Turk Neurosurg 34(3):401-406, 2024

Original Investigation

DOI: 10.5137/1019-5149.JTN.41647-22.1

Received: 21.07.2022
Accepted: 03.02.2023

Published Online: 16.04.2024

Resection or Biopsy: The Efficacy of Different Surgical Approaches for Primary Central Nervous System Lymphoma

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ABSTRACT

AIM: To analyze the efficacy of surgical resection versus brain biopsy combined with postoperative chemotherapy for primary central nervous system lymphoma (PCNSL) and to discuss a clinically standardized treatment protocol.

MATERIAL and METHODS: Patients with a pathological diagnosis of PCNSL and subsequent chemotherapy between 2016 and 2021 at Northern Jiangsu People's Hospital were selected and divided into groups according to whether they underwent microsurgical resection or stereotactic needle biopsy. Statistical analyses were performed to compare efficacy and safety in the two groups.

RESULTS: A total of 21 patients with PCNSL were identified, of whom 12 underwent resection and 9 underwent diagnostic stereotactic biopsy only. Compared with the resection group, the biopsy group had a higher proportion of deep tumors (55.6% vs. 8.3%, p=0.016), and the mean intraoperative bleeding was significantly reduced (13.33 ± 6.61 mL vs. 170.83 ± 101.04 ml, p<0.001). In addition, the mean survival time of patients who died during the postoperative follow-up period was shorter (6.83 ± 1.60 vs. 18.56 ± 10.20 months, p=0.016), and the one-year survival rate was lower (33.3% vs. 83.3%, p=0.032). There was no significant difference between the two groups in terms of the mean progression-free survival time or new functional impairment after surgery.

CONCLUSION: For PCNSL, patients who undergo surgical resection have a better outcome than those who undergo biopsy only, suggesting that when the tumor is located at a surgically resectable site, surgical resection should be actively chosen; when the tumor is located at a deep and unresectable site, brain biopsy should be chosen.

KEYWORDS: Primary central nervous system lymphoma, Stereotactic biopsy, Surgical resection, Chemotherapy

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare intracranial in situ high-grade non-Hodgkin lymphoma, accounting for 1% of all non-Hodgkin lymphomas and 3% of all primary intracranial tumors, with the majority of the pathologies being diffuse large B-cell lymphoma (9). PCNSL often recurs after surgical resection and is sensitive to chemotherapy (and/or radiotherapy). Therefore, when imaging findings suggest PCNSL, the pathological diagnosis is usually confirmed by biopsy, followed by chemotherapy (and/or radiotherapy).This regimen has become a consensus in many neurosurgical centers, especially when the tumor is located deep in the brain tissue or in important functional areas and surgical resection is unavailable, thus generally making it the only feasible option (17,18). However, the choice of surgical resection versus biopsy is controversial when the tumor is located in a surgically resectable area or when it is large enough to cause increased intracranial pressure. In this study,

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patients with PCNSL were taken as the research objects, and the efficacy and safety of surgical resection versus brain biopsy, combined with postoperative chemotherapy, were retrospectively analyzed, and the clinical standardized treatment protocol is discussed.

MATERIAL and METHODS

Patient Selection

Patients with PCNSL treated between January 2016 and January 2021 at the Department of Neurosurgery, Northern Jiangsu People's Hospital were enrolled (No: 2019KY-092, Date: 19.02.2019). The patient inclusion criteria were as follows: (I) pathologically confirmed diagnosis of PCNSL and (II) surgical procedures, including biopsy and tumor resection. The exclusion criteria were as follows: (I) refusal of further chemotherapy (and/or radiotherapy). (II) patients lost to follow-up.

Recorded Variables

The variables extracted from the medical records included general patient indicators (age and sex), imaging characteristics (number, size, and depth of the tumor), intraoperative indicators (operation time and bleeding volume), outcome indicators (1-year postoperative survival rate and imaging progression-free survival time), and complication indicators (additional functional impairment). A deep tumor is located in important nuclear sites such as the basal ganglia, corpus callosum, or periventricular areas, whereas a superficial tumor is located in the frontal lobe, temporal lobe, parietal lobe, occipital lobe, or other superficial sites.

