Literature Review of Spinal Cord Glioblastoma

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Objectives: This systematic review aims to investigate spinal cord glioblastoma (scGBM) and correlations between patient traits and survival outcome, as well as differences in cohorts administered temozolomide or total resections, through an analysis of published cases reported up to October 2016.

Methods: We obtained patient data by querying PubMed and Google Scholar with predetermined search terms and inclusion criteria that enabled the identification of relevant case reports. Survival was compared using Kaplan-Meier curves and log-rank analyses.

Results: Of 153 patients with scGBM identified through a literature search, 135 met the predetermined search and inclusion criteria. Median overall survival (OS) for the resulting cohort was 12 (95% CI, 10-14) months. The female sex was found to significantly predict worse outcomes, and a sizable number of patients with long-term disease were found to have afflictions of the thoracic spinal cord. Neither the pediatric, temozolomide nor total resection subgroups had significantly improved survival characteristics, by log-rank analysis, relative to counterparts.

Conclusions: These data elucidate the characteristics of patients with scGBM. For more sophisticated and in-depth analyses in the future, it is imperative that time-of-treatment information is recorded in future case reports. In addition, all case reports should be made available to prevent publication bias.

Key Words: glioblastoma, spinal cord, survival, treatment, landmark analysis, radiation, chemotherapy, resection

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Glioblastoma (GBM) is a common malignant neoplasm of the central nervous system (CNS) accounting for 50% of primary brain tumors.[1] Primary GBM of the spinal cord, in contrast, is rare and accounts for only 1% to 3% of all primary spinal tumors.[2] There have been fewer than 200 reported cases of spinal cord GBM (scGBM) in total.[3,4] Median survival for this disorder is only 12 months. Although treatments generally mirror those employed for intracranial GBM, optimal therapeutic strategies for scGBM have not been established and the rarity of the disease precludes the conduct of clinical trials to test for treatment efficacy.[4,5] In addition, there are conflicting data on patient outcome from neurosurgical interventions, with analyses documenting survival benefits,[5,6] neurological improvement,[7] no effect,[8] and worsened outcomes.[9,10] Several studies have also suggested a benefit to postoperative radiation, but the magnitude of benefit from this treatment remains unclear.[11–13] Lastly, there is only one known analysis on the benefits of chemotherapy[12] for this disease. We attempt here to investigate patient characteristics, tumor location, possible effects of temozolomide versus other chemotherapies, as well as total resection versus partial resection while screening for reports with sufficient follow-up and diagnosis with neuroimaging.

PATIENTS AND METHODS

Literature Search

We conducted a literature search as shown in the PRISMA diagram (Fig. 1) and included publication dates through October 15, 2016. We searched for records with the medical subject headings "spinal" and any of "glioblastoma," "gliosarcoma," or "glioma" in PubMed. Similarly, we curated articles that contained "spinal" and any of "glioblastoma," "gliosarcoma," or "glioma" in their title with Google Scholar. Abstracts obtained from these two search tools meeting the inclusion criteria were included if patient data were original, consisted of a follow-up period of at least nine months after diagnosis, were diagnosed with neuroimaging (magnetic resonance imaging [MRI] or computed tomography [CT]), and contained treatment information that was complete and clear. Furthermore, we only included patients if their disease was primary spinal cord glioblastoma, excluding patients with secondary metastases from primary intracranial GBM.

Data Collection

Age, sex, tumor location(s), year of publication, treatments (surgery, radiation, and chemotherapy), treatment time relative to diagnosis, and overall survival (OS) from diagnosis were extracted from each article, along with censoring information if loss to follow-up occurred. Age was coded as either pediatric (18 y and younger) or adult (older than 18 y). Tumor location was coded categorically as cervical, thoracic, lumbar, conus, or multiple locations (combinations of the defined locations). Surgical interventions were categorized as either "no surgical intervention," "biopsy," "partial or subtotal resection," or "gross total resection." Patients who underwent multiple

