] Medical Engineering Technology and Data Mining Institute of Zhengzhou University, Zhengzhou 450000, China

ARTICLE INFO

Article history:
Received 28 August 2018
Revised 7 November 2018
Accepted 8 November 2018
Available online 9 November 2018

Keywords:
Primary central nervous system lymphoma
Surgical therapy
Radiotherapy
Chemotherapy

ABSTRACT

Objective: To compare and analyze three therapies on patients with primary central nervous system lymphoma (PCNSL), aiming to provide evidences for future treatment and prognosis.
Methods: Clinical data of 26 cases of PCNSL with normal immune system confirmed by postoperative pathology were retrospectively analyzed. Among them there were six cases with operation only, nine cases with operation and radiotherapy, and 11 cases with operation, radiotherapy and chemotherapy, and their survival rate was compared as well.
Results: The survival time of patients with operation only, operation combined with radiotherapy and operation combined with radiotherapy and chemotherapy was 6–11 months, 15–24 months and 24–51 months, respectively. And their median survival time was only nine months, 21 months and 38 months, respectively.
Conclusions: Operation combined with radiotherapy and chemotherapy can dramatically extend PCNSL patients' survival time, therefore, it can be regarded as the first-line therapy.

1. Introduction

Primary central nervous system lymphoma (PCNSL) is a rare invasive non-Hodgkin's lymphoma (NHL) developed in brain, meningeal and spinal cord and generally not involving full body, and its incidence accounting for 1–3% in central nervous system tumors (Yang, 2007). Most of the pathological types of PCNSL can be classified as activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL). The diagnosis depends on pathological biopsy and currently the safest and most convenient method is stereotactic biopsy (Han and Batchelor, 2017; Carnevale and Rubenstein, 2016). PCNSL is a highly malignant and rapid-onset tumor which will risk patient's life if not treated effectively, and PCNSL has bad therapy efficiency and poor prognosis with short survival time. In recent years, studies have shown that the incidence of PCNSL has been increasing. But for lack of specific imaging features and laboratory findings, it is often difficult to diagnosis before surgery. The current goal of treatment is to improve therapeutic effect and reduce adverse reactions, thereby improve the survival quality of patients.

Due to the high invasiveness and rapid progress of PCNSL, there is no uniform therapy strategies, and the simple surgical resection cannot achieve the desired therapeutic effect. It is now thought that the most important treatment of PCNSL is chemotherapy. However, due to the characteristics of tumor itself and the existence of blood-brain barrier, the traditional drug treatment is not effective. Stereotactic radiosurgery in combination with high-dose methotrexate (HD-MTX) is currently recommended as a newly diagnosed first-line treatment for PCNSL (Haldorsen et al., 2007; Erlanson et al., 1998). Therefore, 26 cases of PCNSL treated in Henan provincial people's hospital between June 2004 and December 2013 were retrospectively analyzed in this study, and their survival time under different therapies was compared as well in order to offer references for precise diagnosis and prognosis in the future and to confirm more effective therapy for patients.

* Corresponding author.
E-mail address: 1151484377@qq.com (H. Liu).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sjbs.2018.11.004
1319-562X/

2. Materials and methods

2.1. General data

This study recruited 26 cases of PCNSL patients who went to department of neuro-tumor of Henan provincial people's hospital from June 2004 to December 2013, including 16 males and 10 females, 42 to 67 years of age (the media age was 54 years old), and their disease course was from two weeks to three months. Inclusion criteria: (1) patient was first diagnosed as PCNSL during the above mentioned period. (2) Human immunodeficiency virus (HIV) was negative and patients had no other immunodeficiency diseases. (3) The initial symptom was central nervous system dysfunction and the lesion located in central nervous system. (4) The disease was confirmed by histology, cytology and pathology, and immunoenzymatic technique. (5) Patient was strictly checked for intumescence of shallow lymph gland, and no lymphoma in full-body lymphohemopoietic tissues and any other body part were found by bone marrow smears examination and chest and abdomen computed tomography (CT) examination. (6) Patient was conducted imaging examination before being diagnosed and after chemotherapy to follow up brain lesion changes. All patients are in compliance with the above criteria.

