Surgery for primary CNS lymphoma? Challenging a paradigm

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Abstract: The standard of care for primary central nervous system lymphoma (PCNSL) is systemic chemotherapy with or without whole brain radiotherapy or intrathecal chemotherapy. In contrast to treatment for other brain tumors, efforts at resection are discouraged. This is a secondary analysis of the German PCNSL Study Group-1 trial, a large randomized phase III study comprising 526 patients with PCNSL. Progression-free survival (hazard ratio [HR]: 1.39; 95% confidence interval [CI]: 1.10-1.74; P = .005) and overall survival (HR: 1.33; 95% CI: 1.04-1.70; P = .024) were significantly shorter in biopsied patients compared with patients with subtotal or gross total resections. This difference in outcome was not due to age or Karnofsky performance status (KPS). When controlled for the number of lesions, the HR of biopsy versus subtotal or gross total resection remained unchanged for progression-free survival (HR = 1.37; P = .009) but was smaller for overall survival (HR = 1.27; P = .085). This analysis of the largest PCNSL trial ever performed challenges the traditional view that the extent of resection has no prognostic impact on this disease. Therefore, we propose to reconsider the statement that efforts at resection should be discouraged, at least if resection seems safe, as is often the case in treatment of single PCNSL lesions.

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Surgery for primary CNS lymphoma? Challenging a paradigm

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Conflict of Interest

Michael Weller has received research support from Merck Serono and Roche and honoraria for advisory board and lecture activities from Merck Serono, MSD, Roche and Magforce

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Abstract

Background: The standard of care for primary central nervous system lymphoma (PCNSL) is systemic chemotherapy plus/minus whole brain radiotherapy or intrathecal therapy. In contrast to other brain tumors, efforts at resection are discouraged.

Methods: This is a secondary analysis of the G-PCNSL-SG-1 trial, a large randomized phase III study comprising 526 patients with PCNSL.

Results: Progression-free survival (hazard ratio (HR): 1.39, 95% CI 1.10-1.74, p=0.005) and overall survival (HR: 1.33, 95% CI 1.04-1.70, p=0.024) were significantly shorter in biopsied patients compared with patients with subtotal or gross total resections. This difference in outcome was not due to differences in age or performance score. When controlled for the number of lesions, the HR of biopsy *versus* subtotal or gross total resection remained unchanged for PFS (HR=1.37, p=0.009), but was smaller for OS (HR=1.27, p=0.085).

Conclusions: This analysis of the largest PCNSL trial ever performed challenges the traditional view that the extent of resection has no prognostic impact in this disease. Therefore, we propose to reconsider the statement that efforts at resection should be discouraged at least if resection seems safe, e.g., often in patients with single PCNSL lesions.

Keywords: CNS lymphoma, surgery, resection

Introduction

PCNSL is a rare brain tumor with an annual incidence in the range of 0.5/100,000 (www.cbtrus.org). All treatment modalities except high-dose methotrexate (HD-MTX) have remained controversial, notably whole brain radiotherapy (WBRT) and intrathecal chemotherapy. Yet, a consistent recommendation of virtually all review articles and national or international guidelines, including the National Comprehensive Cancer Network (NCCN) guidelines, states that efforts at resection of PCNSL should not be undertaken. However, this recommendation is not based on contemporary reports. In 1974, Henry and colleagues[1] reported a survival of 3.3 months in 15 patients managed with supportive care alone, 4.6 months in 28 patients after surgery alone, but 15.2 months in 21 patients treated with radiotherapy, with or without surgery. De Angelis and colleagues[2] observed no complications in 19 patients with stereotactic biopsies whereas 4 of 10 patients who had a complete resection suffered a severe postoperative deficit, indicating an increased surgical risk in this patient population. One of the most influential articles represents a retrospective analysis of 248 patients treated between 1980 and 1995 published in 2000: the survival rates at 1 year were 56.6% for completely resected patients, 31.8% for partially resected patients, and 48.6% for biopsied patients.[3] Another, more recent retrospective study of 32 patients also questioned the value of surgical resection although the authors essentially acknowledged that their study was inconclusive.[4] The G-PCNSL-SG-1 trial which examined the role of WBRT in the treatment of newly diagnosed PCNSL patients eligible for HD-MTX-based chemotherapy provides a unique data base to confirm or refute this statement on the lack of impact of surgery in PCNSL.[5]

Methods

This was an unplanned secondary analysis of the G-PCNSL-SG-1 trial for an association of the type of surgery and extent of resection as documented at study entry and the clinical outcome parameters response, CR rate at 6 months, PFS and OS. Open and stereotactic biopsies were pooled. CR rate at 6 months, PFS and OS were analyzed using the Kaplan Meier Method and the log rank test. With 315 (OS) and 414 (PFS) events, hazard ratios > 1.44 (OS) and > 1.37 (PFS) could be detected (type 1 error 0.05, two-sided, type 2 error 0.8) in the Cox regression model between patients with subtotal or gross total resection (pooled) and patients with biopsy. Populations are defined as follows[5]: 526 patients were eligible for study entry and entered the first study phase of HD-MTX-based chemotherapy (non-randomized), 411 patients completed the first and entered the second phase of the trial where randomization (WBRT versus no WBRT) should have become effective (intention to treat-population, ITT), and 318 patients were treated as randomized (per protocol population, PP).

