Surgery for Primary Central Nervous System Lymphoma: Is It Time for Reevaluation?

Relatively few patients with primary diffuse large B-cell lymphoma (PCNSL) will have tumors that are amenable to resection. In the absence of the highest quality data, at least it is good to know that in the modern era, patients with PCNSL are probably not harmed by judicious tumor resection.

Primary diffuse large B-cell lymphoma of the central nervous system (CNS) is recognized as a distinct entity in the World Health Organization (WHO) classification of lymphoma. On occasion, primary CNS lymphoma (PCNSL) may also comprise other histologic subtypes, including Burkitt lymphoma, lymphoblastic lymphoma, mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, and peripheral T-cell lymphoma. Primary CNS Hodgkin lymphoma can also occur. Approximately 1,500 new cases of PCNSL are diagnosed in the United States each year. These lymphomas represent approximately 2% of all non-Hodgkin lymphomas, and approximately 2.1% of all primary CNS tumors. The incidence of PCNSL increased dramatically between 1973 and 2005, but has since declined except in the population aged 65 years and older.[1] This decline has been most pronounced in males and is largely explained by the dramatic decrease in AIDS-associated PCNSL.[2]

The prognosis for patients with PCNSL has significantly improved. Analysis of Surveillance, Epidemiology and End Results (SEER) data shows that the median overall survival for HIV-negative patients with PCNSL was 7.5 months for those diagnosed between 1973 and 1979. In contrast, median survival was 14 months for those diagnosed between 2000 and 2004 ($P < .0001$).[3] Improvements were also noted in HIV-positive patients, although survival in this subgroup was significantly shorter.

While PCNSL is radiosensitive, median survival following whole-brain radiation as a single modality is only 1 to 2 years, with little evidence of a survival plateau.[4-6] The prolongation of survival is undoubtedly related to the development of effective chemotherapy regimens. Following intravenous administration, the cerebrospinal fluid (CSF) concentration of methotrexate is at most 3% of the plasma concentration. However, the use of folinic acid (leucovorin) rescue allows the administration of high doses of intravenous methotrexate that can reach therapeutic levels in the CSF. More than 30 years ago, it was demonstrated that high-dose methotrexate could be used to treat patients with recurrent lymphoma involving the CNS.[7,8] The use of upfront chemotherapy regimens containing high-dose methotrexate is associated with significant improvements in survival in patients with PCNSL.[5] Modern regimens often combine high-dose methotrexate with other agents, such as cytarabine and temozolomide. Whole-brain radiation improves response rates and is commonly used in addition to chemotherapy for PCNSL. However, radiotherapy increases the risk of neurotoxicity, and there is controversy regarding the use of this modality, as well as questions regarding the optimal dosing and schedule.[9] Several recent reports demonstrate that modern regimens can yield long-term progression-free survival in a significant proportion of patients with PCNSL.[10-13] Comparable results have been reported using osmotic blood-brain barrier disruption with intra-arterial administration of methotrexate and other agents.[14] This latter approach appears to be associated with a reduced risk of late neurotoxicity. Pharmacokinetic studies following intravenous administration of rituximab demonstrate that concentrations in the CSF are approximately 0.1% to 4.4% of serum levels.[15] As in other B-cell lymphomas, there is now evidence that the overall survival of patients with PCNSL is improved when rituximab is given in combination with standard high-dose methotrexate-containing chemotherapy regimens.[16] The use of high-dose chemotherapy and autologous hematopoietic stem cell transplantation is also being explored for PCNSL. Ongoing randomized trials are testing whether the use of transplantation for consolidation following initial chemotherapy for PCNSL is as good as radiotherapy (ClinicalTrial.gov identifiers NCT01011920, NCT00863460) or conventional chemotherapy
The Case Against Surgical Resection of PCNSL

The most common malignant brain tumor is glioblastoma. Observational studies show that surgical resection of glioblastoma, compared with biopsy alone, is associated with better overall survival, and that the extent of resection correlates with survival.[17,18] Similar results have been noted for lower-grade gliomas and other primary brain tumors, as well as for brain metastases from solid tumors. However, most authorities have stated that surgical resection has little role in the management of PCNSL and that stereotactic biopsy alone is the gold standard for these patients.[19] Although recent evidence has led some authorities to challenge this opinion, it is helpful to examine why surgical resection for PCNSL has been almost universally discouraged for so long.