Surgery and Chemotherapy

Patients with imaging findings suggestive of PCNSL were treated with stereotactic biopsy and craniotomy resection under navigation according to the number, size, and location of the tumors. The brain biopsy procedures were as follows: According to the preoperative MRI images, a neuronavigation system was used to plan the targets and puncture paths and avoid intracerebral blood vessels and functional areas. Skull drilling and stereotactic needle biopsies were performed under general anesthesia. The craniotomy resection followed the principle of "removing as much tumor as possible without affecting the function" and obtained gross total resection or subtotal resection.

All patients received chemotherapy after the pathologic diagnosis and were treated with high-dose methotrexate (HD-MTX)-based chemotherapy alone.

Follow-up

All patients were followed up regularly until February 2022, including whether they had any new functional impairment after surgery, survival time, imaging (mainly head-enhanced MRI) for tumor growth, and follow-up treatment.

Statistical Analyses

The data were divided into biopsy versus resection groups according to the surgical modality, and each index was counted separately. The measurement data were expressed as means ± the standard deviation, and the test method was the t-test. The Kaplan–Meier method was used for survival analysis and plotting of survival curves, while the log-rank method was used to compare survival between groups, and the difference was considered statistically significant at $p<0.05$. SPSS 26.0 statistical software was used for the data processing and analysis.

RESULTS

Twenty-one patients, 9 males and 12 females, with a mean age of 63.0 ± 9.8 (43–76) years, were eligible for enrollment. Ten patients (47.6%) had symptoms of increased intracranial pressure and 11 patients (52.4%) had neurological localization signs. All patients underwent plain and enhanced MRI scans; 14 patients (66.7%) had isolated lesions, and seven patients had multiple lesions. Invasion of the deep brain structures was observed in 15 patients (71.4%). No surgical mortality was observed. Four patients showed improvement in their original symptoms and 17 patients had no new symptoms. The mean survival time of the patients who died during the follow-up period was 13.9 ± 9.8 months (5–37 months), with a one-year survival rate of 61.9% (13/21).

The clinical data of the patients are summarized in Table I. Nine patients underwent biopsy and twelve underwent resection. There were no group differences in the baseline indices, including sex, age, isolated/multiple lesions, and tumor volume ($p>0.05$).There were significant differences in the tumor location (superficial/deep), with a higher proportion of deep tumors in the biopsy group ($p<0.05$). In addition, there were no statistical differences in the brain biopsy group with 7 single lesions and 2 cases with multiple lesions, while 7 cases with single lesions and 5 cases with multiple lesions in the resection group ($p>0.05$). Furthermore, in terms of postoperative complications, there were no complications in the biopsy group, and one patient in the resection group had aphasia after surgery, but there was no statistically significant difference in new functional impairment between the two groups ($p>0.05$).

There was a trend toward prolonged overall survival (Figures 1, 2) in the resection group compared with the biopsy group. For the one-year survival rate and the survival time of patients who died during the follow-up, those of the resection group were significantly higher than those of the biopsy group ($p<0.05$), but for the progression-free survival time, the two groups were not significantly different ($p>0.05$). Regarding postoperative complications, there was no significant difference between the two groups in terms of additional functional impairment ($p>0.05$).

Typical case 1

A 48-year-old male presented with headache as the primary symptom on admission. MRI revealed a right temporal lobe tumor with possible hemorrhage. The tumor was resected, and postoperative pathology confirmed PCNSL. The postoperative cranial CT showed complete resection of the tumor and was followed by a high-dose methotrexate-based combination

Table I: Analysis of Statistical Indicators in the Brain Biopsy and Resection Groups

