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Primary Central Nervous System Lymphoma: A Critical Review of the Role of Surgery for Resection

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Abstract

Background: Primary central nervous system lymphomas (PCNSL) are rare CNS tumors that carry a poor prognosis, with most patients suffering recurrence. Progress has been made in the treatment of this pathology, notably with the widespread use of systemic high dose methotrexate. However, unlike most other malignant CNS neoplasms, surgery for cytoreduction is not routinely performed for this disease, mainly as a result of negative experiences decades ago. Since these studies were published, the availability of intraoperative monitoring, MR imaging and neuro-navigation as well as surgical adjuncts such as fluorescence-guided resection have greatly improved the safety of intracranial procedures. More recent data is suggestive of a potential survival benefit for resection of single PCNSL lesions when patients are subsequently treated with modern regimen high-dose methotrexate, yet this evidence is limited, and should be interpreted conservatively.

Methods and findings: A systematic review of the literature was performed to identify trials evaluating surgical options for the treatment of PCNSL.

Conclusion: In this review, we provide a critical overview of the evidence favoring and discouraging resection for PCNSL. This literature suffers from several biases and limitations that must be considered in the context of the extrapolation of this literature into clinical decision-making.

Keywords: Primary central nervous system lymphoma; Surgery; Cytoreduction

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Introduction

Primary central nervous system lymphomas (PCNSL) are relatively rare non-Hodgkin's lymphomas, accounting for 1-2% of primary CNS tumors [1]. The treatment of these tumors, consisting of chemotherapy and in some centers radiation, has evolved over the past decades and remains to be fully optimized, with almost all patients suffering recurrence. Importantly, the role of surgery for resection of these tumors has not been adequately investigated in the current setting, and has been marginalized following negative outcomes from decades-old studies. Most of the studies that evaluate the role of resection predate modern surgical techniques and high-dose methotrexate-based chemotherapy. In this review, we provide a critical overview for the evidence supporting and disregarding the role of resection for PCNSL, and offer a rationale for prospective studies to evaluate the safety and efficacy of cytoreductive surgery for this disease.

The role of cytoreductive surgery for malignant brain tumors

Surgery for cytoreduction has been adopted as an important component of the standard of care for malignant brain tumors, including gliomas and large brain metastases. In addition to symptomatic relief of mass effect, resection of these lesions is believed to contribute to oncologic control, and provide a survival advantage for selected patients. This paradigm is largely based on observational studies that found correlations between extent of resection of the enhancing lesion and survival [2-5]. Resection has also played an important role for the management of low-grade gliomas, in which case cytoreduction is associated with an overall survival advantage and a delay in malignant transformation [6,7].

Retrospective literature does not provide the best evidence for attributing survival to resection as it is subject to selection and

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survivorship biases. Patients with better neurological condition, patients with lesions on non-eloquent brain, and patients with higher performance status are more likely to be offered surgery, and independent of resection, might have a better outcome. Moreover in the case of astrocytomas, IDH1 mutation, an established molecular feature with a favorable prognosis is also associated with resectability [8].

A growing number of clinical trials support the role of resection for malignant brain tumors. First, Patchell et al., showed that resection plus radiation leads to improved survival over radiation alone for brain metastases [9]. Also, Stummer et al., showed that 5-ALA-based intraoperative tumor visualization technology improves the extent of resection and is associated with a progression-free survival benefit in the case of malignant gliomas [10]. Vuorinen et al., reported on a clinical trial for elderly glioblastoma patients, in which debulking offered an overall survival benefit compared to biopsy [11]. However, PCNSL remains a diagnosis for which resection is not currently common practice.

The standard of care for PCNSL

PCNSL is considered an extranodal non-Hodgkins lymphoma and can occur in both immunocompetent and immunocompromised patients. Patients with this diagnosis often present similarly to those diagnosed with other brain malignancies, and include focal neurologic deficits, neurocognitive symptoms, headaches, seizures, and ocular symptoms. The majority of these tumors are solitary in nature (50-70%), and are usually supratentorial [12]. On MRI, PCNSL typically appear as homogenously enhancing lesions with surrounding edema **(Figure 1A)**. However, the appearance of these tumors on radiology is notoriously similar to other brain malignancies and pathologic diagnosis is usually needed. Although cytology and flow cytometry from cerebrospinal fluid (CSF) can be attempted, these analyses have low-yield for definite diagnosis. Because pathologic diagnosis is required, a stereotaxic needle biopsy of the intracranial mass is the most accepted diagnostic procedure. In fact, recent guidelines now emphasize the importance of tissue diagnosis for PCNSL as opposed to diagnosis by cytological analysis of CSF through a lumbar puncture [13].

