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Clinical study

Management, outcomes, and prognostic factors of adult primary spinal cord gliomas

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ABSTRACT

Purpose: Primary spinal cord tumors are rare, particularly in the adult population, and national guidelines remain ambiguous with regard to management approaches. To address this knowledge gap, we evaluated management, outcomes, and prognostic factors of these neoplasms.
Methods: The National Cancer Database was queried (2004–2016) for newly-diagnosed, histologically-confirmed WHO grades I-III astrocytomas and glioblastoma. Statistics included Kaplan-Meier overall survival (OS) analysis, along with Cox proportional hazards modeling.
Results: Of 1,033 subjects, 196 (19%) were pilocytic astrocytomas (PAs), 539 (52%) were grade II/III astrocytomas, and 298 (29%) were glioblastomas (GBMs). Respectively, 11%, 30%, and 27% did not undergo resection (biopsy only). RT was delivered to 27%, 54%, and 73%; chemotherapy was given to 5%, 21%, and 37%, respectively. The median OS was not reached for PAs, but was 101.2 months for grade II/III astrocytomas, and 23.9 months for GBMs ($p < 0.001$). Neither chemotherapy nor RT (or dose thereof) was associated with increased OS for grade II/III astrocytomas ($p > 0.05$ for all), though there was a trend toward improved OS with the use of chemotherapy for patients with GBM. Surgical resection was associated with improved OS for grade II/III astrocytomas and GBM ($p < 0.05$). Independent prognostic factors for survival in this cohort included histologic classification and resection (compared to biopsy only) ($p < 0.05$ for both).
Conclusions: This study sheds light onto the management of these rare tumors; surgery was associated with OS benefit for patients with GBM and Grade II/III astrocytomas. Neither RT nor chemotherapy were associated with OS benefit. Although not implying causation, these data can be used to guide patient counseling and therapeutic approaches.

1. Introduction

Primary tumors of the spinal cord are rare, especially in adults; gliomas are the most common intramedullary spinal cord neoplasms [1–3]. Classification is similar to intracerebral gliomas using the World Health Organization (WHO) grading system, namely grade I (pilocytic astrocytomas (PAs)), II (low-grade glioma), III (anaplastic glioma), and IV (glioblastoma (GBM)).

Management of these rare tumors remains difficult owing to the dearth of randomized data and inability to extrapolate from trials of intracerebral glioma [1–3]. However, management options include various combinations of surgery, chemotherapy, and radiation therapy (RT). Resection is often considered the cornerstone of management, with several series demonstrating improved survival after surgical resection [3,7,8,10]. Gross total resection (GTR) is very often not possible, however, owing to the intramedullary location and infiltrative nature of spinal cord astrocytomas. Moreover, the relationship between extent of resection and oncologic outcomes in patients with high-grade primary spinal cord astrocytoma, in particular, is not entirely clear [9,10,20,21], leading some to advocate for biopsy alone followed by adjuvant therapy [10,11,22]. The role of chemotherapy, however, also remains uncertain for higher-grade disease, owing to a lack of evidence. It is also unclear whether RT should be delivered for routine postoperative management, and the optimal dose for both definitive and adjuvant settings also requires further investigation.

The National Comprehensive Cancer Network (NCCN) allows for a variety of strategies [4]. GTR is endorsed if feasible. The NCCN

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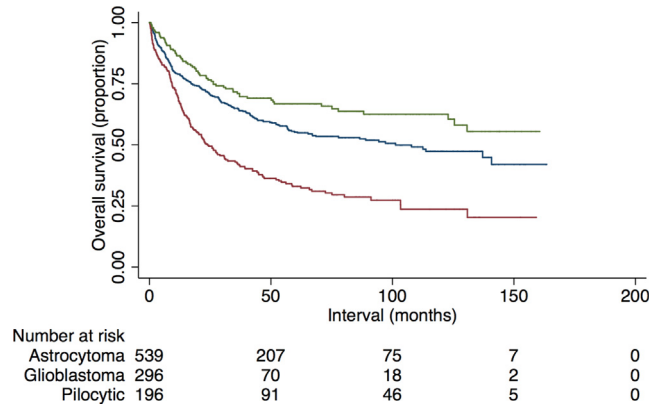

Fig. 1. Comparison of overall survival based on World Health Organization grade.