Characteristic	Brain biopsy with chemotherapy group (n=9)	Surgical resection with chemotherapy group (n=12)	Statistical values	p-value
Gender: Male/Female	3/6	6/6	0.737	0.470
Age (years) (mean ± SD)	59.33 ± 11.63	65.75 ± 7.50	-1.538	0.140
Single leision/multiple leisions (n)	7/2	7/5	-0.909	0.375
Superficial/Deep (n)	4/5	11/1	2.635	**0.016**
Tumor volume (mL) (mean ± SD)	18.56 ± 14.76	14.53 ± 17.30	0.560	0.582
Surgery time (min) (mean ± SD)	117.78 ± 42.07	182.92 ± 37.08	-3.763	**0.001**
Bleeding volume (mL) (mean ± SD)	13.33 ± 6.61	170.83 ± 101.04	-4.639	**0.000**
New functional impairment (cases)	0	0.25 ± 0.45	-1.648	0.116
Progression-free survival time (months) (mean ± SD)	9.33 ± 6.16	16.75 ± 13.23	-1.552	0.137
Survival time of patients who died during the follow-up period (months) (mean ± SD)	6.83 ± 1.60	18.56 ± 10.20	-2.759	**0.016**
One-year survival rate (n)	3/9	10/12		**0.032**

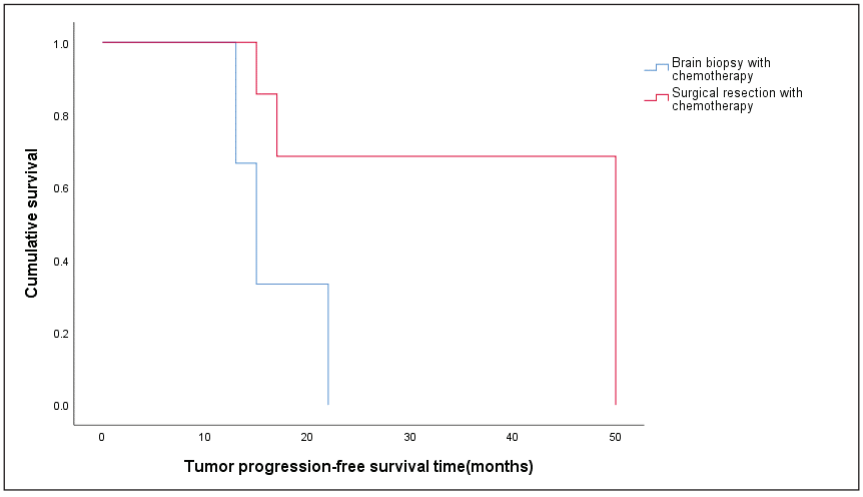

Figure 1: Kaplan–Meier survival curves for progression-free survival time of tumors in both treatment groups.

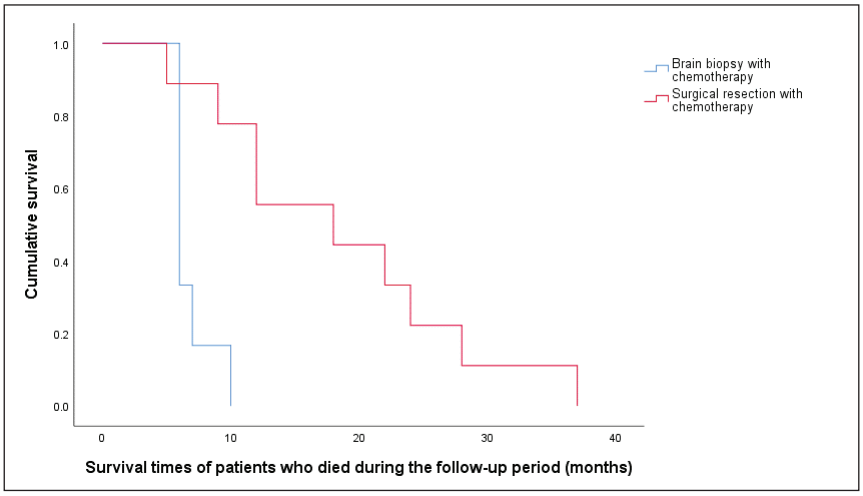

Figure 2: Kaplan–Meier survival curves for survival times of patients who died during the follow-up period in both treatment groups.

chemotherapy regimen. After 3 courses of chemotherapy, the cranial MRI showed no tumor recurrence. The patient survived for approximately 50 months (Figure 3).