2.2. Methods

Retrospective analysis: (1) clinical symptoms and basic vital signs: clinical symptoms and signs, previous medical history. (2) imaging data: according to CT examination and magnetic resonance imaging (MRI) examination, patient's lesion was in central nervous system, and tumor location, number, shape, plain scanning and enhanced imaging performance were determined. (3) Blood routine test data: patients were conducted blood routine test before operation. (4) Pathological data: pathological specimen was obtained through operation and patients were diagnosed as NHL by pathological section and immunohistochemical method. (5) analysis of therapies and efficacy: 26 patients were divided into three groups, the first group includes six patients that received surgical therapy only because of financial reasons; the second group contains nine patients who were given surgical treatment and whole brain radiotherapy; and the third group covers the rest 11 patients that were conducted surgical treatment, radiotherapy as well as chemotherapy, in which radiotherapy included conventional radiotherapy, x-knife and gamma-knife, and chemotherapy contained intravenous drip of Nimustine/Carmustine/cytosine arabinoside and injection of armor ammonia pterin into ventricle through Omaya sac. Analysis of therapeutic efficacy is mainly on comparison of survival time with phone call follow-up as primary method. The dead line of follow-up was June 2015 and the survival time was calculated from the next day of surgery.

2.3. Statistical analysis

Survival curve was drawn with Kaplan-Meier method by software SPSS13.0 and then survival rate for each group was compared based on Fisher's exact probability.

3. Results

3.1. Clinical characteristics

PCNSL has no specific clinical symptom and its primary symptom is increasing intracranial hypertension with local functional defects. In this study 14 patients (53.8%) had headache, dizziness and nausea; 10 patients (38.5%) had disorder of limb's activity; four patients had paresthesia (such as masklike face and insensitive tactile sense, etc.); three patients (11.5%) became irritable and anxious; three cases (11.5%) had ataxia; one patient (3.8%) had change of the acuity of vision campus visualis and one patient (3.8%) had epilepsy.

3.2. Imaging characteristics

CT and MRI were carried out on all patients. 21 patients (80.8%) had single lesion, at following lesion locations: 11 cases in frontal lobe, eight in temporal lobe, three in corpus callosum region, two in basal ganglia region, one in cerebrum parietal lobe and one in posterior-superior part of sella turcica. Five patients (19.2%) had multiple lesions, and there were totally 18 lesions. According to the CT plain film scanning, a majority of lesions were round or ellipse and among them there were four cases of low density, six cases of isodensity, six cases of slightly high density and 10 cases of high-low mixes density.

MRI signal showed that slightly hypointensity on T1 and slightly hyperintensity on T2 were found in 11 cases (see Fig. 1A and B), hypointensity on T1 and isointensity on T2 in three cases, isointensity on T1 and T2 in five cases, isointensity on T1 and hyperintensity on T2 in four cases, and mixed signal on T1 and T2 in three cases. Mostly, T2-FLAIR showed hyperintensity or slightly hyperintensity (see Fig. 1C). Under enhanced-MRI, snow mass-shaped lesions (see Fig. 2) or "ball-like" lesions were found and there were six lesions of typical sharp angle sign (see Fig. 1D) and three cases of notch sign. 21 cases were shown distinct boundary and five cases were unclear border. Edema occurred around tumor in different degree (see Figs. 1D and 2C), so did mass effect. Additionally, the five cases with unclear border were conducted diffusion weighted imaging (DWI) and results showed that one of them appeared isointensity, two of them were hyperintensity (see Fig. 3A) and two of them were slightly hyperintensity.

3.3. Routine blood examination

According to the routine blood examination of the above patients, it's found that regarding the ratio of lymphocyte, 14 cases was less than 30%, seven patients were within 30–40%, and three were more than 40%.

3.4. Pathological characteristics

Pathology analysis showed that 26 patients were diagnosed as NHL, 23 cases of diffuse large B-cell lymphoma, one case of T-cell lymphoma and two cases of B cell type mixed with some T cells.

