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Craniotomy and Survival for Primary Central Nervous System Lymphoma

BACKGROUND: Cytoreductive surgery is considered controversial for primary central nervous system lymphoma (PCNSL).

OBJECTIVE: To investigate survival following craniotomy or biopsy for PCNSL

METHODS: The National Cancer Database-Participant User File (NCDB, n = 8936), Surveillance, Epidemiology, and End Results Program (SEER, n = 4636), and an institutional series (IS, n = 132) were used. We retrospectively investigated the relationship between craniotomy, prognostic factors, and survival for PCNSL using case–control design.

RESULTS: In NCDB, craniotomy was associated with increased median survival over biopsy (19.5 vs 11.0 mo), independent of subsequent radiation and chemotherapy (hazard ratio [HR] 0.80, $P < .001$). We found a similar trend with survival for craniotomy vs biopsy in the IS (HR 0.68, $P = .15$). In SEER, gross total resection was associated with increased median survival over biopsy (29 vs 10 mo, HR 0.68, $P < .001$). The survival benefit associated with craniotomy was greater within recursive partitioning analysis (RPA) class 1 group in NCDB (95.1 vs 29.1 mo, HR 0.66, $P < .001$), but was smaller for RPA 2-3 (14.9 vs 10.0 mo, HR 0.86, $P < .001$). A surgical risk category (RC) considering lesion location and number, age, and frailty was developed. Craniotomy was associated with increased survival vs biopsy for patients with low RC (133.4 vs 41.0 mo, HR 0.33, $P = .01$), but not high RC in the IS.

CONCLUSION: Craniotomy is associated with increased survival over biopsy for PCNSL in 3 retrospective datasets. Prospective studies are necessary to adequately evaluate this relationship. Such studies should evaluate patients most likely to benefit from cytoreductive surgery, ie, those with favorable RPA and RC.

KEY WORDS: CNS, Lymphoma, Resection, Survival, Prognosis

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Primary central nervous system lymphoma (PCNSL) accounts for 1% to 2% of all primary central nervous system (CNS) tumors.[1] PCNSL carries poor prognosis, with 5-yr survival of 15% to 30%.[2-4] The current management paradigm for patients with PCNSL involves stereotactic needle biopsy for diagnosis followed by systemic high-dose methotrexate-based chemotherapy.[5] Surgery for cytoreduction is not standard for PCNSL, though it is occasionally performed for symptomatic relief of severe mass effect or if the lesion mimics other pathology on imaging studies.[5,6] This treatment paradigm contrasts with the management of other intra-axial tumors including brain metastasis and diffusely infiltrative gliomas, where surgery contributes to oncologic control and is associated with a survival advantage.[7-12]

Cytoreductive surgery was excluded from first-line management of PCNSL largely due to results from studies concluding resection offered no benefit and potentially worsened outcomes.[13-25] However, many of these studies

ABBREVIATIONS: ACS, American College of Surgeons; **CoC,** Commission on Cancer; **CI,** confidence interval; **CNS,** central nervous system; **GTR,** gross total resection; **HR,** hazard ratio; **ICD O-3,** International Classification of Diseases for Oncology, third edition; **IS,** institutional series; **KPS,** Karnofsky Performance Score; **NCDB,** The National Cancer Database; **OR,** odds ratio; **OS,** overall survival; **PH,** proportional hazard; **PCNSL,** primary central nervous system lymphoma; **RC,** risk category; **RPA,** recursive partitioning analysis; **SEER,** Surveillance, Epidemiology, and End Results; **STR,** subtotal resection; **TTR,** total tumor resection

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had relatively small sample sizes and were conducted prior to the modern neurosurgical era. Currently, several technological advancements such as fluorescent tumor visualization, magnetic resonance imaging, neuronavigation, and intraoperative monitoring have contributed to improved outcomes for intra-axial neurosurgery.[26-28] Additionally, many of the studies discouraging resection of PCNSL were conducted prior to the standardization of high-dose systemic methotrexate,[13-17] a major component of the current treatment for PCNSL. Evaluation of the therapeutic benefit of cytoreductive surgery warrants further analysis in this context.[6]

We investigated the association between craniotomy and survival for PCNSL in contemporary series that complement each other in sample size and granularity of clinical variables. Our institutional series (IS) includes data from 132 patients and contains detailed information on clinical parameters. We cross-validated these findings using data from 8936 patients in the National Cancer Database–Participant User File (NCDB) and 4636 patients in Surveillance, Epidemiology, and End Results Program (SEER).

METHODS

Institutional Series

After receiving patient consent and institutional review board approval, we collected data on patients diagnosed with PCNSL at our institution between 2000 and 2017. We excluded patients with lymphoma outside the CNS and those with spinal lymphoma. We retrospectively reviewed patient records for clinical information, including age at diagnosis, comorbidities, lesion characteristics, and survival.

National Cancer Database—Participant User File

The NCDB is a retrospective nationwide dataset sponsored by the American College of Surgeons (ACS) and the American Cancer Society, constituting 70% of incident invasive cancer cases in the United States.[29] Data were collected at over 1500 Commission on Cancer (CoC)-accredited hospitals between 2004 and 2013. This database has been validated for several variables.[30] We identified patients diagnosed with non-Hodgkin's lymphoma (International Classification of Diseases for Oncology, third edition [ICD O-3] codes 9590-9599, 9670-9699, 9700-9719, 9720-9729, 9827) within the CNS (ICD O-3 codes C71.0-C71.9) between 2004 and 2013. Patients lacking histological confirmation, having non-CNS primary site, unknown follow-up, or disease involving the meninges, spine, or optic nerves were excluded.