Primary CNS lymphoma is often multifocal. Surgery is often contraindicated because of involvement of deep structures, or because of ocular or leptomeningeal disease. In addition, the use of surgery raises concerns about spillage of tumor cells through the subarachnoid spaces.[5] Even if tumors appear to be grossly localized, autopsy studies show that a capsule is not present and that margins are indistinct and merge with surrounding normal or edematous tissue.[20] Even patients with solitary enhancing lesions may have widespread microscopic lymphoma infiltration into both cerebral hemispheres, at least later in the course of the disease.[21] This is supported by the fact that patients with PCNSL often show progression at sites in the CNS that are distant from the original location.[20,22,23] Aggressive surgery for PCNSL has also been discouraged because of high rates of significant postoperative neurologic deficits that followed attempts at complete surgical resection in older series.[24,25]

Most of the information we have regarding the role of surgery in PCNSL comes from retrospective series of small cohorts, often treated in a heterogeneous fashion and in a manner that would now be considered to be inadequate. A historical series of PCNSL patients from the Armed Forces Institute of Pathology database examined outcomes following surgery.[26] The average overall survival was only 4.6 months, even when immediate postoperative deaths were excluded, compared with 3.3 months for patients managed with supportive care alone. Although few details were provided, the authors concluded that “... surgery, other than for diagnostic biopsy, is not usually beneficial.” In a small series from Europe, the median survival was 0.9 months when patients were treated with surgery, compared with 1.85 months for patients who received supportive care alone.[27] A retrospective analysis from the University of Pittsburgh also failed to show any improvements in survival when results of PCNSL resection were compared with results following biopsy alone.[28] In a series from the Mayo Clinic, the median survival of PCNSL patients who underwent surgical resection was 16.8 months, compared with 24.5 months for those who only had a stereotactic biopsy ($P = .58$).[23] A small retrospective series from Princess Margaret Hospital also failed to find survival differences when the outcomes of PCNSL patients who had gross total resections were compared with the outcomes of those who had biopsy alone.[24] Other analyses containing small numbers of patients have also failed to show evidence of improved survival associated with resection of PCNSL.[29-31]

A retrospective analysis from the CNS Lymphoma Study Group in Japan did show a significant improvement in overall survival when PCNSL patients who underwent subtotal or total resections were compared with those who only had biopsies ($P < .05$).[32] However, a multivariate analysis demonstrated that surgical resection did not influence survival if patients received subsequent radiotherapy. More recently, the influence of surgery was analyzed in 248 cases of PCNSL treated between 1980 and 1995 at 19 French and Belgian medical centers.[33] The 1-year survival was estimated to be 31.8% for patients who had a partial resection, compared with 56.6% for those who had complete resections and 48.6% for those diagnosed with a stereotactic biopsy ($P = .040$). The authors concluded that management with partial resection was associated with statistically inferior survival and that stereotactic biopsy should be used for diagnosis. In another European series, 25 patients with PCNSL were treated with gross total resection or partial resection because of symptoms associated with increased intracranial pressure at presentation.[34] Although surgery was useful for the management of acute neurologic deterioration, no difference in survival was noted when these patients were compared with others who received a stereotactic biopsy alone.

A literature review identified 85 patients with PCNSL treated with surgery alone.[35] Subtotal or gross total resection was performed in 46 patients, and resection was attempted in 39 patients. The median survival was only 1 month, and survival beyond 3 years was only seen in a single patient. Overall survival was not influenced by the extent of resection. A subsequent literature review analyzed results from 50 series of patients with PCNSL published between 1980 and 1995.[5] The
median survival was just 1.5 months for patients treated with surgery alone, compared with 2 months for patients who only had biopsies without additional treatment. Overall survival was improved if patients received subsequent radiation or surgery. Nevertheless, no significant differences in overall survival were seen when gross total resection, subtotal resection, or biopsy alone was followed by additional therapy in this population ($P = .66$).

The Case for Resection of PCNSL

In light of results from the previous analyses, it is understandable that for the last 30 years most authorities have stated that there is a limited role for surgery in the treatment of PCNSL. In most cases, the only roles for the neurosurgeon have been those of performing a stereotactic biopsy, placing ventricular catheters and shunts, or performing emergent decompression.[34,36] However, these recommendations have largely been based on small uncontrolled series. Some reports were published before the introduction of magnetic resonance imaging; in addition, there have been significant advances in neurosurgical technique. Furthermore, interpretation of these studies is difficult because it is often impossible to determine the reason why some patients were selected for resection. It is possible that these patients were different than others in a way that was clinically significant.

The poor survival reported with resection alone is understandable, given the fact that modern-day treatment regimens were not subsequently administered, and this makes it impossible to determine whether surgery should play a role in the overall treatment approach for patients with PCNSL. Whether attempts at gross total resection are useful for present-day patients with PCNSL who go on to be treated with modern chemotherapy regimens remains a fundamental and unanswered question.

Case reports have described successful treatment of PCNSL with surgery alone. Davies et al described 20-year survival without progression following gross total resection of a PCNSL.[37] The patient did not receive any corticosteroids or subsequent radiation therapy. Sonstein et al described a similar patient who was well more than 5 years following gross total resection of a PCNSL.[38] Following surgery, the patient received a short course of corticosteroids but did not receive additional chemotherapy or radiation. Berry et al described a patient with PCNSL who relapsed 44 months after surgery alone, and then lived another 21 months following another resection and radiotherapy.[24] These results provide a rationale for the view that surgery may be useful for some patients with PCNSL; a recent study provides additional evidence supportive of such an approach.