3.5. Effects of the treatment and follow-up

Data of 26 patients during survival time were analyzed and made into survival curve (see Fig. 4). Six patients with pure surgical excision recurred in short time and died of the tumor within one year. Seen from Fig. 4, patients with pure surgical excision had a survival time of 6–11 months and a median survival time of nine months; patients with surgical excision and radiotherapy had a survival time of 15–24 months and a median survival time of 21 months; and patients with surgical excision and radiotherapy and chemotherapy had a survival time of 24–51 months and a median survival time of 38 months, which was significantly longer than the first two therapies, and the longest survival time was over four years.

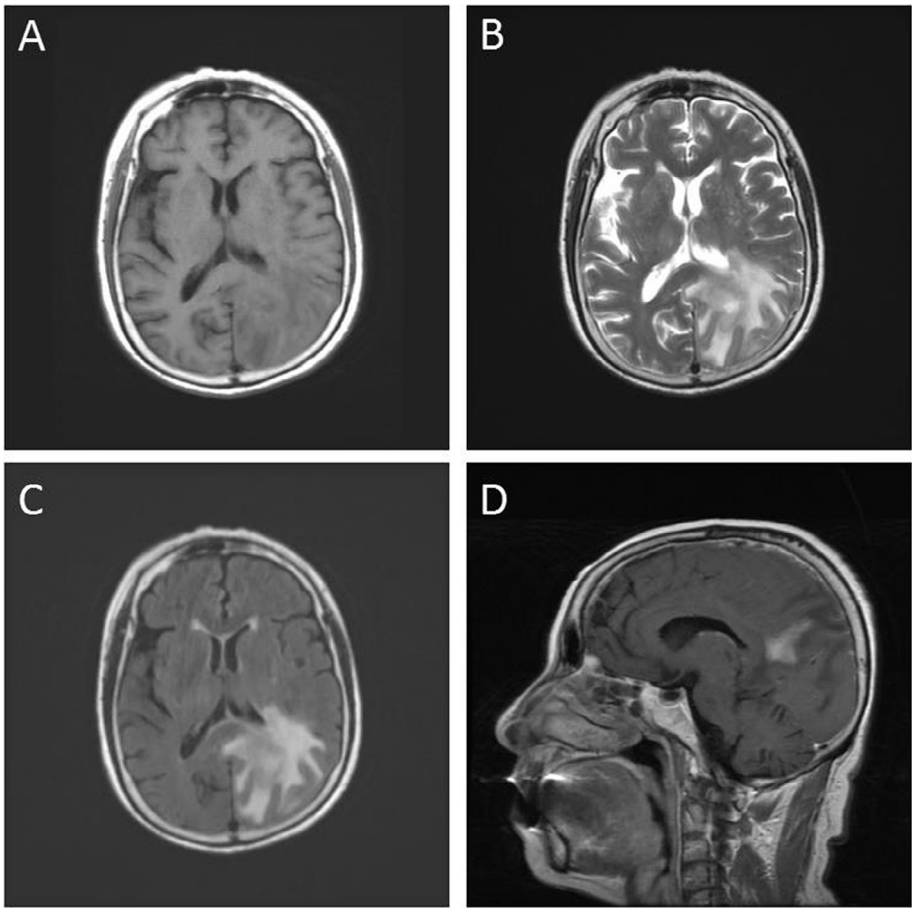

Fig. 1. Case 1: MRI of primary central nervous system lymphoma A: Slightly hypointensity on T1WI, B: Hyperintensity on T2WI, C: Hyperintensity on T2-FLAIR, D: with enhanced scanning, the lesion became more uneven with edge of ‘‘sharp angle sign” and ‘‘villous edema” of slightly prolonged T1 and prolonged T2 appearing around the lesion.