Discussion also states that RT is not recommended as definitive treatment or as adjuvant treatment, except in the setting of subtotal resection or a lack of symptomatic treatment. The ill-defined role of chemotherapy is also acknowledged.

Addressing the optimal management for primary spinal cord tumors remains a challenge due to the rarity of primary spinal cord tumors. As a result, we evaluated management, outcomes, and prognostic factors of these neoplasms using the large, contemporary National Cancer Database (NCDB), the largest such study to do so.

2. Materials and methods

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which consists of de-identified information regarding tumor characteristics, demographics, and survival for approximately 70% of the US population [5]. All pertinent cases are reported regularly from CoC-accredited centers and compiled into a unified dataset, which is then validated. The data used in the study were derived from a de-identified NCDB file (2004–2016). The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

Inclusion criteria for this study were patients $\geq$ 18 years of age with newly-diagnosed, histologically-confirmed WHO grades I-III astrocytomas (the NCDB cannot differentiate grades II and III disease) and glioblastoma. The ICD-0–3 histology codes that were included were astroscytoma (9382, 9383, 9384, 9400, 9401,

Table 1
Demographic and clinical characteristics for all the patients.

Characteristic	All patients (n = 1033)	Astrocytoma, non pilocytic (n = 539)	Pilocytic astocytoma (n = 196)	Glioblastoma (n = 298)	P-value
Age					
$\leq$ 50	572 (55.4%)	271 (50.3%)	132 (67.4%)	169 (56.7%)	0.001
51–65	273 (26.4%)	154 (28.6%)	41 (20.9%)	78 (26.2%)	
66–79	147 (14.2%)	89 (16.5%)	22 (11.2%)	36 (12.1%)	
80+	41 (4.0%)	25 (4.6%)	1 (0.5%)	15 (5.0%)	
Sex					
Male	542 (52.5%)	277 (51.4%)	111 (56.6%)	154 (51.7%)	0.430
Female	491 (47.5%)	262 (48.6%)	85 (43.4%)	144 (48.3%)	
Race					
White	842 (81.5%)	442 (82.0%)	156 (79.6%)	244 (81.9%)	0.509
African American	125 (12.1%)	59 (11.0%)	30 (15.3%)	36 (12.1%)	
Other/ not recorded	66 (6.4%)	38 (7.1%)	10 (5.1%)	18 (6.0%)	
Charlson-Deyo comorbidity score					
0	810 (78.4%)	429 (79.6%)	146 (74.5%)	235 (78.9%)	0.116
1	106 (10.3%)	52 (9.7%)	22 (11.2%)	32 (10.7%)	
2	90 (8.7%)	39 (7.2%)	22 (11.2%)	29 (9.7%)	
$\geq$3	27 (2.6%)	19 (3.5%)	6 (3.1%)	2 (0.7%)	
Practice type					
Academic	400 (38.7%)	212 (39.3%)	69 (35.2%)	119 (39.9%)	0.029
Non Academic	273 (26.4%)	158 (29.3%)	42 (21.4%)	73 (24.5%)	
Not recorded	360 (34.9%)	169 (31.4%)	85 (43.4%)	106(35.6%)	
Insurance status					
Medicare	216 (20.9%)	132 (24.5%)	28 (14.3%)	56 (18.8%)	0.049
Private	581 (56.2%)	289 (53.6%)	124 (63.3%)	168 (56.4%)	
Medicaid	125 (12.1%)	61 (11.3%)	26 (13.3%)	38 (12.8%)	
Not insured	56 (5.4%)	26 (4.8%)	13 (6.6%)	17 (5.7%)	
Other governemnt/ not recorded	55 (5.3%)	31 (5.8%)	5 (2.6%)	19 (6.4%)	
Surgery type					
Biopsy only	264 (25.6%)	161 (29.9%)	22 (11.2%)	81 (27.2%)	<0.001
Subtotal resection	175 (16.9%)	99 (18.3%)	35 (17.9%)	41 (13.7%)	
Gross todal resection	270 (26.1%)	113 (21.0%)	64 (32.7%)	93 (31.2%)	
Surgery NOS	324 (31.4%)	166 (30.8%)	75 (38.3%)	83 (27.9%)	
Radiation therapy					
None	487 (47.1%)	249 (46.2%)	143 (73.0%)	95 (31.9%)	<0.001
0–44 Gy	77 (7.5%)	47 (8.7%)	6 (3.1%)	24 (8.1%)	
45–49.9 Gy	108 (10.5%)	54 (10.0%)	12 (6.1%)	42 (14.1%)	
$\geq$ 50 Gy	311 (30.1%)	166 (30.8%)	29 (14.8%)	116 (38.9%)	
Dose not reported	50 (4.8%)	23 (4.3%)	6 (3.1%)	21 (7.1%)	
Chemotherapy					
Concurrent	179 (17.3%)	90 (16.7%)	8 (4.1%)	81 (27.2%)	<0.001
Yes, non– concurrent	55 (5.3%)	24 (4.5%)	2 (1.0%)	29 (9.7%)	
No	799 (77.4%)	425 (78.9%)	186 (94.9%)	188 (63.1%)	