The German PCNSL Study Group 1 trial

The German PCNSL Study Group 1 (G-PCNSL-SG-1) trial is one of only three randomized therapy trials that have ever been published for PCNSL.[11] This noninferiority trial was designed to test whether whole-brain radiotherapy for patients with PCNSL could be omitted following upfront chemotherapy without compromising overall survival. An improvement in progression-free survival was observed in patients who were consolidated with whole-brain irradiation, although a difference in overall survival was not identified. The lack of an overall survival benefit may be due to the development of delayed neurotoxicity in the patients who received radiotherapy. Although the trial design (Figure 1) has been criticized, and although there was an unusually high rate of protocol violations, some experts have used these results to argue that radiation can be omitted from PCNSL treatment regimens.

A number of additional analyses of the G-PCNSL-SG-1 trial have been published in which the outcomes of various subsets have been examined; these subsets include elderly patients, those with leptomeningeal disease, and those who experienced relapse. Another correlative analysis examined whether tumor resection was associated with better outcomes in the trial.[39] The extent of resection was correlated with 6-month complete remission rate, progression-free survival, and overall survival.

Of 526 eligible patients in the study, 67 (13%) had gross total resections, 70 (14%) had subtotal resections, and 379 (73%) had stereotactic or open biopsies. There were no differences between groups except that patients with only one lesion were more likely to have had a gross total or subtotal resection than patients with more than one lesion (31% vs 19%; $P = .005$).

Patients who underwent resection (gross total or subtotal) were more likely to be in complete remission 6 months after surgery compared with patients who underwent biopsy only ($P = .003$). Patients who underwent biopsy were also 39% more likely to have disease progression ($P = .005$) (Figure 2A), and 33% more likely to die compared with patients who underwent tumor resection ($P = $.003$).
After adjusting for the number of lesions, progression-free survival was still significantly better following resection ($P = .012$), although the improvement in overall survival was no longer statistically significant ($P = .085$). On the basis of this analysis, the authors proposed a reconsideration of the position that surgery for PCNSL should be discouraged—with reconsideration especially suggested for patients with single lesions that might be safely resected. In addition, they proposed that extent of resection be considered when PCNSL patients are stratified in future trials. The nature of this unplanned secondary analysis makes it impossible to draw firm conclusions regarding the role of surgical resection of PCNSL. Patients who underwent resection were more likely to have solitary lesions. Patients with localized PCNSL that is amenable to resection intrinsically have a better prognosis, and it is unknown whether they would have done just as well without tumor removal.[40] While progression-free survival was significantly better after adjustment for the number of lesions, it is still possible that patients whose tumors were resected differed in other important ways. A significant number of patients did not complete the trial, and the benefits of surgical resection were no longer evident when the intent-to-treat population was examined. Still, patients in this trial were treated in a manner more representative of today’s approach: they received methotrexate-based chemotherapy following surgical resection or biopsy. Thus, patients in this study differ from the patients in prior studies that have been the basis for recommendations against surgery for PCNSL, and the quality of these newer data is no worse than that of previous data.

National Comprehensive Cancer Network (NCCN) guidelines have not been modified on the basis of this analysis. In contrast, several recent authoritative reviews now recommend future studies to evaluate the role of surgery for PCNSL,[41] or consideration of surgery in the case of single well-circumscribed lesions, when risk of resection is low.[42-44]

### Summary

Although they are the product of a retrospective unplanned subset analysis, the results of the correlative analysis of G-PCNSL-SG-1 may challenge long-held beliefs regarding the role of surgery for PCNSL. It is unlikely that a randomized trial will ever be performed, and for practical purposes it seems unlikely that the results of the recent analysis will be applicable to very many patients. First, relatively few patients with PCNSL will have tumors that are amenable to resection. Second, it is important to consider why surgical resection was attempted in G-PCNSL-SG-1, given longstanding recommendations not to resect PCNSL. It is likely that some patients had surgical debulking because of increased intracranial pressure and a risk of brain herniation. However, it is also reasonable to assume that the majority of patients had contrast-enhancing masses that, at the time of presentation, were thought to be primary brain tumors or metastases. Standard treatment in these situations is resection. In either case, it seems likely that few, if any, patients in this study had a known diagnosis of lymphoma before surgery.

Instead, the diagnosis of lymphoma was probably made in retrospect. Patients rarely have surgery for “lymphoma”; they have craniotomies for resection of a “brain tumor.” It is possible that a stereotactic biopsy or a frozen section biopsy of a localized lesion could result in a situation where a neurosurgeon would need to make a decision whether or not to attempt a resection of a PCNSL. Otherwise, it is difficult to imagine many scenarios where a surgeon would need to make this decision.

Thus, it is not clear that we really know much more now about surgery for PCNSL than we did almost 40 years ago when it was advised, “. . . if a localized tumor can be safely removed, this should be attempted.”[45] In the absence of the highest quality data, at least it is good to know that in the modern era, patients with PCNSL are probably not harmed by judicious tumor resection.

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Figure 1: Design of the German Primary CNS Lymphoma Study Group Random...

Figure 2: Results of the German Primary CNS Lymphoma Study Group 1 Tri...

References:


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