Age was evaluated as a continuous variable in whole years. Charlson-Deyo score was coded equivalently to Charlson comorbidity score, except Charlson-Deyo score of 2 was coded for Charlson score $\geq$2. Radiation was coded as external beam therapy vs no radiation. Chemotherapy was coded as single or multi-agent chemotherapy vs no chemotherapy. NCDB lacks information on specific chemotherapeutic agents. The data used in the study are derived from a de-identified NCDB file. The ACS and the CoC have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Surveillance, Epidemiology, and End Results Program

SEER is a population-based tumor registry sponsored by the National Cancer Institute, covering approximately 28% of the United States population.[30] We identified patients diagnosed with non-Hodgkin's lymphoma (ICD O-3 codes 9590-9599, 9670-9699, 9700-9719, 9720-9729, 9827) within the CNS (ICD O-3 codes C70.1-C72.9) between 1995 and 2013. We excluded patients lacking histological confirmation and those diagnosed at autopsy.

Recursive Partitioning Analysis Class

We stratified patients by Memorial Sloan Kettering recursive partitioning analysis (RPA) classes[31] which are delineated as follows: class 1 (patients <50 yr old); class 2 (patients $\geq$50 yr old with Karnofsky Performance Score [KPS] $\geq$70); and class 3 (patients $\geq$50 yr old with KPS < 70).

Risk Category Classification

Risk category (RC) is a scale we designed to incorporate age, frailty, single vs multiple lesions, and superficial vs deep brain lesion location. Number of lesions and lesion location have been previously shown to be independently predictive of surgical complications.[32] Lesions involving brainstem, basal ganglia, corpus callosum, or periventricular areas were classified as deep. Departing from the prognostic system of Ferreri et al,[33] we classified the cerebellum as superficial despite worse prognosis because of its relative surgical accessibility. Frailty has been validated in geriatric patients to approximate health status[34,35] and is defined as physiologic vulnerability to adverse events.[34] Frailty affects complication rates after intracranial surgery.[32,36] The modified frailty index was developed from the Canadian Study on Health and Aging[37,38] with increasing frailty score associated with poorer outcomes across many surgical procedures,[39-41] including craniotomy for glioblastoma resection.[36] This index gives 1 point for each variable present: difficulty with activities of daily living; history of diabetes mellitus; lung or respiratory disease; congestive heart failure; myocardial infarction; other cardiac disease; arterial hypertension; clouding, delirium, or cognitive impairment; history of transient ischemic attack; history of stroke; and peripheral vascular disease. To account for operative selection factors, RC adds 1 point each for age >55 yr, multiple lesions, and deep lesion location (**Figure**, **Supplemental Digital Content 1**). We grouped patients into low-RC (0-3 points) and high-RC ($\geq$4 points) groups.

Statistical Analysis

Analysis was performed using STATA version 14 (StataCorp LLC, College Station, Texas). Kaplan-Meier plots were generated from STATA software. Descriptive statistics, t-tests, Fisher's exact tests, chi-squared tests, log-rank tests, and Cox proportional hazards (PH) analysis (Breslow method for ties) were used as appropriate and are reported in tables. Missing data were treated by omitting specific data points without removing observations. Multivariable Cox regression was performed in stepwise fashion after fitting regressions for each variable, with $P < .05$ as entry criterion and $P > .20$ as removal criterion. Data were right-censored. Vital status and time to death or censorship were coded using NCDB variables. Tests with 2-tailed; $P < .05$ were considered statistically significant.

PH assumption test returned $P < .01$, indicating non-PH. PH assumption violations do not invalidate the model if there is clinical or biological explanation for varied hazard over time, and the hazard ratio remains a good effect measure.[42] As expected, our study shows

highest incidence of PCNSL in older patients. We expect PH assumption violation due to increase in deaths from causes other than PCNSL late in follow-up period. We performed PH assumption test for each variable, then plotted these on log-log plots and Kaplan-Meier vs predicted survival plots (**Figure**, **Supplemental Digital Content 2**). Landmark analyses at 30 and 90 d for each variable with shorter follow-up time returned valid PH assumption. PH assumption violation only occurred late in follow-up period, consistent with clinical prediction.

RESULTS

Baseline Patient Characteristics

The IS included 132 patients. Multiple lesions (odds ratio [OR] 0.38, $P = .009$) and deep brain lesion location (OR 0.27, $P < .001$) were associated with higher odds of biopsy than craniotomy.

In NCDB, we identified 8936 patients matching study criteria. Patients were slightly more likely to undergo biopsy over craniotomy if they had deep lesions (OR 0.60, $P = .004$) or higher Charlson-Deyo score (OR 0.85, $P = .009$).

In SEER, 4636 patients matching study criteria were included. The biopsy group had a higher proportion of males than the gross total resection (GTR) group (58.5% vs 51.3%, $P < .001$) and subtotal resection (STR) group (58.5% vs 52.8%, $P < .001$).

Stratified baseline patient characteristics for each dataset are summarized in Table 1.