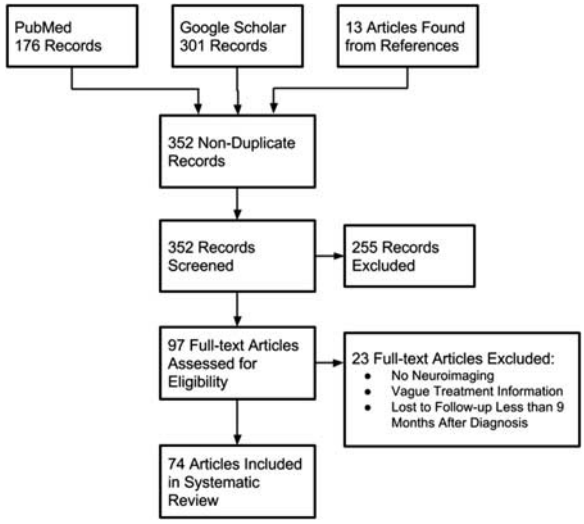

FIGURE 1. Case report retrieval and selection with criteria application in a PRISMA (preferred reporting items for systematic reviews and meta-analyses) chart.

surgeries were recorded based on the most aggressive type of surgery performed; for example, a biopsy followed by a gross total resection was coded as "gross total resection" (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/AJCO/A192).

Cordectomies were coded as gross total resection. Radiation administration was recorded as a dichotomous variable (yes or no). Chemotherapy was recorded as either "no chemotherapy," "unspecified chemotherapy," "nontemozolomide chemotherapy," or "temozolomide," in addition to the type of chemotherapy. Patients who received temozolomide in addition to another type of chemotherapy were recorded as "temozolomide" (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/AJCO/A192). Karnofsky Performance Score (KPS) was estimated by an experienced clinician based on reported patient symptoms when such presenting symptoms were available and when KPS was not reported by the report's author.

Statistical Analysis

Survival data were analyzed using R's "survival" package[14] and presented using R's "survminer" package. Median OS with 95% confidence interval (CI) was determined using Kaplan-Meier survival statistics.[15] In groups with multilevel categorical data such as chemotherapy and surgery, survival differences were determined by pairwise comparison against "biopsy" as a baseline for surgical interventions and "no chemotherapy" for chemotherapy treatments. In addition, we carried out log-rank tests between categorical data with "no chemotherapy" versus "chemotherapy," "no radiation" versus "radiation," and "no neurosurgical resection" versus "neurosurgical resection."

RESULTS

Clinical Characteristics

Our search identified 176 publications of scGBM from PubMed, 301 publications from Google Scholar, and 13 publications through references (Fig. 1). Of 97 relevant records, 74 had a sufficient length of follow-up, complete treatment data, and original patient information. We identified 13 additional reports by hand-searching that also fit the criteria for analysis (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/AJCO/A192).

TABLE 1. Clinical Characteristics and Treatments in 135 Patients Diagnosed With Spinal Cord Glioblastoma

Patient Characteristics			
Stratification	**n (%)**	**Deaths**	**OS Months (95% CI)**
Age			
0.7-18	57 (42)	50	12 (10-14)
19-76	78 (58)	76	12.5 (10-16)
Sex			
Male	77 (57)	69	13.5 (10-18)
Female	58 (43)	57	11 (10-14)
Karnofsky			
0-60	38 (28)	34	14 (10-20)
70-100	9 (7)	8	14 (10-NA)
Location			
Cervical only	45 (33)	42	10 (8-17)
Thoracic only	39 (29)	36	13 (10-20)
Lumbar only	2 (2)	2	19 (2-NA)
Conus only	9 (7)	9	10 (10-NA)
Multiple-locations	40 (30)	37	13 (10-15)
Surgery			
No surgical intervention	3 (2)	3	2 (1.8-NA)
Biopsy	25 (19)	24	12 (5-16.5)
Subtotal resection	78 (58)	70	10.5 (9-14)
Total resection	29 (22)	29	14 (13.5-21)
Radiation			
No radiation	20 (15)	19	5.5 (3-16.6)
Radiation	115 (85)	107	13 (11-14)
Chemotherapy			
No chemotherapy	47 (35)	44	8 (5-13)
Unspecified chemotherapy	21 (16)	20	13 (9-18)
Nontemozolomide chemotherapy	20 (15)	20	13.5 (10-37)
Temozolomide	47 (35)	42	14 (12-18)
Treatment combinations			
Palliative	4 (3)	4	2 (1.8-NA)
Resection	11 (8)	10	5 (3-NA)
Radiation	5 (4	5	3 (2-NA)
Chemotherapy	0 (0)	0	NA
Resection+radiation	27 (20)	25	11 (8-21)
Resection+chemotherapy	5 (4)	5	12 (11-19.6)
Radiation+chemotherapy	19 (14)	18	12 (11-19.6)
Resection+radiation +chemotherapy	64 (47)	59	14 (12-16)