Results

Of the 526 patients of the primary eligibility population, 67 patients had a gross total resection, 70 patients had a subtotal resection, and 379 had a biopsy, 48 open and 331 stereotactic. Gross total resection in patients with more than one lesion required gross total removal of all lesions. No data for type of surgery were provided for 10 patients. There was no difference in the three groups regarding age or KPS which was determined at study entry, that is, *after* surgery (Table). There was also no such difference for age or KPS when gross total and subtotal resections were pooled and compared with the biopsied population (data not shown). Biopsied patients had more often multiple lesions than resected patients (p=0.003).

The complete remission rate at 6 months was 56.7% for gross totally resected, 41.4% for subtotally resected, and 34.3% for biopsied patients (p=0.001). Of note, we do not attribute the increase in the complete remission rate at 6 months to surgery alone even after gross total resection since PCNSL is a very aggressive lymphoma expected to recur within 6 months even after gross total resection without adequate chemotherapy or chemoradiotherapy.

There was no difference for PFS or OS between patients with a gross total *versus* subtotal resection. However, biopsied patients had inferior PFS and OS compared with gross totally resected patients or gross totally and subtotally resected patients pooled (Table, Figure). When biopsied patients were compared with subtotally or gross totally resected patients, the hazard ratios for PFS were 1.39 (95% CI 1.10-1.74, p=0.005) for all 526 patients, 1.34 (95% CI 1.00-1.79, p=0.047) for the PP population, 1.57 (95% CI 0.80-3.08, p=0.186) for the ITT-minus-PP population, and 1.09 (95% CI 0.68-1.74, p=0.73) for patients not entered into the ITT population. The hazard ratios for OS were 1.33 (95% CI 1.04-1.70, p=0.024) for all 526 patients, 1.30

(95% CI 0.94-1.79, p=0.116) for the PP population, 1.33 (95% CI 0.62-2.85, p=0.46) for the ITT-minus-PP population, and 1.04 (95% CI 0.65-1.65, p=0.88) for patients not entered into the ITT population.

In a sensitivity analysis of the primary eligibility population of 526 patients, we investigated whether the number of lesions was a confounder, i.e., whether patients with a larger number of lesions with presumed worse prognosis underwent surgery less frequently. To this aim, we subdivided our sample into patients with one lesion (60.8%, n=262) and those with two or more lesions (39.2%, n=169). For 95 patients the number of lesions was not documented. We found indeed that 19% of the patients with more than one lesions underwent gross total or subtotal resection in contrast to 31% of the patients with only one lesion (p=0.005). Moreover, the number of lesions was indeed a prognostic factor (PFS: HR=1.40, 95% CI 1.13-1.73, p=0.002, OS: HR=1.40, 95% CI 1.11-1.77, p=0.005). However, after adjustment for the number of lesions, the HR of biopsy *versus* subtotal or gross total resection remained unchanged for PFS (HR=1.39, 95% CI 1.08-1.79, p=0.012) and was only slightly smaller for OS (HR=1.27, 95% CI 0.97-1.67, p=0.085). Comparable results were obtained when the number of lesions was used as a continuous covariate or when patients with one or two lesions were compared to patients with at least three lesions. The localization of lesions (supratentorial, cortical, subcortical, spinal, cerebellar/brainstem) was not associated with OS or PFS (data not shown).

Discussion

This analysis of the largest PCNSL trial ever performed challenges the traditional view that the extent of resection has no prognostic impact in this disease and that efforts at resection should therefore be avoided. We observed that gross totally or subtotally resected patients appeared to derive a benefit from surgery (Figure). Neither differences in age nor in postoperative KPS accounted for these differences in outcome (Table). The impact of extent of resection was similar for PFS, but less prominent for OS when adjusted for the number of lesions. However, the benefit from surgery did not become apparent in the negatively selected population of 115 patients from the primary eligibility population who started HD-MTX-based chemotherapy, but did not enter into the second phase of the study. This raises the possibility that there is a subpopulation of patients with aggressive, treatment-resistant tumors where cytoreductive surgery does not result in improved outcome. Limitations of this analysis, which was not planned in the study protocol, include the retrospective nature and the lack of a central review of neuroimaging for extent of resection. Yet, the determination of the extent of resection was among the prospectively collected, prespecified parameters of study documentation. Moreover, pooling of gross total and subtotal resections avoids the problem of not having performed a central review of early postoperative scans to assess extent of resection. The determination of KPS after surgery might also be a limitation since patients may have an improved KPS after gross total or subtotal resection, supported by the use of steroids. It remains possible that low preoperative KPS values dissuaded surgeons from performing resections and that this bias enriched the group of biopsied patients somewhat for poor KPS. Yet, the postoperative KPS was similar and apparently

independent of type of surgery (Table), indicating that such biases were not introduced to a relevant extent.