Relationship Between Craniotomy vs Biopsy and Survival

In NCDB, patients who underwent craniotomy had longer median survival (19.5 mo, 95% confidence interval [CI; 16.8, 22.0]) vs biopsy (11.0 mo, 95% CI [10.1, 12.3]; hazard ratio [HR] 0.83, 95% CI [0.79, 0.88], $P < .001$; Figure 1A). In multivariable analysis, craniotomy (HR 0.80, 95% CI [0.75, 0.84], $P < .001$), age (HR 1.03 for each 1-yr increase, 95% CI [1.03, 1.03], $P < .001$), lower Charlson-Deyo score (HR 1.18, 95% CI [1.14, 1.25], $P < .001$), receiving chemotherapy (HR 0.40, 95% CI [0.37, 0.42], $P < .001$) and receiving radiation therapy [HR 0.90, 95% CI [0.84, 0.95], $P < .001$) were independently predictive of survival. Deep vs superficial lesion location was not predictive of survival in univariable or multivariable analysis (Table 2). In IS, median survival was 46.0 mo (95% CI [35.7, 133.4]) with craniotomy vs 24.7 mo (95% CI [13.8, 54.9]) with biopsy (HR 0.68, 95% CI [0.39, 1.16], $P = .15$; Figure 1B).

We analyzed SEER to investigate whether extent of resection influenced the association between craniotomy and survival. Median survival was 29 mo for GTR (95% CI [24, 34]), 24 mo for STR (95% CI [13, 40]), and 10 mo for biopsy (95% CI [10, 12]; Figure 1C). Resection was associated with survival benefit over biopsy for both GTR (HR 0.68, 95% CI [0.62, 0.74], $P < .001$] and STR [HR 0.73, 95% CI [0.61, 0.89], $P = .001$) groups.

Combined Effect of Craniotomy and Chemotherapy on Survival

We found that combining craniotomy and chemotherapy was associated with an additive increase in survival. Median survival was 25.1 mo with chemotherapy and biopsy, and 37.4 mo with chemotherapy and craniotomy (log-rank $P < .001$; Figure 2). This effect remained when the model was adjusted for age.

Effect of Recursive Partitioning Analysis on the Relationship Between Craniotomy and Survival

Because NCDB lacks information on KPS, we could only stratify patients into RPA class 1 or RPA 2-3 in NCDB, but these results were complemented by analysis of all classes in IS. Median survival was 46.9 mo (95% CI [36.7, 57.6]) in the RPA 1 group vs 11.4 mo (95% CI [10.5, 12.5]) in the RPA 2-3 group (HR 0.58, 95% CI [0.54, 0.63], $P < .001$; **Figure**, **Supplemental Digital Content 3A**). In IS, median survival was not reached at 135 mo of follow-up for RPA class 1. Median survival was 37.2 mo for RPA class 2 and 16.5 mo for RPA class 3 (HR 0.52 for each class decrease, 95% CI [0.35, 0.79], $P = .002$; **Figure**, **Supplemental Digital Content 3B**). These results replicate findings by Abrey et al,[31] and validate RPA as a prognostic indicator for PCNSL.

We investigated whether RPA class influenced survival differences between craniotomy and biopsy. Within the RPA1 group in NCDB, craniotomy was associated with median survival of 95.1 mo (95% CI [61.2, 112.7]) vs 29.1 mo for biopsy (95% CI [17.6, 37.6]; HR 0.66, 95% CI [0.57, 0.77], $P < .001$; Figure 3A). The IS showed a similar trend (HR 0.17, 95% CI [0.02, 1.45], $P = .10$; Figure 3B). We next evaluated the effect of worse prognosis (clustering RPA class 2-3) on survival by surgery type. There was a smaller but significant survival benefit associated with craniotomy for RPA 2-3 patients in NCDB, with median survival of 14.9 mo (95% CI [12.9, 16.8]) for craniotomy, and 10.0 mo (95%CI [9.0, 10.9]) for biopsy (HR 0.86, 95% CI [0.81, 0.91], $P < .001$; Figure 3C). In IS, RPA 2-3 showed no difference in survival for craniotomy vs biopsy ($P = .53$; Figure 3D).

Effect of RC on the Relationship Between Craniotomy and Survival

Because RPA classification does not account for patient and lesion characteristics that might influence whether craniotomy or biopsy is performed, we designed an RC that incorporates these factors. We then evaluated the relationship between craniotomy and survival in patients with similar RC. The low-RC group had median survival of 76.0 mo (95% CI [41.0, 133.4]) vs 19.3 mo (95% CI [11.0, 29.3]) for high-RC (HR 0.43, 95% CI [0.25, 0.75], $P = .003$; Figure 4A). Low-RC was associated with survival independent of RPA class on multivariable analysis of IS (HR 0.52, 95% CI [0.28, 0.93], $P = .03$).