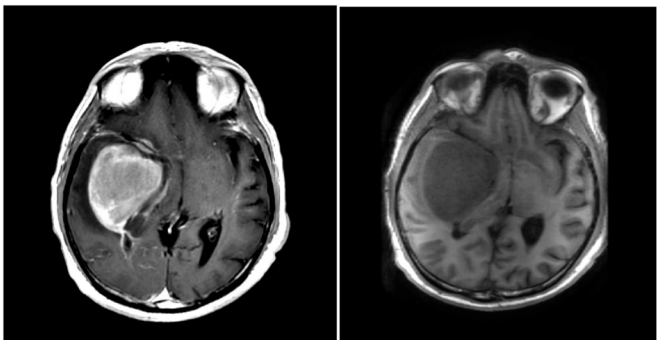

Figure 1A Post (L) and pre (R) contrast T1 MRI demonstrating a right temporal homogenously enhancing lesion with surrounding edema (**A)** The patient underwent surgery for symptomatic relief and local mass effect, and had gross total resection.

Once the diagnosis of PCNSL is made, the most accepted treatment is high dose systemic methotrexate, but the best combination of drugs and the role of whole-brain radiotherapy are unclear [14]. PCNSL has worse outcomes compared to other systemic or extranodal lymphomas, and an important limitation for progress for PCNSL has been the paucity of tumor tissue available for thorough molecular analysis, as readily done in systemic lymphomas and other CNS malignancies.

Occasionally, patients with PCNSL undergo surgical resection as these lesions can mimic other pathology on imaging studies, or in cases of a need for symptomatic relief secondary to severe mass effect, as recommended on the guidelines **(Figure 1B)**. Obtaining an intraoperative pathology consult with frozen specimen is a common practice in brain tumor surgery. In these cases, PCNSL is ruled out prior to continuing with an extensive resection. Whereas there is debate for the optimal regimen for managing these tumors, surgery with a cytoreductive goal has traditionally been abandoned.

Treatment of other non-CNS lymphomas

In many non-CNS lymphomas, no current standard treatment strategy exists, and similarly, the role of surgical resection has not been fully investigated. A growing body of evidence demonstrates the potential for improved outcomes and survival in certain systemic lymphomas with surgical resection. For example, in patients with intestinal diffuse large B-cell lymphoma, those treated with surgical resection followed by chemotherapy had improved progression-free and overall survival versus chemotherapy alone [15]. Also, the surgical treatment for pediatric intra-abdominal lymphomas is typically limited to diagnostic laparotomies and chemotherapy. However, in a recent retrospective study with a cohort of patients with intra-abdominal follicular lymphoma who underwent complete resection, the 2-year overall survival was similar for patients with complete resection and a “watch and wait” strategy and those

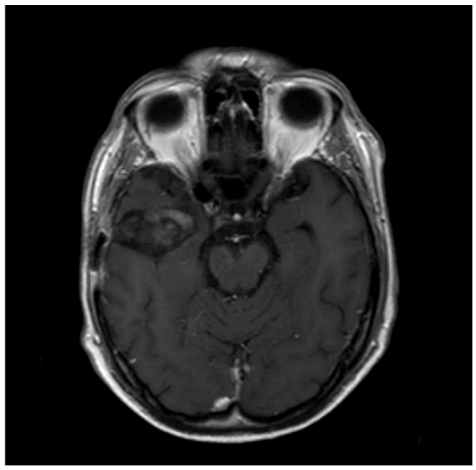

Figure 1B Post (L) and pre (R) contrast T1 MRI demonstrating a right temporal homogenously enhancing lesion with surrounding edema (**B)** Pathology report showed PCNSL.

who received chemotherapy without resection [16]. While the inherent risks of surgery and gross total resection in systemic lymphoma differ from PCNSL, these studies highlight the potential benefit of cytoreduction on overall survival.