9410, 9411, 9412, 9420, 9421), pilocytic astrocytoma (9425), or glioblastoma (9440, 9441, 9442). In addition to cases with missing overall survival (OS) information, the only other exclusion criteria were a lack of coding for surgery and/or RT.

Statistics, performed using STATA (version 14, College Station, TX), were two-sided, with a threshold of $p < 0.05$ for statistical significance. Multivariable logistic regression modeling determined characteristics predictive for delivery of chemotherapy or RT. Survival analysis was performed by the Kaplan-Meier method, and group comparisons done with the log-rank test. OS referred to the interval between the date of diagnosis and the date of death, or censored at last contact. Univariate analysis and cox multivariate analysis were performed to ascertain factors associated with OS.

3. Results

A flow diagram of patient selection is shown in Supplementary Fig. 1. In total, 1,033 subjects met selection criteria, of whom 196 (19%) were PAs, 539 (52%) were grade II/III astrocytomas, and 298 (29%) were GBMs. Table 1 displays clinical characteristics of these populations. Most PAs underwent resection in some manner, with only 22 (11%) receiving biopsy only. However, 30% of grade II/III astrocytomas and 27% of GBMs received a biopsy only. RT was delivered to a minority (27%) of PA cases, while a majority of patients with both grade II/III astrocytomas (54%) and GBMs (68.1%) received RT. Chemotherapy was most commonly delivered to GBMs (37%), followed by grade II/III astrocytomas (21%), and least in PAs (5%). Chemotherapy was less often utilized for biopsy-only cases, whereas RT was less often administered following GTR (Supplementary Table 1).

The median follow-up for all patients was 29.6 months. Fig. 1 displays the OS of all patients by WHO grade. The median OS was not reached (95% confidence interval, 26.3 months- not reached) for PAs, 101.3 months (17.3 months – not reached) for grade II/III astrocytomas, and 23.9 months (9.3–103.4 months) for GBM ($p < 0.001$).

Fig. 2 illustrates outcomes of PAs by treatment paradigm. As seen in Fig. 2A, there was a trend toward improved OS observed with receipt of any surgery when compared to biopsy alone (130.7 months versus 77.7 months, $p = 0.274$), and no differences were detected in median OS based on receipt of GTR versus subtotal resection (STR) (Fig. 2B, 88.2 versus 130.7 months, $p = 0.0573$). The addition of adjuvant RT was associated with worse median OS when compared to observation (Fig. 2C, 77.7 months versus not reached, $p = 0.006$).

Fig. 3 gives outcomes of grade II/III astrocytomas based on management. Chemotherapy was associated with poorer OS in operated (Fig. 3A, 43 versus 141 months, $p < 0.001$) cases, but not amongst patients not receiving surgery (Fig. 3B, 41 versus 31 months, $p = 0.598$) cases. RT was not associated with OS in operated (Fig. 3C, not reached versus 113.8 months, $p = 0.175$) or nonoperated (Fig. 3D, 39.6 versus 28.3 months, $p = 0.193$) patients. Survival was also similar for RT dose < 50 Gy versus ≥ 50 Gy (Fig. 3E, 94 versus 89 months, $p = 0.774$). Any degree of surgical resection was associated with superior median OS when compared to patients receiving biopsy only (Fig. 3F, 113.8 versus 32.4 months, $p < 0.001$).