We compared survival after craniotomy or biopsy in low-RC patients in IS. Median survival was 133.4 mo (95% CI [46.0,

TABLE 1. Baseline Patient Characteristics of Included Observations From the NCDB, IS, and SEER Databases

	IS			NCDB			SEER			
	Biopsy (n = 72)	Craniotomy (n = 60)	*P*-value	Biopsy (n = 5513)	Craniotomy (n = 3423)	*P*-value	Biopsy (n = 3350)	STR (n = 216)	GTR (n = 1070)	*P*-value
Median survival (95% CI)	37.2 mo (21.9, 76.0)			13.5 mo (12.6, 14.5)			15 mo (14, 17)			
Median age	67	63		65	65		62	65	63	
Number male	35 (48%)	27 (45%)	$P = .68$	2859 (51.9%)	1703 (49.8%)	$P = .06$	1959 (58.5%)	114 (52.8%)	549 (51.3%)	$P < .001$*
Histology										
B-cell	61 (85%)	53 (88%)	$P = .73$	4917 (89.2%)	3088 (90.2%)	$P = .12$	2797 (83.5%)	186 (86.1%)	930 (86.9%)	$P = .02$
Other	11 (61%)	7 (12%)		596 (10.8%)	335 (9.8%)		553 (16.5%)	30 (13.9%)	140 (13.1%)	
Radiation therapy										
External beam radiation	8 (80%)	8 (67%)	$P = .83$	1548 (28.3%)	946 (28.2%)	$P = .92$				
No radiation	2 (20%)	4 (33%)		3919 (71.7%)	2406 (71.8%)					
Chemotherapy										
Received chemo	25 (89%)	23 (92%)	$P = .74$	3605 (73.4%)	2094 (71.3%)	$P = .05$				
No chemo	3 (11%)	2 (8%)		1308 (26.6%)	844 (28.7%)					
Location										
Deep	51 (71%)	24 (40%)	$P < .001$	93 (4.5%)	53 (2.8%)	$P = .004$				
Superficial	21 (29%)	36 (60%)		1976 (95.5%)	1879 (97.2%)					
RPA class										
1	14 (20%)	12 (20%)		972 (17.6%)	576 (16.8%)					
2 (≥2 in NCDB)	33 (45%)	35 (58%)	$P = .23$	4541 (82.4%)	2874 (83.2%)	$P = .25$				
3	25 (35%)	13 (22%)		N/A	N/A					
Comorbid diagnosis	0.3	0.14	$P = .19$							
Charlson-Deyo score										
0				3486 (63.2%)	2460 (65.3%)					
1				1146 (20.8%)	687 (18.8%)	$P = .003$				
2				881 (16.0%)	571 (15.9%)					
Number of lesions										
Single	34 (47%)	42 (80%)	$P = .009$							
Multiple	38 (52%)	18 (30%)								
Maximum dimension										
≥3 cm	23 (32%)	21 (35%)	$P = 1$							
<3 cm	27 (38%)	24 (40%)								
Risk category										
Low RC (0-3)	33 (46%)	39 (65%)	$P = .03$							
High RC (4+)	39 (54%)	21 (35%)								

Italic font indicates that χ^2 statistic was significant. Higher Charlson-Deyo score indicates higher comorbidity: 0 = Charlson score of 0, 1 = Charlson score of 1, 2 = Charlson score ≥ 2. GTR = gross total resection, STR = subtotal resection. Location was coded as "superficial" for lesions confined to cerebellum or frontal, parietal, temporal, or occipital lobes. Brainstem and periventricular or intraventricular lesions were classified as "deep." We have reported count and proportion for categorical variables as well as mean and standard deviation for continuous variables. *Pairwise comparisons were done between GTR vs biopsy and STR vs biopsy, and both returned $P < .001$.

133.4]) with craniotomy vs 41.0 mo (95% CI [6.3, 100.0]) with biopsy (HR 0.33, 95% CI [0.14, 0.80], $P = .01$; Figure 4B). In contrast, there was a trend toward shorter survival in high-RC patients who underwent craniotomy vs biopsy (HR 1.90, 95% CI [0.93, 3.88], $P = .08$; Figure 4C).

Surgeon Intent of Cytoreduction

After reviewing operative reports of all craniotomy cases in IS, we identified surgeon's intention to perform cytoreduction in 51 of 60 cases. The most common rationale for resection was diagnostic uncertainty, followed by the ability to safely resect obvious tumor in order to mitigate mass effect or the likelihood of future mass effect. Fourteen of the 51 cases in which the surgeon intended to perform cytoreduction were classified as GTR. The remaining 37 STR were performed with the goal of maximal safe resection, with surgical or anatomical considerations cited as rationale for not obtaining GTR.

For the 9 cases in which the surgeon performed craniotomy but seemingly did not intend to perform cytoreduction, resection was discontinued due to intraoperative frozen section consistent with PCNSL after multiple biopsies or minor excisions.

DISCUSSION

Older studies established the current treatment paradigm discouraging surgery for PCNSL.[6,13-25] However, recent studies have highlighted the potential role for cytoreductive surgery for this disease.[43,44] Using complementary institutional and population-based analyses, we found that craniotomy is associated with survival benefit over biopsy in patients with PCNSL. The survival benefit associated with craniotomy remains independent of chemotherapy, radiotherapy, and baseline prognostic factors. In NCDB, patients who underwent craniotomy had almost doubling of median survival time over patients who had biopsy only. In SEER, both GTR and STR were associated with increased survival over biopsy, and there was a trend toward longer survival with more extensive resection.

Patients with better prognostic factors had an even longer survival benefit with craniotomy. In NCDB, RPA class 1 patients undergoing craniotomy had over 3-fold increase in median survival time, with a similar trend in IS. To incorporate surgical considerations, we created an RC that was predictive of survival and found that craniotomy in low-RC patients more than tripled the median survival time compared to biopsy. This novel clinical scale is illustrated in Table 3.