Rationale underlying the traditional non-surgical management of PCNSL

The traditional management of PCNSL has moved away from primary surgical resection for a variety of arguments. A common reason against resection is the diffuse nature of the disease at the time of presentation and diagnosis. Although up to two thirds of the patients present with a single lesion on imaging, microscopic disease is often present beyond the radiographically visible lesion. The histopathology of PCNSL lesions demonstrates that these are diffuse, showing an angiocentric growth pattern, with cuffs of tumor cells around cerebral vasculature. Further, islands of tumor cells can be seen invading into the brain parenchyma [17-19].

Diffuse disease and inaccessible location are additional arguments against PCNSL. PCNSL can be found in eloquent or difficult to access areas such as deep brain structures, making resective surgery in these cases difficult and considerably morbid. The enthusiasm for respective surgery for PCNSL is further attenuated as PCNSL can present with intraocular or leptomeningeal dissemination, and cytoreduction is thought of as futile in this scenario [20]. Further, there is a concern that surgery might create dissemination of tumor cells in to the subarachnoid space [21]. In addition, PCNSL can respond rapidly to corticosteroids and chemotherapy, with eventual resolution of mass effect and neurological symptoms, foregoing the need for debulking surgery. Lastly, most surgeons would recommend waiting for a period after surgery to allow for wound healing, and there is a concern that minor delays in treatment worsen outcomes for PCNSL [22]. Due to these considerations, surgical resection with the goal of cytoreduction has not been the primary surgical strategy in the management of this disease.

Evaluation of the surgical experience for PCNSL

The diffuse nature of PCNSL mirrors that of gliomas, where there is evidence suggestive of a therapeutic benefit to debulking [2,6,10,11]. Importantly, there is no known biological basis for favoring maximal resection of other invasive CNS pathologies over PCNSL. Only 30% of PCNSL cases involve basal ganglia, brainstem or corpus callosum, with the remaining being lobar lesions (70%) that may be amenable to surgical resection [12]. A series of studies have evaluated the role of resection for PCNSL. Previous reviews provide a thorough historical and critical overview of these studies [20,23,24]. Most of the studies that evaluated the role of resection for PCNSL failed to show a survival benefit from it, and in some cases, have shown considerable morbidity related to surgery **(Table 1)**. These studies have shaped current views on the role of respective surgery for PCNSL; however their interpretation must take into account the following:

1. Most of these reports are post-hoc retrospective analyses of data from studies that were not designed or powered to evaluate the benefit of surgery for PCNSL.

2. The therapeutic benefit of surgery was often evaluated in the absence of standardized chemotherapy, such as concomitant high-dose systemic methotrexate and steroids, making any extrapolation of the findings irrelevant to the current standard of care for these patients.

3. Resective surgery is likely considerably safer than in the past. Technological advancements such as of modern imaging, intraoperative monitoring and navigation techniques, as well as fluorescence-guided microsurgery [25] allow for resections of brain tumors with reasonable morbidity.

Evidence favoring surgical resection for PCNSL

Recent results are questioning the non-resective paradigm for PCNSL. Weller et al., investigated the role of resection through a post-hoc analysis of the German PCNSL Group-1 trial, a randomized Phase III study population of 526 patients [26]. This study was designed to investigate the role of whole brain radiation therapy in patients treated with high-dose methotrexate, and therefore, all patients had this chemotherapy regimen [14]. This analysis showed that patients that underwent partial or gross total resection had significant progression-free survival and overall survival benefits compared to those that underwent biopsy **(Figure 2).** This difference in survival was independent of age or Karnofsky Performance Score (KPS), given that these variables were comparable between groups. Whereas the progression-free survival benefit remained independent from the number of lesions, the overall survival benefit associated with resection over biopsy was not significant upon controlling for the number of lesions [26]. Interestingly, there was no observed difference in progression-free survival or overall survival between patients who received gross total resection and subtotal resection. While this study was limited as a post-hoc analysis of randomized data, it suggests a survival benefit associated with cytroreductive surgery for PCNSL. However, the fact that the trial was not designed to test the role of surgery and the post-hoc nature of the analysis comprise potential biases. First, patients with low KPS were excluded from the original study, therefore making surgery appear safer [14]. Moreover, patients with multiple lesions had resection less frequently than patients with a single lesion, while number of lesions was a prognostic factor on this study. Yet, the results from this study raise an important question, and provide a justification for investigating the role of resection in a prospective and controlled setting.