Typical case 2

A 56-year-old male patient was admitted with the main symptom of headache with unresponsiveness. MRI revealed a tumor in the deep right temporo-occipital lobe and posterior hippocampus. The patient was treated with high-dose methotrexate combined with rituximab chemotherapy. The tumor shrank significantly after 2 months and disappeared after 5 months. The patient survived for approximately 22 months and had a good quality of life (Figure 4).

DISCUSSION

Primary central nervous system lymphoma (PCNSL) is characterized by rapid growth and recurrence after surgery. Compared with other primary tumors of the brain, especially gliomas, PCNSL is more sensitive to chemotherapy and radiotherapy. Therefore, the recommended first-line regimen is high-dose MTX-based chemotherapy (HD-MTX) and/or whole-brain radiotherapy (WBRT). However, there is still a lack no consensus regarding the treatment of PCNSL (2,3,8,11). Because of the high sensitivity of PCNSL to chemotherapy and radiotherapy, most physicians are of the opinion that stereotactic brain biopsy is the gold standard for confirming the diagnosis, followed by chemotherapy/radiotherapy (2,3,8,9). Surgical resection should be considered only when the tumor causes brain herniation, which is life-threatening (4,5,14). In addition, some doctors believe that although surgical resection causes brain injury and may even cause permanent functional deficits, it can alleviate the symptoms of increased intracranial pressure to a certain extent and provide an opportunity for combined chemotherapy/radiotherapy, which can effectively prolong survival (6). To address these issues, we retrospectively analyzed 21 patients with PCNSL who were divided into biopsy and resection groups according to the surgical approach. We analyzed which option was more reasonable by comparing the efficacy and safety between the two groups. The results show that the efficacy in the resection group was significantly better than that in the biopsy group. On the other hand, the proportion of patients with tumors located in deep vital functional areas was significantly higher in the biopsy group compared with the resection group, which means that resection by craniotomy was very difficult in most cases in the biopsy group. Accordingly, we propose a personalized principle for the surgical approach to PCNSL. For tumors that are superficially located and can be surgically resected without serious complications, surgical resection combined with chemotherapy should be the main treatment instead of brain biopsy combined with chemotherapy, regardless of whether there are obvious brain herniation and severe intracranial hypertension symptoms.