Analogous analyses for GBMs are shown in Fig. 4. OS was similar by receipt of chemotherapy in operated (Fig. 4A, 39 versus 26 months, $p = 0.556$) and nonoperated (Fig. 4B, 9 versus 14 months, $p = 0.907$) cases. Similar findings were observed for RT in both the operated (Fig. 4C, 72.4 versus 21.4 months, $p = 0.257$) and nonoperated (Fig. 4D, 18.3 versus 3.2 months, $p = 0.141$) settings. OS was also similar for RT dose < 50 Gy versus ≥ 50 Gy (Fig. 4E, 28 versus 31 months, $p = 0.431$). Any degree of surgical resection was associated with greater median OS when compared to patients receiving biopsy only (Fig. 4F, 26.3 months versus 13.5 months, $p = 0.0126$).

Table 2 shows predictors of OS following Cox proportional hazards modeling. In addition to corroborating the histology-related

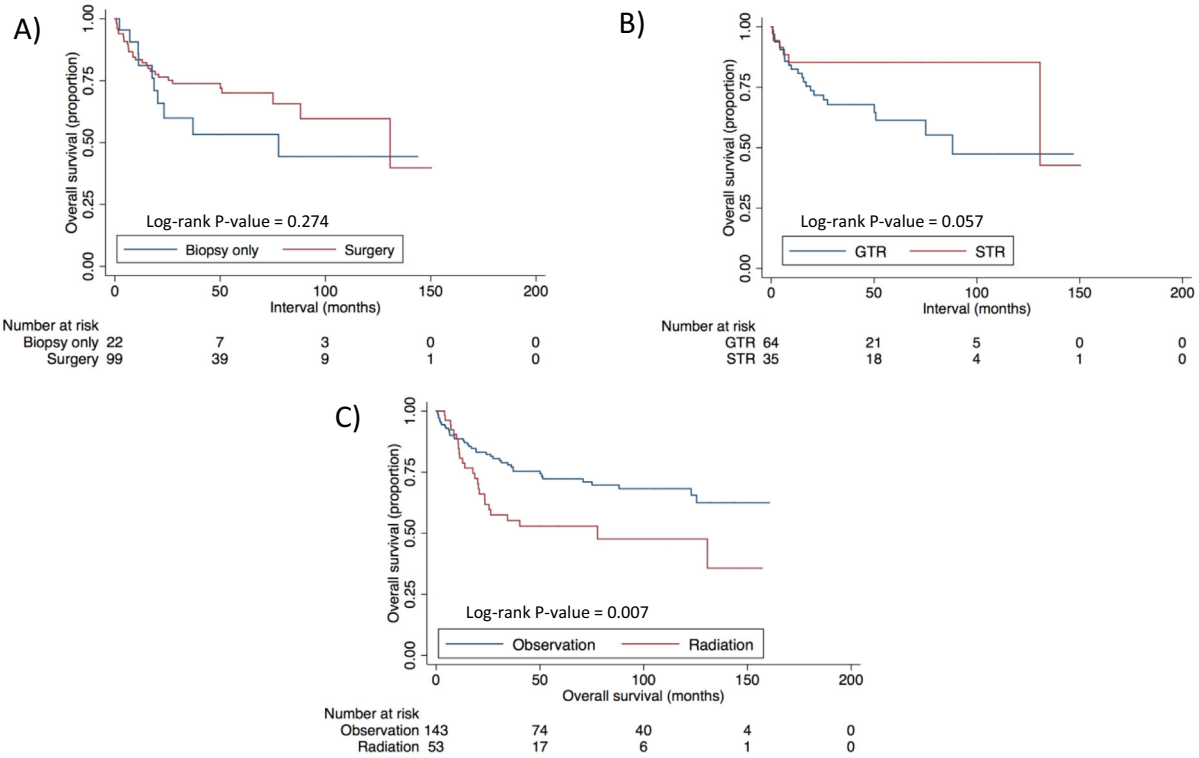

Fig. 2. Management of pilocytic astrocytomas, comparing any surgery to biopsy only (A), and addition of adjuvant RT to resection (B).