Weller et al[43] first demonstrated an association between craniotomy and survival over biopsy for PCNSL, yet as a post hoc analysis of a clinical trial, this study was subject to selection bias and lacks generalizability. Jelicic et al[44] demonstrated that total tumor resection (TTR) was significantly associated with increased overall survival (OS), but they lacked the follow-up to reach median OS in the TTR group. Our study validates these findings and demonstrates a more robust effect in a much larger population. Additionally, we identified that patients with better

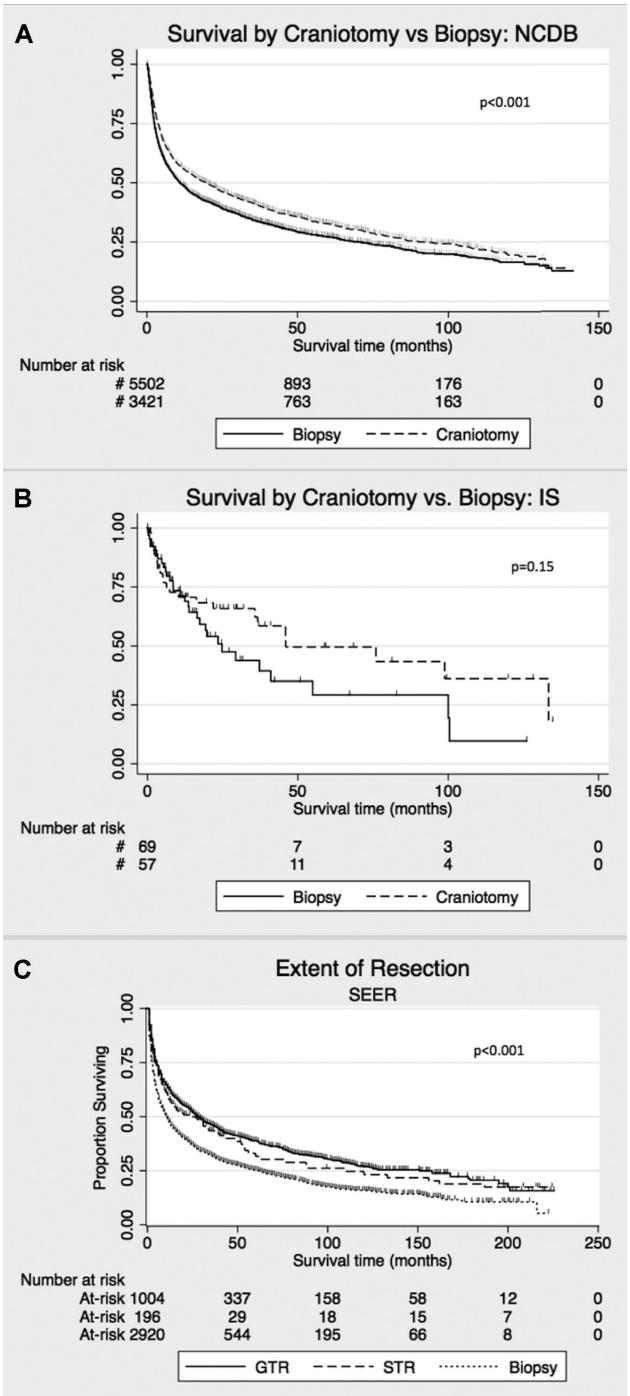

FIGURE 1. *Analysis of survival comparing craniotomy vs biopsy for PCNSL patients.* **A**, *KM plot comparing survival with craniotomy vs biopsy for all comers in NCDB.* **B** *Survival analysis stratified by extent of resection in the SEER database.* **C**, *KM plot comparing survival for craniotomy vs biopsy for all comers from the institutional dataset. GTR = gross total resection, STR = subtotal resection. Censored events are represented as hash marks. Log-rank P-values are reported on the graphs.*

TABLE 2. Multivariable Analysis in the NCDB

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Charlson-Deyo score	1.25	1.21, 1.29	$P < .001$	1.18	1.14, 1.25	$P < .001$
Age	1.03	1.03, 1.03	$P < .001$	1.03	1.03, 1.03	$P < .001$
Surgery	0.83	0.79, 0.88	$P < .001$	0.80	0.75, 0.84	$P < .001$
Radiation	1.04	0.99, 1.10	$P = .148$	0.90	0.84, 0.95	$P < .001$
Chemotherapy	0.39	0.37, 0.42	$P < .001$	0.40	0.37, 0.42	$P < .001$
Location	0.95	0.77, 1.16	$P = .645$			

Charlson-Deyo score is equivalent to Charlson comorbidity score, except Charlson-Deyo score of 2 indicates Charlson score ≥ 2. Age was evaluated as a continuous variable in whole years. Surgery is coded as craniotomy vs biopsy. Radiation was coded as external beam therapy vs no radiation and chemotherapy was coded as single or multi-agent chemotherapy vs no chemotherapy based on available data. Location was coded as superficial or deep.