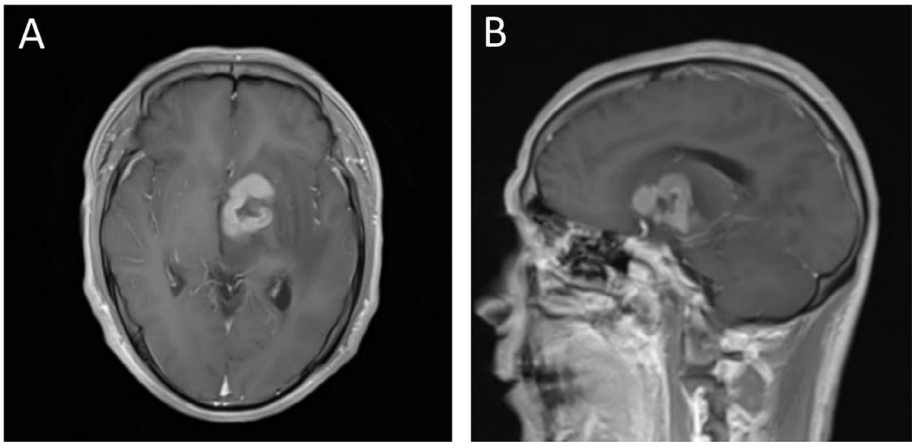

Fig. 2. Case 2: Enhanced MRI of primary central nervous system lymphoma With enhanced MRI scanning, the lesion was shown gyriform enhancement, the enhanced region showed enhanced region showed gap-shaped lesion while no enhanced region showed snow mass-shaped change; no enhancement was found in edema area around tumor, left lateral ventricular and suprasellar cistern and aqueduct of midbrain were deformed under pressure, and the central line structure moved to right. A: Axial view; B: Sagittal view.

4. Discussion

PCNSL is primary NHL located in central nervous system which is relatively rare, resulting in inconsistent incidence rate data which generally were 1–12% (Lister et al., 2002; García Franco et al., 2009). However, with increase of patients with organ transplantation, acquired immune deficiency syndrome (AIDS), congenital immunodeficiency as well as massive application of hormones, more and more people have PCNSL and their average age has been coming down over the years (Li et al., 2006). Although the pathogenesis of PCNSL has been discussed and explored around the world in recent years, its specific causes haven’t been identified

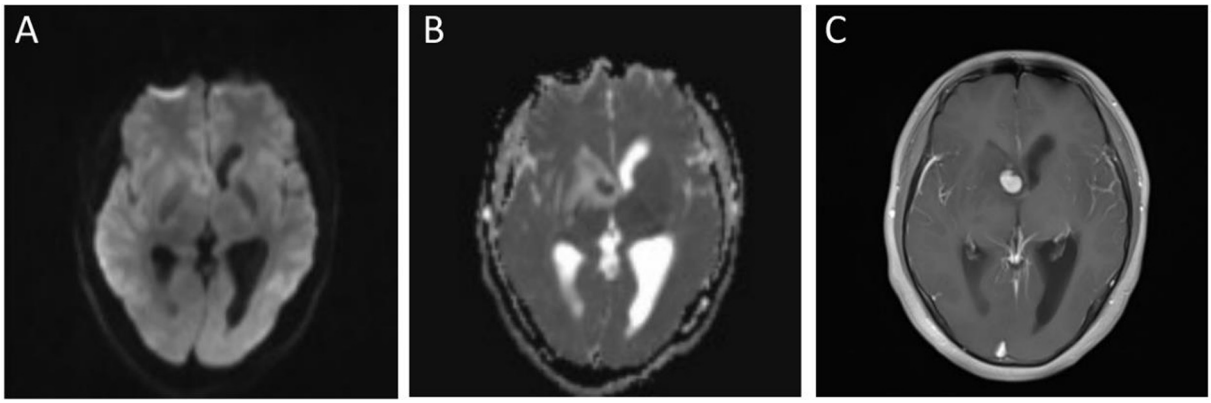

Fig. 3. Case 3: MRI of primary central nervous system lymphoma A: Hyperintensity on DWI, B: Hypointensity on ADC, C: The lesion became more even with enhanced scanning, no gap shape was shown around enhanced region while the defect without enhancement appeared "notch sign", large area of edema was found around the lesion and no enhancement was found in edema belt.