CI indicates confidence interval; NA, not applicable; OS, overall survival.

The dataset consisted of 135 patients, and their clinical characteristics and applied treatments were tabulated in Table 1. The median age was 22 (range, 0.7 to 76) years, and 57% (77/135) were male and 43% (58/135) were female. Forty-two percent were 18 years of age or younger (57/135) whereas 58% (78/135) were older than 18.

Treatments and Outcomes

The median OS was 12 (95% CI, 10-14) months. Age (adult vs. pediatric scGBM) was not a significant predictor of worsened survival by log-rank ($P = 0.67$). The pediatric subgroup was evenly split between males 49% (28/57) and females 51% (29/57). In contrast, the adult population skewed toward the male sex, 63% (49/78). Sex (male vs. female), however, was a significant predictor of worsened outcome by comparison

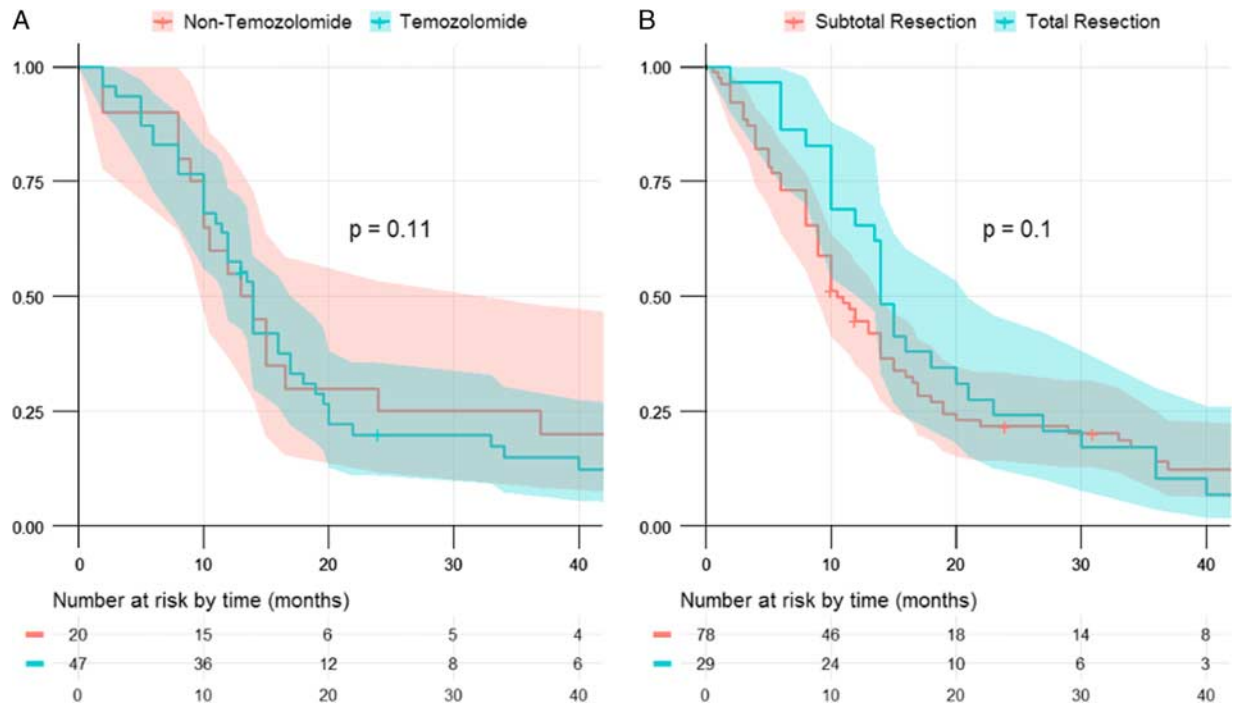

FIGURE 2. Actuarial Kaplan Meier survival curves with log-rank test results reported for comparison of survival outcome among subgroups treated with chemotherapy or surgical resection subgroups. A, Median overall survival was 14 months (95% CI, 12-18) for patients that received temozolomide versus 13.5 months (95% CI, 10-37) for those that received other types of chemotherapy; B, 10.5 months (95% CI, 9-14) for patients that underwent subtotal resections versus 14 months (95% CI, 13.5-21) for patients that underwent total resections.

of survival with log-rank statistics ($P = 0.007$; Fig. 2) with males living an average of 13.5 (95% CI, 10-18) months versus 11 (95% CI, 10-14) months for females.

The most common location was in the cervical spinal cord alone, at 33% (45/135), followed by tumors spanning multiple regions of the spinal cord, affecting 30% (40/135), and then the thoracic region of the spinal cord afflicting 29% (39/135) of the population. However, we detected no difference in patient survival between tumors involving single and multiple regions of the spinal cord ($P = 0.943$). Furthermore, no significant difference in survival characteristics was determined between location subgroups by log-rank analysis ($P = 0.43$; Fig. 2). However, we found that long-term survivors were afflicted disproportionally by tumors that were completely or partially in the thoracic portion of the spinal cord; 100% (11/11) of patients that lived 40 months or longer had tumors in the thoracic region.