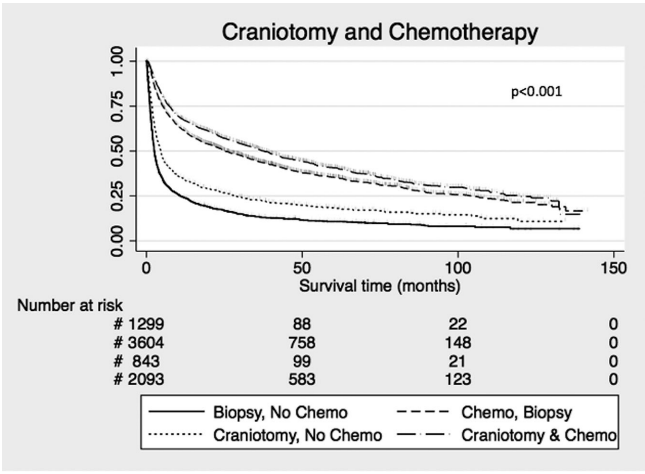

FIGURE 2. *Effect of craniotomy and chemotherapy on survival in the NCDB. Censored events are represented as hash marks. Log-rank P-values < .001 for all curves.*

RPA and low-RC were associated with longer survival in the setting of craniotomy.

While most lymphomas are treated with systemic therapy, evidence suggests that cytoreductive surgery may play a role in treatment for non-CNS lymphoma. Resection in addition to chemotherapy increases survival over chemotherapy alone for patients with intestinal diffuse large B-cell lymphoma.[45] In a recent retrospective cohort study, 2-yr OS for patients undergoing complete resection of intra-abdominal follicular lymphoma was similar to those treated with chemotherapy.[46] For PCNSL, available chemotherapeutic regimens are not as effective as those for systemic lymphoma. Additionally, CNS tumors can cause high morbidity and mortality due to their location. Resection can rapidly improve neurological symptoms and increase the window of time for medical therapy to become effective. Consequently, multimodality treatment is likely beneficial for patients with this disease, as suggested by our finding of significant median survival increase with both craniotomy and chemotherapy vs chemotherapy alone.

The retrospective nature of this study may introduce well-described biases in data collection and analysis. We could not control for some variables that may affect survival in this disease such as tumor molecular profiles.[47,48] Resectability is another consideration; more resectable lesions may confer better prognosis, irrespective of surgery type. We attempted to address this possible confounder using RC stratification; however, we recognize that resectability is a complex variable that is poorly represented by numerical scales.[49]

Factors influencing patient selection for craniotomy or biopsy may also affect survival. Large-scale datasets lack the information to evaluate these parameters. Although many patients in IS who underwent biopsy also had worse prognostic factors, our RC analysis addresses some of these limitations by grouping patients with similar preoperative and lesion characteristics.

Limitations

The nation-wide datasets we analyzed have been advocated for use in the clinical evaluation of rare diseases like PCNSL.[29] While this approach has many advantages, inherent limitations include missing data, the possibility of coding mistakes, and lack of granularity.[30] For instance, NCDB codes for craniotomy, which could be performed to obtain biopsy rather than with the intent of resection. Consequently, we evaluated extent of resection in SEER to demonstrate the association between cytoreduction rather than craniotomy on survival. Our operative report review in IS also addresses this question, as surgeons intended to resect tumor in the vast majority of cases. Because many SEER data reporters also report to NCDB, we limited our SEER analysis to the question of cytoreduction and survival to avoid analyzing overlapping observations. The lack of information on