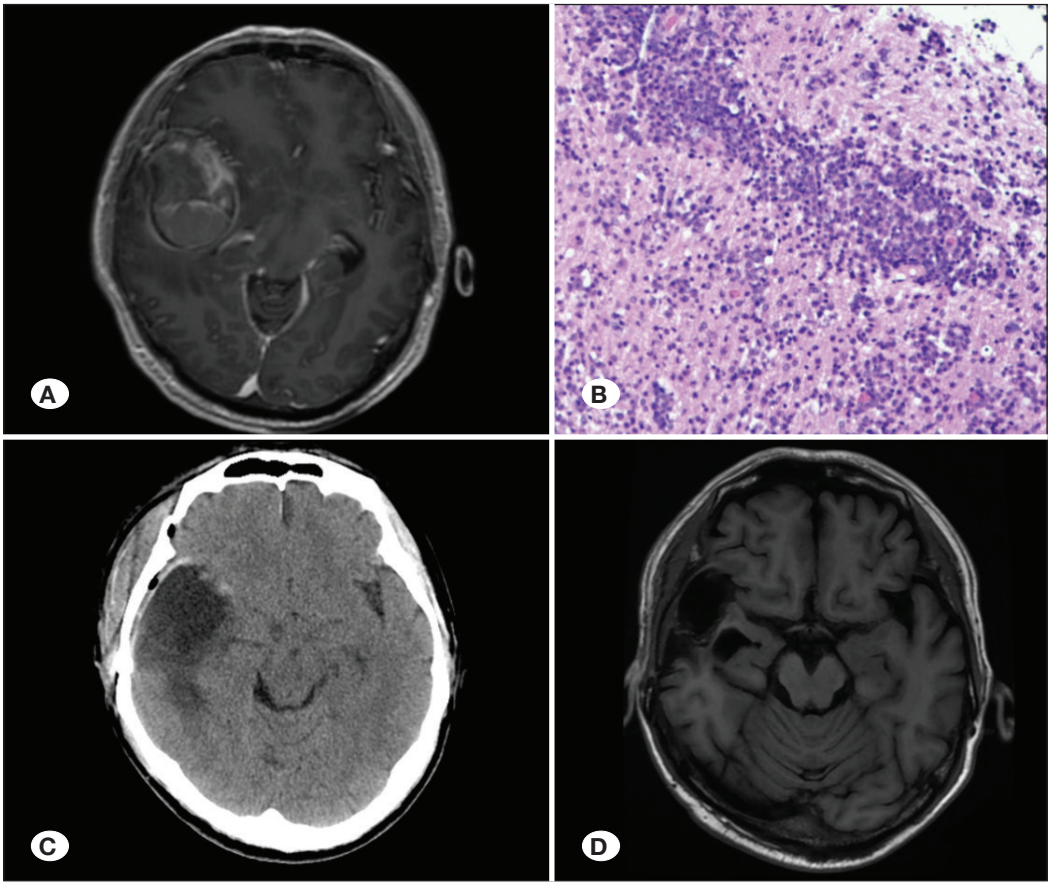

Figure 3: Case 1: male, 48 years old, patient in resection group, **A)** preoperative contrast-enhanced T1W, axial MRI suggested a possible right temporal lobe tumor with hemorrhage, and the enhancement effect was not obvious; **B)** pathological diagnosis of PCNSL; **C)** postoperative cranial CT suggested complete resection of the tumor; **D)** T1W, axial cranial MRI reviewed after three courses of chemotherapy suggested the formation of softening foci, and no tumor recurrence was seen.