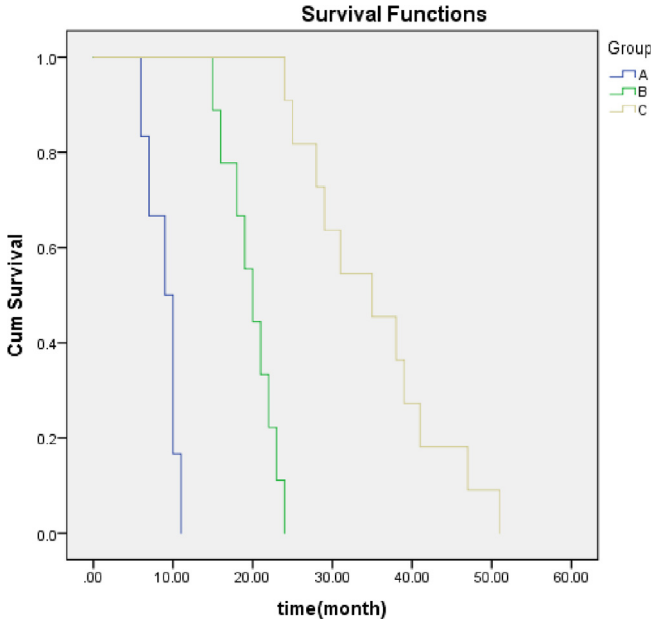

Fig. 4. Kaplan-meier survival curve A: Pure surgical excision, B: Surgical excision together with radiotherapy, C: Surgical excision combined with radiotherapy and chemotherapy.

except the fact that it's related to immune mechanism (Brunn et al., 2007). The mechanism of PCNSL is complicated. Most scholars believe that it originates from the pluripotent cells which have not differentiated around the blood vessels. It may be related to allogeneic antigen stimulation, immunosuppression and immune surveillance dysfunction (Gu et al., 2010).

Clinical manifestations of PCNSL mainly are increased intracranial pressure signs such as dizziness, nausea and vomiting. In this study, patients with increased intracranial pressure account for 53.8%. PCNSL has various pathogenic sites so that pathogenic signs vary from different pathogenic sites, therefore, the clinical manifestations of patients with PCNSL are complicated including disorder of limb's activity, aphasia, varying degrees of epilepsy, defective vision, puerperal psychosis or personality change and ataxia, etc. 26 cases in his study had six different clinical manifestations, which shows that PCNSL doesn't have specific features, leading to hard diagnosis and high misdiagnosis. As imaging especially MRI has been applied in clinic, the imaging features of PCNSL have been understood further, which is beneficial for its diagnosis (Zhang et al., 2016; Choi et al., 2017). Research has shown that USPIO (superparamagnetic iron oxide) enhanced MRI can be used to diagnose central nervous system inflammation and lymphoma, and is suitable for patients who cannot tolerate contrast medium inability due to impaired or incomplete renal function (Farrell et al., 2013). PCNSL can appears at any part inside brain, mostly at frontal, parietal and occipital lobe and other periventricular areas and its lesion are mostly round, oval or irregular shape, generally single, sometimes multiple (Haldorsen et al., 2007). And the lesion border usually is relatively clear which, however, cannot conceal its malignant nature. Few patients with PCNSL will appear calcification and necrosis and haemorrhage are rare. Slight or moderate edema and different degrees of mass effect always were found around tumor based on different sizes of tumor. CT plain scanning usually shows isodensity or high density, MRI signal shows generally isointensity or hypointensity on T1WI and isointensity or hyperintensity on T2WI. With enhanced MRI scanning, lesions mostly showed homogeneous density with specific features like "sharp angle sign" or "notch sign" (Boiardi and Silvani, 1997; Li and Sui, 2007) which offered effective evidence for the diagnosis of PCNSL (Yu et al., 2005), and in this study among 26 cases, six cases showed "sharp angle sign" and three cases showed "notch sign". DWI examination was conducted on PCNSL and it was found that restricted diffusion became more apparent, usually with hyperintensity or slight hyperintensity (Haldorsen et al., 2011), which is in line with this study.