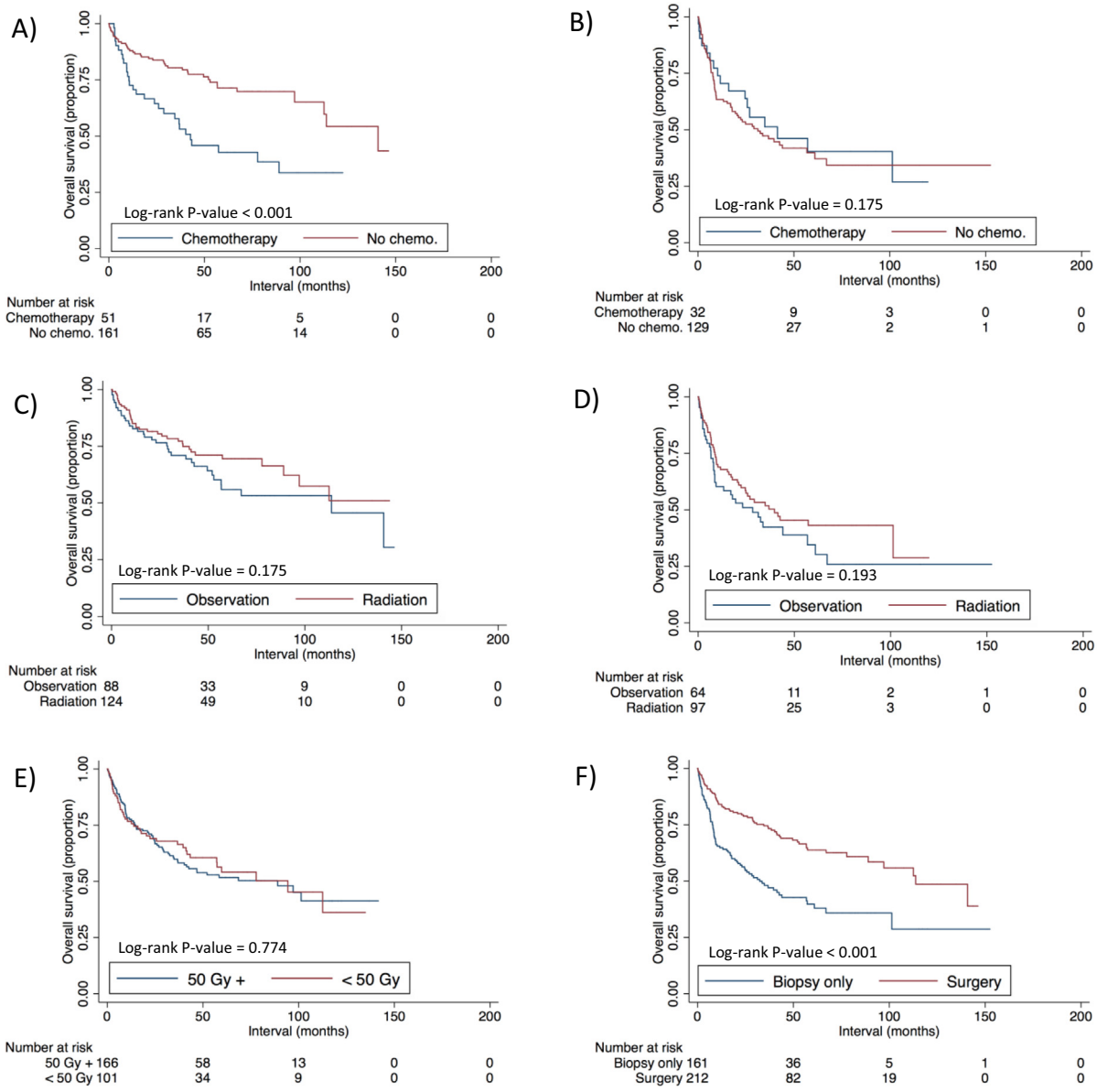

Fig. 3. Management of grade II/III astrocytomas, comparing chemotherapy versus lack thereof for operated (A) and nonoperated (B) cases, comparing radiotherapy versus lack thereof for operated (C) and nonoperated (D) cases, comparing radiotherapy dose (E), and comparing any surgery to biopsy only (F).

findings, surgical resection was independently associated with improved survival, regardless of type ($p < 0.05$ for all). However, receipt of chemotherapy or RT were not associated with OS ($p > 0.05$ for all).