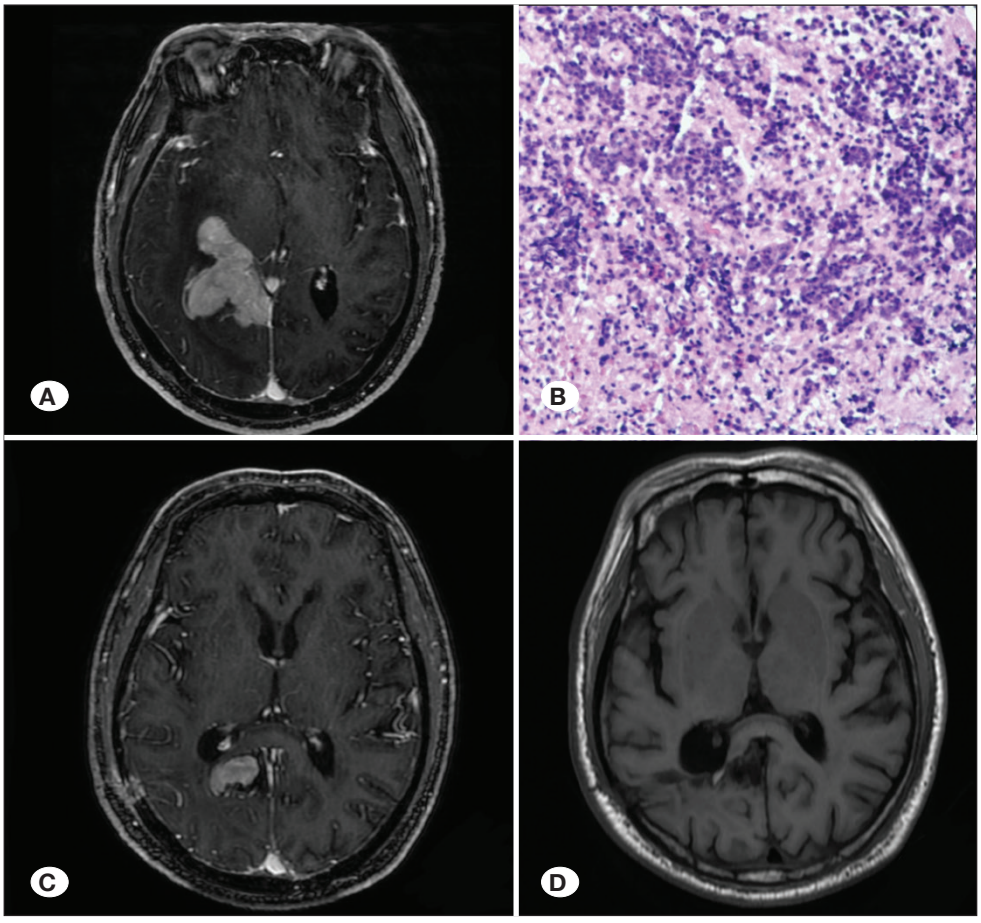

Figure 4: Case 2: male, 56 years old, patient in the biopsy group. **A)** preoperative contrast enhanced, T1W, axial MRI revealed a deep right temporo-occipital lobe and posterior hippocampal tumor with significant enhancement effect; **B)** pathological diagnosis of PCNSL; **C)** significant tumor reduction after two courses of chemotherapy (contrast enhanced, T1W, axial MRI); **D)** complete disappearance of tumor after six courses of chemotherapy (T1W, axial MRI).

The incidence of PCNSL is approximately 0.44/100,000 (9), indicating that it is very rare in the clinic. The number of patients included in this study was small, which may have led to some limitations. A systematic review of the literature showed that earlier studies with small sample sizes did not show that surgical resection was superior to biopsy (5); however, recent studies with large sample sizes have demonstrated the benefits of surgical resection in the treatment of PCNSL (11). A study by Weller et al. of 526 patients with PCNSL showed that surgical resection was associated with significantly longer progression-free survival and overall survival than biopsy alone and that total tumor resection was associated with longer overall survival than subtotal resection and biopsy (12). A retrospective analysis of 248 patients also demonstrated a longer one-year survival rate for complete surgical resection than for brain biopsy (1). Yang et al. analyzed 4812 PCNSL patients with PCNSL in the SEER database and concluded that surgical resection might improve the prognosis of some patients with PCNSL, and chemotherapy might prolong survival in patients with tumor resection (13). A 14-year retrospective single-center study of 167 Chinese patients with PCNSL also showed that surgical resection and postoperative combination therapy with HD-MTX chemotherapy were beneficial for prolonging survival (15).

In the 21 patients with PCNSL in our hospital, the survival time after surgical resection combined with chemotherapy was significantly longer than that after brain biopsy combined with chemotherapy, which may be related to the tumor site. The tumors in the surgical resection group were mostly located in the frontal, temporal, and other superficial lobes, which were relatively easy to operate on, could effectively reduce the intracranial pressure of patients after surgery, and provided opportunities for postoperative chemotherapy (6). In contrast, the tumors in the brain biopsy group were mostly located deep in important functional areas, such as the basal ganglia and thalamus. Brain biopsy did not remove the lesions, and the tumors remained after surgery. Although combined chemotherapy could reduce the tumor volume to a certain extent, tumors can increase rapidly during the inter-chemotherapy period, which might affect the brainstem and other key parts, thereby exacerbating the disease and even leading to death (16).

CONCLUSION

With the development of modern neurosurgical technologies and the skills of neurosurgeons, tumor resection has become relatively proficient and safe. Personalized principles should be followed for PCNSL. When tumors are located at a surgically resectable site, a brain biopsy should not be selected arbitrarily; instead, surgical resection should be actively selected. When the tumor site is deep and surgical resection is difficult, brain biopsy could be an option.

AUTHORSHIP CONTRIBUTION

Study conception and design: CW

Data collection: YZ, ZW, DW

Analysis and interpretation of results: YZ, ZW

Draft manuscript preparation: YW, ZW

Critical revision of the article: YW, ZW

Other (study supervision, fundings, materials, etc...): DW, BY, JW, SH, WZ

All authors (YZ, ZW, DW, BY, JW, SH, WZ, CW) reviewed the results and approved the final version of the manuscript.

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