PCNSL develops quickly and its course varies from days to months, therefore, once diagnosed, patients should receive reasonable treatment immediately. Current therapies include surgical excision, surgical excision together with radiotherapy and surgical excision combined with radiotherapy and chemotherapy. Among them surgical excision is the base of other therapies and it can diagnose the disease clearly and can directly relieve intracranial hypertension, but it is not effective for the treatment of PCNSL unless combined with other therapies (Nayak and Batchelor, 2013; Michalski et al., 1990). In this study six patients received pure surgical excision for personal reasons and his survival time was 6–11 months and median survival time was only nine months. Whole brain radiotherapy is one of first-line regimens at present and it is effective for treatment of PCNSL whose response rate is over 90%, but this therapy is easy to bring nerves toxic effects, especially for older patients, even result in death; besides, radiotherapy is likely to relapse usually with a recurrence rate over 80% within 10–14 months and with a median survival time of 18 months or so according to statistics (Agha et al., 2007; Nguyen et al., 2005). In this study, patients receiving surgical exci-

sion together with radiotherapy had a survival time of 15–24 months and a median survival time of 21 months, which is similar to previous studying outcomes. Radiotherapy combined with chemotherapy drugs can increase patients' survival rate, and currently the most common used chemotherapy drug regimen is high-dose methotrexate (MTX) together with other chemotherapy drug (Deckert et al., 2011; Caroli et al., 2004). The combination of multiple chemotherapy drugs containing HD-MTX is superior to single-agent HD-MTX. Studies have also shown that HD-MTX combined with whole brain radiotherapy (WBRT) is superior to chemotherapy alone (Choi et al., 2017), but the long-term use of WBRT is extremely harmful to the patient's nervous system, and may even lead to dementia or death. Patients in the third group in this study received chemotherapy regimen of MTX with intravenous drip of Nimustine, Carmustine and cytosine arabinoside, and their survival time is obviously longer than patients with pure surgical excision and patients with surgical excision together with radiotherapy, with a survival time of 24–51 months and a median survival time of 40 months.

The reason why national medical scholars pay attention to PCNSL is that it develops fast with mo specific features resulting in poor diagnosis and prognosis and short survival time. With increase of clinical treatment experience and improvement of therapies, current thinking holds that surgical excision combined with radiotherapy and drug chemotherapy drug can extend patients' survival time. And this thinking also has been verified in this study through comparative analyses of different therapies. However, current therapies still have some shortness, such as injury to patients' nerves system, large possibility of recurrence, and so on. Besides, little has been known about the nature of PCNSL and its pathogenesis which also are the focuses of future work.

Acknowledgement

The work was financially supported by The National Science Fund for Distinguished Young Scholars (Grant No.: 81603469)

References

Agha, A., Bashir, K., Anwar, E., 2007. Use of losartan in reducing microalbuminuria in normotensive patients with type-2 diabetes mellitus. Nepal Med. Coll. J. 9, 79–83.

Boiardi, A., Silvani, A., 1997. Primary cerebral non-Hodgkin's lymphoma (PCNSL): a review of new trends in management. Ital. J. Neurol. Sci. 18, 1–7.

Brunn, A., Montesinos-Rongen, M., Strack, A., Reifenberger, G., Mawrin, C., Schaller, C., Deckert, M., 2007. Expression pattern and cellular sources of chemokines in primary central nervous system lymphoma. Acta Neuropathol. 114, 271–276.

Caroli, E., Acqui, M., Ferrante, L., 2004. Primary cerebral lymphoma: a retrospective study in 22 immunocompetent patients. Tumori J. 90, 294–298.

Carnevale, J., Rubenstein, J.L., 2016. The challenge of primary central nervous system lymphoma. Hematol. Oncol. Clin. North Am. 30 (6), 1293–1316.