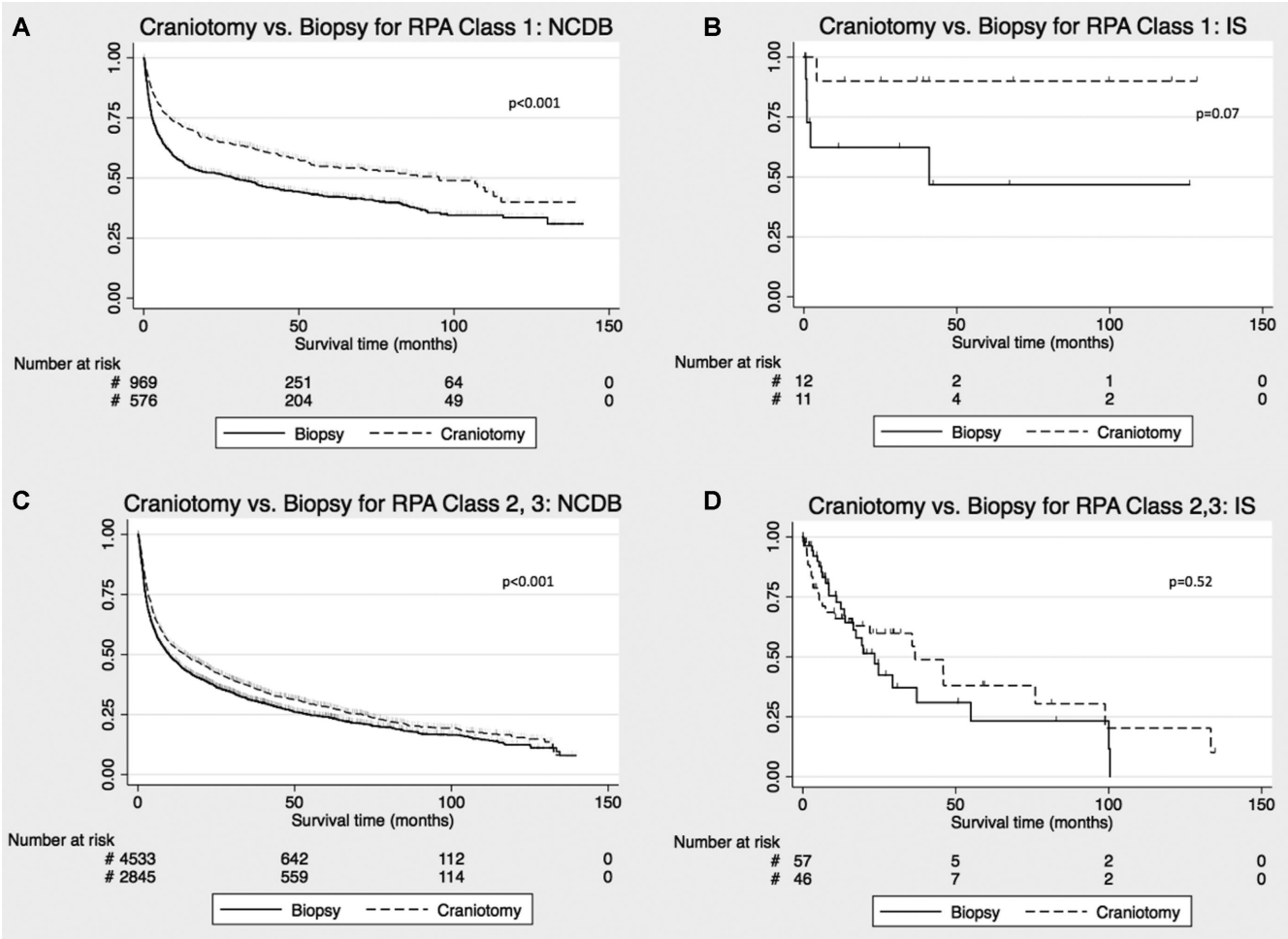

FIGURE 3. *Survival analysis comparing craniotomy vs biopsy stratified by RPA prognostic categories for PCNSL patients. KM plot comparing survival with craniotomy vs biopsy in RPA class 1 patient in the NCDB* **A** *and IS* **B**. *KM plot comparing survival with craniotomy vs biopsy for RPA class 2 and 3 patients in the NCDB* **C** *and IS* **D**. *Censored events are represented as hash marks. Log-rank P-values are reported on the graphs.*

chemotherapy and radiotherapy in SEER also limited the utility of this database.

While 1 study reports that over 80% of patients have deep lesions,[50] another series found that 70% of patients with PCNSL presenting for neurosurgical evaluation have lobar lesions,[23] and thus potentially resectable tumors. Our findings add to the growing body of evidence that using modern neurosurgical techniques, craniotomy for PCNSL is not only safe,[32] but may also be associated with prolonged survival, particularly for those patients in favorable prognostic categories. However, given the methodological limitations of this and prior studies, current evidence falls short of demonstrating causality. Prospective studies to evaluate the management paradigm for PCNSL are warranted. Future studies should stratify patients based on prognostic factors, which likely influence survival after craniotomy.

CONCLUSION

Resection for PCNSL is considered high risk based on a series of smaller studies conducted prior to the implementation of modern neurosurgical techniques. The purpose of this study was to investigate the relationship between craniotomy and survival for PCNSL, building on recent reports re-evaluating the current paradigm. We used a retrospective analysis of over 9000 patients in 3 complementary datasets. We report an association between craniotomy and survival, most pronounced in subgroups with favorable prognostic factors. In contrast to prior literature, this study has a long follow-up time, large number of observations, and applicability to uncertain real-world practice. While methodological limitations preclude the demonstration of causality, this study adds to the evidence that prospective trials re-evaluating the