The most recent study published examining the possible benefit of surgical resection in PCNSL is a 10-year retrospective series of 27 patients, with 12 undergoing total tumor resection, with all patients receiving high dose methotrexate. Patients who received complete resection had a significantly longer overall survival compared to partial resection or biopsy only patients **(Figure 2)** [27]. Although this study was limited by its small sample size, retrospective nature, and lack of reported complications, it suggests that a potential benefit for gross

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Table 1 Studies evaluating the role of resection for PCNSL [28-40].

Study	Design	Class	N	Comments	Role of surgery	Limitations
Henry et al., 1974 [28]	Retrospective	III b	64	OS 3.3 months for supportive care, 4.6 for surgery alone, 15.2 for RT +/- surgery	Unclear role for surgery, improved outcomes with chemotherapy	Predates modern surgical techniques, chemotherapy and imaging, no data on resection extent
Jellinger et al., 1975 [29]	Retrospective	III b	68	OS of 1.9 months with supportive care, 0.9 months with surgery, but 17.2 months with surgery and RT.	Outcomes worse with surgery	Predates modern surgical techniques, chemotherapy and imaging, no data on resection extent
Berry et al., 1981 [30]	Retrospective	III b	21	4/19 patients with post-resection deterioration, single long-term survivor with resection, 21 had RT, no patient completed a course of chemotherapy.	No benefit for resection versus biopsy	Predates modern surgical techniques, chemotherapy and imaging, no data on resection extent
Pollack et al., 1986 [31]	Retrospective	III b	27	4 with GTR, 11 with STR, 12 with biopsy. Only recorded complications in biopsy patients. 27 had RT, 9 had chemotherapy	No benefit for resection versus biopsy, no difference in resection vs. supportive care	Predates modern surgical techniques, chemotherapy and imaging. Small cohort of surgical patients
Murray et al., 1986 [32]	Retrospective	III b	11	GTR with greater survival (53mo) vs. STR (12.75mo). 10/11 had RT.	GTR with greater survival than STR	Predates modern surgical techniques, 7/11 patients with no chemotherapy, no data on complications
De Angelis et al., 1990 [33]	Prospective	II b	29	4 had RT alone, 28 received chemotherapy and RT. 0/19 complications for stereotaxic biopsy and 4/10 that had resection suffered severe postop deficit.	Higher morbidity with resection	Predates modern surgical techniques, unclear patient characteristics of surgical cohort
Hayakawa et al., 1994 [34]	Retrospective	III b	119	103 of 119 patients with pathology confirmed PCNSL underwent surgery, biopsy (48.5%) partial (33.3%), subtotal (13.6%), total (13.5%), chemo (CHOP, C-MOPP, VEMP) and radiation administered	Surgery or chemotherapy was not beneficial, survival improved with radiation. Death from hemorrhage seen only in biopsy cohort.	Predates modern surgical techniques, chemotherapy and imaging. Prolonged survival seen with total/subtotal removal, but underpowered
Davies et al., 1994 [35]	Case report	IV	1	Solitary PCNSL with progression free survival after resection for 20 years	N/A	
Tomlinson et al., 1995 [36]	Retrospective	III b	89	No difference in OS for resection vs. bx on univariate or multivariable analysis	No benefit for resection.	Predates modern surgical techniques, chemotherapy and imaging, no data on resection extent. Only 1/3 received chemotherapy
Sonstein et al., 1998 [37]	Case report	IV	1	Total resection of PCNSL, survival >5 years post resection	N/A	
Bataille et al., 2000 [12]	Retrospective	III b	248	1 year OS: 56.6% for GTR, 31.8% for STR, 48.6% for biopsy only.	STR associated with worse OS	Predates modern chemotherapy, limited followup after GTR

Caroli et al., 2004 [38]	Retrospective	III b	22	Death in 2/14 patients undergoing surgical removal, no mortality in patients with biopsy	Surgery with higher mortality	Predates modern surgical techniques, no data on resection extent. 8/22 patients received chemotherapy
Bellinzona et al., 2005 [39]	Retrospective	III b	32	No clear benefit was demonstrated for surgery. Unclear RT/ chemo follow up	Positive additive effect of surgery on RT and chemo, unclear survival benefit	Predates modern surgical techniques, poorly powered to evaluate effect of resection on survival
Weller et al., 2012 [26]	Post-hoc analysis of randomized controlled trial	II b	526	PFS and OS were shorter for bx vs. STR or GTR, independent of KPS or age. PFS was longer for STR or GTR than bx independent of number of lesions on multivariate analysis, but not OS.	Supports STR and GTR vs. biopsy, especially for single lesions.	Post-hoc analysis
Jelicic J et al., 2015 [27]	Retrospective	III b	27	Significantly longer OS in total resection cohort vs. subtotal or biopsy	Supports total resection vs. subtotal or biopsy with high dose methotrexate and RT	Excluded patients with early death prior to treatment, no complications reported, small series