Choi, Y.S., Lee, H.J., Ahn, S.S., et al., 2017. Primary central nervous system lymphoma and atypical glioblastoma: differentiation using the initial area under the curve derived from dynamic contrast-enhanced MR and the apparent diffusion coefficient. Eur. Radiol. 27 (4), 1344–1351.

Deckert, M., Engert, A., Brück, W., et al., 2011. Modern concepts in the biology, diagnosis, differential diagnosis and treatment of primary central nervous system lymphoma. Leukemia 25, 1797–1807.

Erlanson, M. et al., 1998. Expression of cyclin E and the cyclin-dependent kinase inhibitor p27 in malignant lymphomas-prognostic implications. Blood 92 (3), 770–777.

Farrell, B.T., Hamilton, B.E., Dosa, E., et al., 2013. Using iron oxide nanoparticles to diagnose CNS inflammatory diseases and PCNSL. Neurology 81 (3), 256–263.

García Franco, C.E., Algarra, S.M., Ezcurra, A.T., Guillén-Grima, F., San-Julián, M., Mindán, J.P., Buxalleu, W.T., 2009. Long-term results after resection for soft tissue sarcoma pulmonary metastases. Interact. Cardiovasc. Thorac. Surg. 9, 223–226.

Gu, Y., Hou, Y.Y., Zhang, X.B., et al., 2010. Primary central nervous system Burkitt lymphoma as concomitant lesions in the third and the left ventricles: a case study and literature review. J. Neurooncol. 99 (2), 277–281.

Haldorsen, I.S., Espeland, A., Larsson, E.M., 2011. Central nervous system lymphoma: characteristic findings on traditional and advance dimaging. AJNR Am. J. Neuroradiol. 32, 984–992.

Haldorsen, I.S., Krossnes, B.K., Aarseth, J.H., Scheie, D., Johannesen, T.B., Mella, O., Espeland, A., 2007. Increasing incidence and continued dismal outcome of primary central nervous system lymphoma in Norway 1989–2003: time trends in a 15-year national survey. Cancer 110, 1803–1814.

Han, C.H., Batchelor, T.T., 2017. Diagnosis and management of primary central nervous system lymphoma. Cancer 123 (22), 4314–4324.

Li, M.Z., Luo, L., Gao, N.K., Fu, C.Y., Dou, C.W., Wang, T., Li, Y.X., 2006. Classification and treatment in primary intracerebral malignant lymphoma. Chin. J. Neurosurg. 22, 259–260.

Li, Y., Sui, Q.L., 2007. The MRI diagnosis of intracranial primary central nervous system lymphoma. J. Clin. Radiol. 26, 223–226.

Lister, A., Abrey, L.E., Sandlund, J.T., 2002. Central nervous system lymphoma. Hematol. Am. Soc. Hematol. Educ Program, 283–296.

Michalski, J.M., Garcia, D.M., Kase, E., Grigsby, P.W., Simpson, J.R., 1990. Primary central nervous system lymphoma: analysis of prognostic variables and patterns of treatment failure. Radiology 176, 855–860.

Nayak, L., Batchelor, T.T., 2013. Recent advances in treatment of primary central nervous system lymphoma. Curr. Treat. Options Oncol. 14, 539–552.

Nguyen, P.L., Chakravi, A., Finkelstein, D.M., Hochberg, F.H., Batchelor, T.T., Loeffler, J.S., 2005. Results of whole-brain radiation as salvage of methotrexate failure for immunocompetent patients with primary CNS lymphoma. J. Clin. Oneol. 23, 1507–1513.

Yang, X.J., 2007. An appraisal of the world health organization classification of tumor the central nerves system. Chin. J. Nerv. Mental Dis. 33, 513–517.

Yu, T.G., Dai, J.Z., Feng, X.Y., 2005. MRI and 1H-MRS characteristics of primary central nervous system lymphomas (PCNSL). J. Clin. Radiol. 24, 668–672.

Zhang, S., Li, H., Zhu, R., Zhang, M., 2016. Application value of magnetic resonance imaging in diagnosing central nervous system lymphoma. Pak. J. Med. Sci. 32, 389–393.