4. Discussion

The largest investigation of its kind to date, this study of a large, contemporary national database sheds light onto the management of primary spinal cord gliomas, as well as outcomes and prognostic factors thereof. Although this study has limitations and cannot prove causation, it remains important because these tumors are rare (especially in adults) and single- or multi-institutional experiences are limited.

The findings herein corroborate other series [6–9] and NCCN guidelines [4] suggesting that surgical resection is the most important aspect of management for non-PA tumors. Our results did demonstrate that any degree of surgical resection (other than simple biopsy) was associated with an OS benefit for grade II-III astrocytomas and GBM of the spinal cord. However, the present study did not find OS differences based on the extent of surgical resection. Although contrary to other small-volume data [10], it should be noted that retrospective studies likely carry the bias that GTRs are more often achievable with less infiltrative disease that yields "cleaner" surgical dissection planes [3]. Regarding PAs, the excellent OS regardless of surgical approach (or delivery of adjuvant therapy) also supports current NCCN recommendations [4]. The reasons for the improved survival associated with surgical resection are unclear. It is likely that removal of the tumor leads to improved tumor control, and since death in patients with primary spinal cord gliomas is primarily due to tumor progression [6], improved local control leads to improves OS. It is also possible that the OS improvement with surgical resection is partially due to a selection bias, and tumors that are resectable are both biologically less aggressive and advanced, and consequently more likely to be associated with improved OS. Of note, the finding that there is no OS benefit observed with greater extent of resection suggests