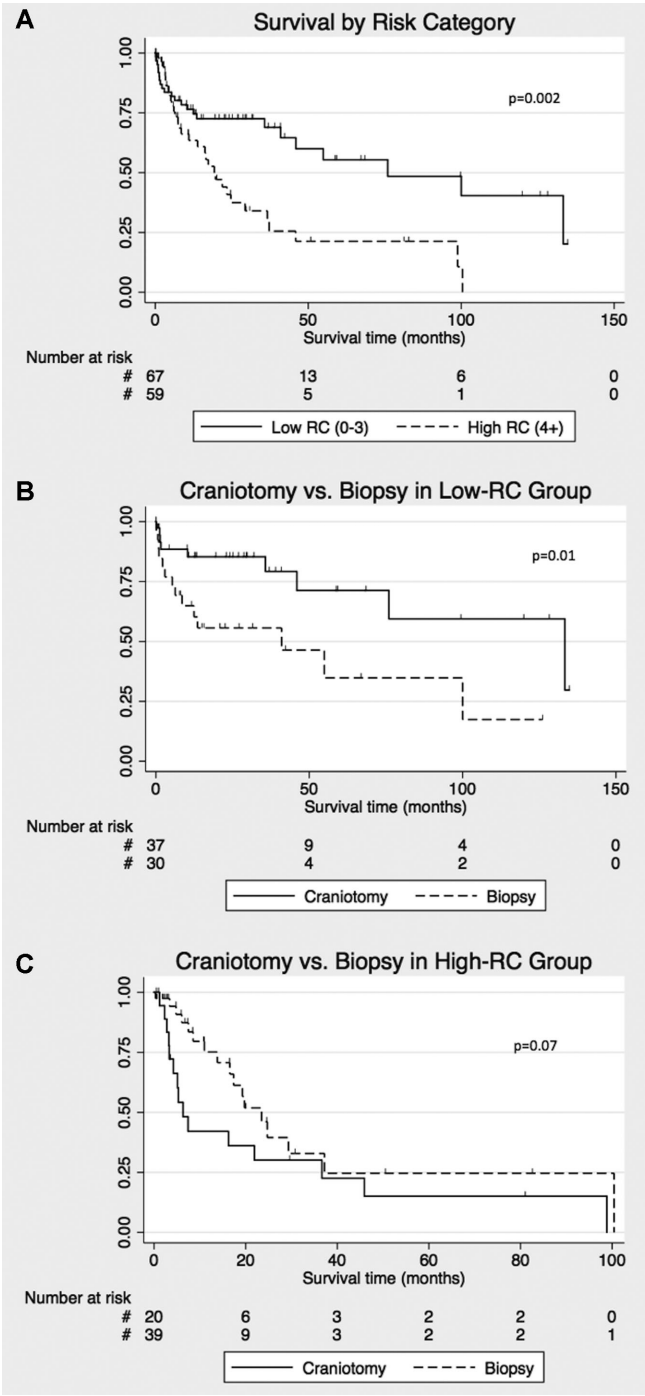

FIGURE 4. *Risk category stratification analysis and its effects on survival differences between craniotomy and biopsy for PCNS patients in the institutional database.* **A**, *RC stratification of low-RC (score 0-3) vs high-RC (score 4+) shows a significantly longer survival for low-RC on the KM analysis.* **B**, *KM plot comparing survival with craniotomy vs biopsy for low-RC patients with PCNSL, and in* **C**, *high-RC patients. Censored events are represented as hash marks. Log-rank P-values are reported on the graphs.*

TABLE 3. Clinical Risk Category Scale for Calculating Surgical Risk in Patients With PCNSL

Risk factor	Point score
Difficulty with activities of daily living	1
History of diabetes mellitus	1
Lung or respiratory disease	1
Congestive heart failure	1
History of myocardial infarction	1
Other cardiac disease	1
Arterial hypertension	1
Clouding, delirium, or cognitive impairment	1
History of Transient Ischemic Attack (TIA)	1
History of stroke	1
Peripheral vascular disease	1
Age > 55 yr	1
Multiple CNS lesions	1
Deep lesion involving brainstem, basal ganglia, corpus callosum, or periventricular area	1

Total score of 4 or more indicates high surgical risk.

management of PCNSL are warranted, and provides a paradigm for guiding patient selection for such studies.

Disclosures

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Supplemental Digital Content 1. Figure. T1 post-contrast MRI of a biopsied deep PCNSL lesion that underwent a biopsy (left) and a superficial lesion that was managed with a craniotomy for resection (right).

Supplemental Digital Content 2. Figure. Further analysis of proportional hazards assumption violation in the multivariable Cox model in NCDB. **A,** Log-log plot, and **B,** K-M vs predicted curves of craniotomy vs biopsy landmarked at 30 d. **C,** Log-log plot, and **D,** K-M vs predicted curves of chemotherapy vs no chemotherapy. **E** Log-log plots, and **F,** K-M vs predicted curves of radiation vs no radiation treatment.

Supplemental Digital Content 3. Figure. RPA stratification distinguishes prognostic categories for PCNSL patients. **A,** KM plot for RPA1 class 1 vs higher on NCDB-PUF. **B,** KM plot for RPA1 class 1, class 2 and class 3 in the institutional dataset. Censored events are represented as hash marks. Log-rank *P*-values are reported on the graphs.

COMMENTS

The authors used 3 datasets (NCDB, SEER, institutional series) to retrospectively examine the relationship between craniotomy and survival in PCNSL. They appropriately acknowledge the limitations of their study and discuss some of the obvious pitfalls, including: 1) the fact that more resectable lesions may confer a better prognosis, 2) patients selected for craniotomy may be better surgical candidates and thus could be expected to have longer survival, and 3) some "craniotomies" for PCNSL are actually "glorified biopsies" without intent of aggressive resection. The authors attempted to address some of these issues by utilizing a risk category classification to stratify patients into similar groups and by evaluating extent of resection in the SEER and institutional series. Given that the current paradigm against cytoreductive surgery for PCNSL is based on older studies, and in light of multiple threads of data, including this study, suggesting a positive relationship between extent of resection and survival, I agree with the authors' call for future prospective studies to evaluate resection of lobar PCNSL lesions utilizing modern neurosurgical techniques.

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Using 3 retrospective databases (NCDB, SEER, and an institutional database) the authors have put together an important and thoughtful analysis of the questions surrounding the value of resection of a cerebral lymphoma mass. Their overall findings, that resection of a lymphoma mass appears to impart survival benefit should be interpreted carefully. The selection biases inherent in choosing resective candidates for surgery in undiagnosed lesions will naturally favor those with single, more superficial lesions in patients with more favorable survival characteristics. The data does not support the practice of chasing diffuse lymphoma lesions.

Nonetheless, given the strength of the data, analyzed carefully by the authors, I think it is reasonable to conclude that if a surgeon has performed a craniotomy for an undiagnosed mass lesion in non-eloquent brain, and the intraoperative pathology suggests lymphoma, it is proper to resect the remaining mass to the extent the surgeon considers safe rather than halting the procedure. Finishing the resection has been common practice–and common sense–for many. This publication gives strong rationale for this action, as long as it can be accomplished without significant morbidity.

The benefits of resection are maximal at early follow-up and fade with longer-term follow-up, as is the case with most malignant disease. However, in their institutional database analysis, the authors identified a low-risk group via recursive partition analysis that maintains the benefits of resection over long-term follow-up. A prospective study would help to quantify this benefit.

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