Gross Total Resection (GTR), Subtotal Resection (STR), Progression Free Survival (PFS), Overall Survival (OS), Radiation Therapy (RT). II b – single RCT with limitations, III b – retrospective case control studies, IV – case series, adopted from definition by Sackett et al. [40]

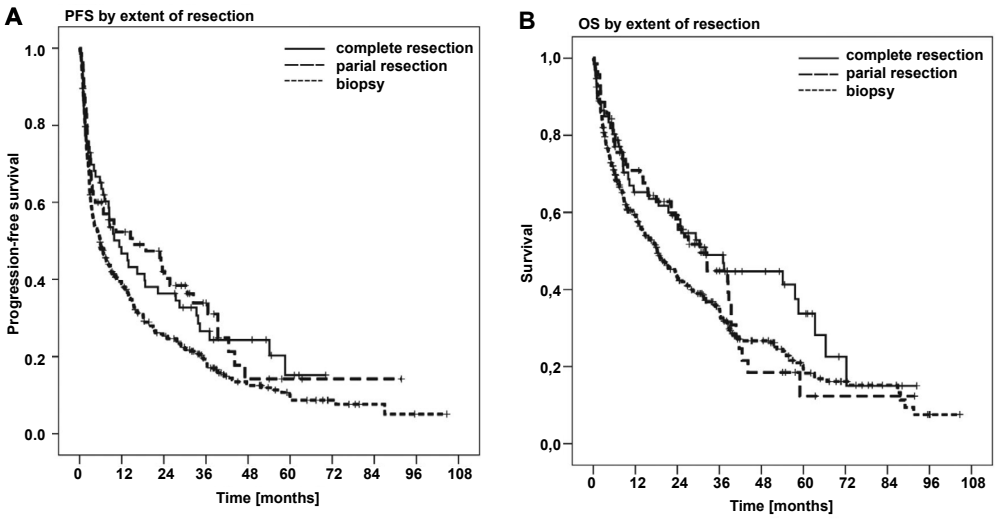

Figure 2 Progression free survival (PFS) and overall survival (OS) by extent of resection in 526 subjects, analyzed with the Cox regression model. PFS significantly increased in patients with gross or subtotal resection vs. biopsy (p=0.005), no difference seen in gross total vs. subtotal resection (p=0.023). OS improved for both gross total resection alone and gross or subtotal resection vs. biopsy (p=0.024). No difference in OS seen between gross and subtotal resection (p=0.297).

total resection in PCNSL exists. Recent guidelines published for immunocompetent patients with PCNSL recommended surgery for large, compressive lesions; however no consensus could be reached regarding the use of surgical resection for solitary, accessible lesions [13]. This highlights the paucity of high-quality data to address this question, especially in the era of modern neurosurgical techniques and widely accepted chemotherapy.

Conclusion

The treatment paradigm for PCNSL has evolved since the introduction of high-dose methotrexate. Early studies that examined the role of surgical resection for PCNSL were inconclusive, showed a lack of therapeutic benefit, or in some cases even found resection to be associated with worse outcome. Most of these old studies were performed prior to widespread adoption of today's chemotherapy regimens. Further, it is important to note that high operative morbidity for open resection of PCNSL described on these early studies was in the context of resection that preceded the wide spread use of MR imaging, neuro-navigation and fluorescence-guided surgery, techniques that have improved the safety in current neurosurgical practice [28-40]. Recent data suggests that there might be a therapeutic benefit for resection of PCNSL, but this evidence is subject to biases, and should be interpreted with caution.

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Further, with growing evidence in cases of systemic lymphoma that demonstrate survival benefit with cytoreduction, the role of surgery in PCNSL should be reconsidered. In this context, there is a need for prospective studies to investigate the safety and therapeutic benefit of cytoreductive surgery for PCNSL.

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