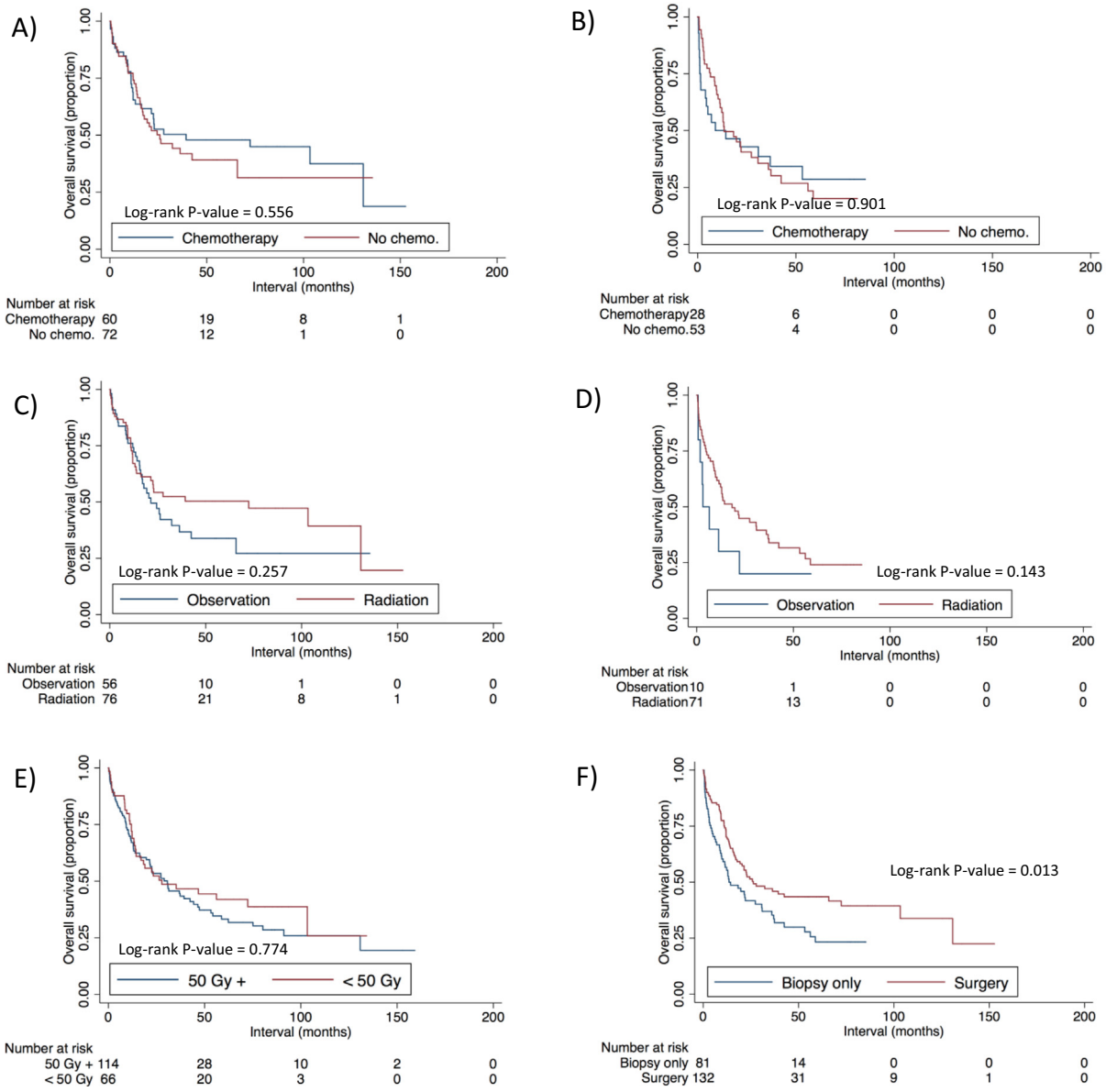

Fig. 4. Management of glioblastomas, comparing chemotherapy versus lack thereof for operated (A) and nonoperated (B) cases, comparing radiotherapy versus lack thereof for operated (C) and nonoperated (D) cases, comparing radiotherapy dose (E) , and comparing any surgery to biopsy only (F).

that surgeons should endeavor to perform maximal safe resection as possible, as gross total resection if associated with a higher risk of morbidity may cause the patient greater treatment related toxicity with no or limited clinical benefit.

Herein, RT (and the dose thereof) was not associated with OS for operated or nonoperated cases. These findings are similar to those reported by Raco et al. [6], but contrary to other studies [11–12]. These inconsistencies should be contextualized by noting several caveats. Retrospective selection biases likely resulted in RT having been delivered to "higher-risk" subsets [7]. Additionally, heterogeneity in patients in single-institutional series, as well as the NCDB, make for difficult extrapolation. Moreover, since the NCDB does not carry non-OS endpoints, and thus improvements in local control and/or progression-free survival with RT cannot be excluded [13].

Similarly, chemotherapy was not associated with OS in GBM, and it was noted to be associated with poorer OS in grade II/III disease. Other studies have also failed to show a benefit from chemotherapy [6,12] but suffer from similar selection biases as the current investigation. The poorer OS for grade II/III cases may be the result of preferential chemotherapy administration to patients with poor prognostic factors. When positing the results conservatively and in light of other work, it is the authors' opinion that routine chemotherapy utilization may not offer an overt clinical benefit in all cases, but can still be considered in high-risk patients.

The NCDB is a novel and unique resource to study rare malignancies such as primary spinal cord astrocytomas, but carries several recognized limitations in addition to those noted above [14–17]. First, it is well-recognized that the NCDB is a heterogeneous database with limited granularity of the coded data. Second, the small sample sizes of many subgroup comparisons make robust conclusions difficult, although existing studies suffer the same problem. Third, this study was not appropriate to assess the question of up-front versus delayed (e.g. at time of recurrence) chemotherapy and/or RT. Fourth, although molecular classification

Table 2
Univariate and multivariate analysis for factors predictive of overall survival.