The largest previous analysis of biopsy *versus* subtotal *versus* gross total resection which indicated inferior outcome at least with subtotal resection may no longer be appropriate to estimate the safety and efficacy since neurosurgery has developed and standards of adjuvant therapy have dramatically changed, too, since these patients were treated.[3] Accordingly, given that no prospective study to look at the role of surgery in isolation will ever be performed, we propose to reconsider the statement that efforts at resection should be discouraged at least if resection seems safe, e.g., often in patients with single lesions, and (ii) that extent of resection should be considered for stratification or at least be assessed in future PCNSL trials.

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Figure

PFS (A) and OS (B) by extent of resection: gross total resection *versus* subtotal resection *versus* biopsy in the primary eligibility population of 526 patients (PFS: p=0.005 for biopsy versus gross or subtotal resection, p=0.023 for gross total versus subtotal resection; OS: p=0.024 for biopsy versus gross or subtotal resection, p=0.218 for gross total versus subtotal resection; see also Table).

Table

	Gross total resection	Subtotal resection	Biopsy
N patients (%)	67 (13%)	70 (14%)	379 (73%)
Median age (range)	63 years (19-80)	62 years (22-79)	63 years (19-84)
Number of lesions:			
N=1	43 (64.2%)	37 (52.8%)	176 (46.5%)
N>1	7 (10.4%)	24 (34.3%)	137 (36.1%)
No data	17 (25.4%)	9 (12.9%)	66 (17.4%)
Median KPS (range)[4]	80 (30-100)	80 (30-100)	70 (20-100)
Complete remission rate at 6 months	38/67 (56.7%)	29/70 (41.4%)	130/379 (34.3%)
		OR=0.54, 95% CI 0.27-1.06, p=0.074[1]	OR=0.40, 95% CI 0.24-0.68, p<0.001 [1] OR=0.74, 95% CI 0.44-1.24, p=0.252 [2] OR=0.55, 95% CI 0.37-0.81, p=0.003 [3]

Median PFS (95% CI)	11 months (5-18)	15 months (0-31)	6 months (4-8)
PFS events (%)	48/67 (72%)	49/70 (70%)	317/379 (84%)
		HR=0.97, 95% CI 0.65-1.44, p=0.87[1]	HR=1.35, 95% CI 0.99-1.83, p=0.053[1] HR=1.42, 95% CI 1.05-1.91, p=0.023[2] HR=1.39, 95% CI 1.10-1.74, p=0.005[3]
Median OS (95% CI)	32 months (18-46)	31 months (21-40)	18 months (14-23)
OS events (%)	39/67 (58%)	44/70 (63%)	268/379 (71%)
		HR=1.26, 95% CI 0.81-1.96, p=0.297[1]	HR=1.44, 95% CI 1.03-2.02, p=0.032[1] HR=1.22, 95% CI 0.89-1.68, p=0.218[2] HR=1.33, 95% CI 1.04-1.70, p=0.024[3]

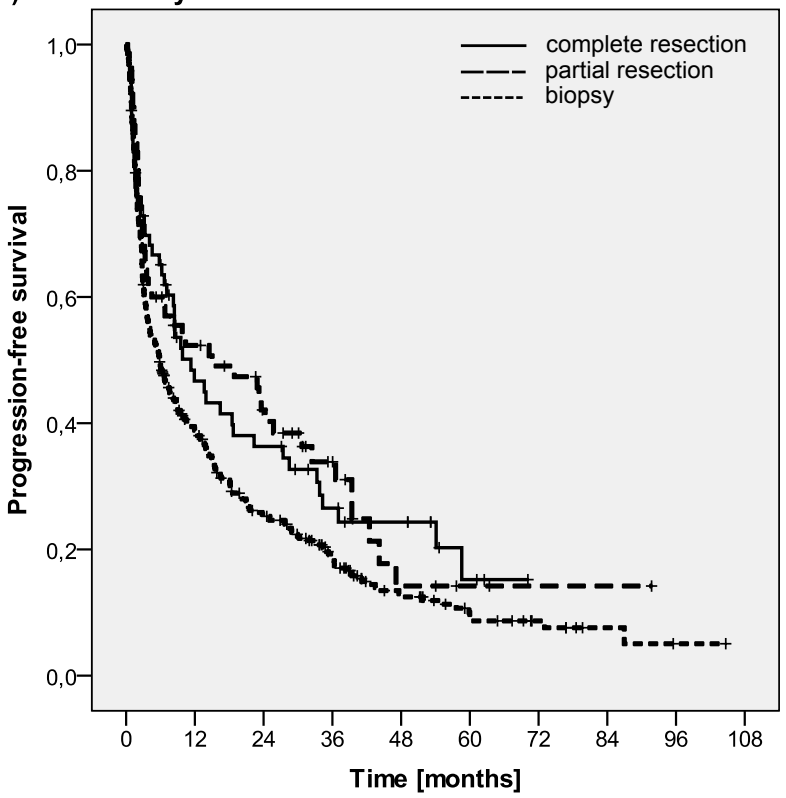
[1]versus gross total resection

[2]versus subtotal resection

[3]versus subtotal and gross total resections pooled

[4]at study entry, that is, after surgery

(A) PFS by extent of resection



(B) OS by extent of resection