	Univariate analysis			Multivariate analysis		
Characteristic	Hazard ratio	95% confidence interval	P-value	Hazard ratio	95% confidence interval	P-value
Histology						
Astrocytoma, non pilocytic	1 (reference)			1 (reference)		
Pilocytic astrocytoma	0.699	0.531–0.922	0.011	0.745	0.562–0.988	0.041
Glioblastoma	1.893	1.558–2.300	<0.001	1.828	1.495–2.235	<0.001
Age						
≤ 50	1 (reference)			1 (reference)		
51–65	0.991	0.802–1.225	0.937	0.926	0.708–1.211	0.575
66–79	1.129	0.870–1.465	0.362	1.209	0.814–1.796	0.347
80+	0.913	0.542–1.536	0.730	0.929	0.496–1.739	0.818
Sex						
Male	1 (reference)			1 (reference)		
Female	0.948	0.792–1.134	0.557	0.943	0.786–1.132	0.530
Race						
White	1 (reference)			1 (reference)		
African American	0.919	0.686–1.230	0.569	0.971	0.718–1.314	0.851
Other/ not recorded	0.817	0.553–1.06	0.309	0.791	0.530–1.182	0.252
Charlson-Deyo comorbidity score						
0	1 (reference)			1 (reference)		
1	0.900	0.667–1.216	0.494	0.984	0.721–1.344	0.920
2	0.938	0.680–1.295	0.697	1.000	0.719–1.389	0.998
≥3	0.499	0.236–1.054	0.068	0.523	0.244–1.118	0.094
Practice type						
Academic	1 (reference)			1 (reference)		
Non Academic	0.918	0.731–1.152	0.458	0.825	0.654–1.041	0.104
Not recorded	0.947	0.769–1.167	0.609	0.978	0.747–1.279	0.868
Insurance status						
Medicare	1 (reference)			1 (reference)		
Private	1.047	0.831–1.318	0.698	1.148	0.823–1.601	0.416
Medicaid	0.829	0.588–1.169	0.286	0.881	0.571–1.359	0.567
Not insured	1.024	0.660–1.590	0.915	1.025	0.615–1.709	0.924
Other governemnt/ not recorded	0.777	0.480–1.257	0.303	0.767	0.447–1.315	0.335
Surgery type						
Biopsy only	1 (reference)			1 (reference)		
Subtotal resection	0.301	0.204–0.442	<0.001	0.290	0.169–0.430	<0.001
Gross todal resection	0.659	0.520–0.836	0.001	0.676	0.529–0.866	0.002
Surgery NOS	0.543	0.433–0.682	<0.001	0.565	0.444–0.719	<0.001
Radiation therapy						
None	1 (reference)			1 (reference)		
0–44 Gy	0.886	0.601–1.308	0.543	0.665	0.442–1.002	0.051
45–49.9 Gy	1.540	1.150–2.063	0.004	1.162	0.845–1.600	0.356
≥ 50 Gy	1.362	1.107–1.676	0.004	1.033	0803–1.328	0.803
Not reported	1.340	0.884–2.030	0.168	1108	0.724–1.695	0.637
Chemotherapy						
Concurrent	1 (reference)			1 (reference)		
Yes, non-concurrent	1.551	1.049–2.294	0.028	1.370	0.921–2.039	0.120
No	0.897	0.707–1.138	0.371	0.959	0.728–1.263	0.765

of gliomas (largely intracerebral) is a rapidly emerging concept [18,19], its impact remains unclear for spinal cord tumors, and the NCDB largely does not code this information. The distinction between grade II and III gliomas is also not present within the NCDB, which is the reason they were merged in this analysis. Lastly, the NCDB does not offer information on clinical workup, reasons for implementation of a particular therapy, or salvage management. These shortcomings must be considered in light of the findings herein, although our conclusions are consistent with existing data and NCCN recommendations.

5. Conclusion

The present study describes current patterns of care and clinical outcomes for patients with primary spinal cord tumors. These results suggest that for non-PA spinal cord tumors, surgical resection is associated with improved OS, and use of chemotherapy may not be associated with improved OS, though larger prospective data is required to confirm these results.

6. Disclaimers

None. This has never been presented/published before in any form. All authors declare that conflicts of interest do not exist.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2020.12.015.

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