Almost all the patients, 98% (132/135), underwent a neurosurgical operation. Among patients who underwent surgery, 19% (25/132) had just a biopsy, 59% (78/132) received a partial resection, and 20% (22/132) underwent a gross total resection. In addition, 85% (115/135) of patients received radiotherapy. We found no significant difference in survival between patients that underwent total resections versus those that underwent a subtotal resection by log-rank analysis ($P = 0.10$; Fig. 3).

A wide range of alkylating chemotherapies, including temozolomide, nimustine (ACNU), carmustine (BCNU), lomustine (CCNU), ranimustine (MCNU), cyclophosphamide, ThioTEPA, dacarbazine, and combinations including the 8-in-1 protocol and PCV (procarbazine, lomustine, and vincristine) were administered to the patient population. But nonalkylating chemotherapies like paclitaxel and bevacizumab were also used.[12] Of note, ACNU and MCNU were not approved for use in the United States. Sixty-five percent (88/135) of patients were treated with chemotherapy, but the type of drug was unspecified in 24% (21/88) of these cases. Among the other 67 patients with specified chemotherapy, temozolomide was the most commonly administered drug at 70% (47/67). We found no significant difference between patients that received temozolomide versus those that received some other type of chemotherapy ($P = 0.11$; Fig. 3).

The management of scGBM often involves multiple treatment modalities. The most common treatment combination in our study cohort was neurosurgical resection plus radiation and chemotherapy in 47% (64/135), followed by resection plus radiation in 20% (27/135), and then by radiation and chemotherapy in the absence of resection in 19% (19/135). The least common treatment combination was resection plus chemotherapy, and this occurred in only 4% (5/135) of the population. The median time to neurosurgical resection, the start of radiation, and the start of chemotherapy was respectively 1 (range, 0 to 1) month, 2 (range, 1 to 4) months, and 2 (range, 1 to 7) months after diagnosis. However, time to treatment information was sparse, presented in just 5%, 5%, and 7% of the cases for patients treated with surgery, radiation, and chemotherapy, respectively. Time of death was available for 93% (126/135) of patients.

DISCUSSION

This systematic review was carried out to better understand scGBM's characteristics, distribution, and response to treatment, including temozolomide and total resection (vs. alternative chemotherapies and subtotal resection, respectively). This disease is very rare and has a poor prognosis. There is no molecular marker specific for scGBM, and markers such as isocitrate

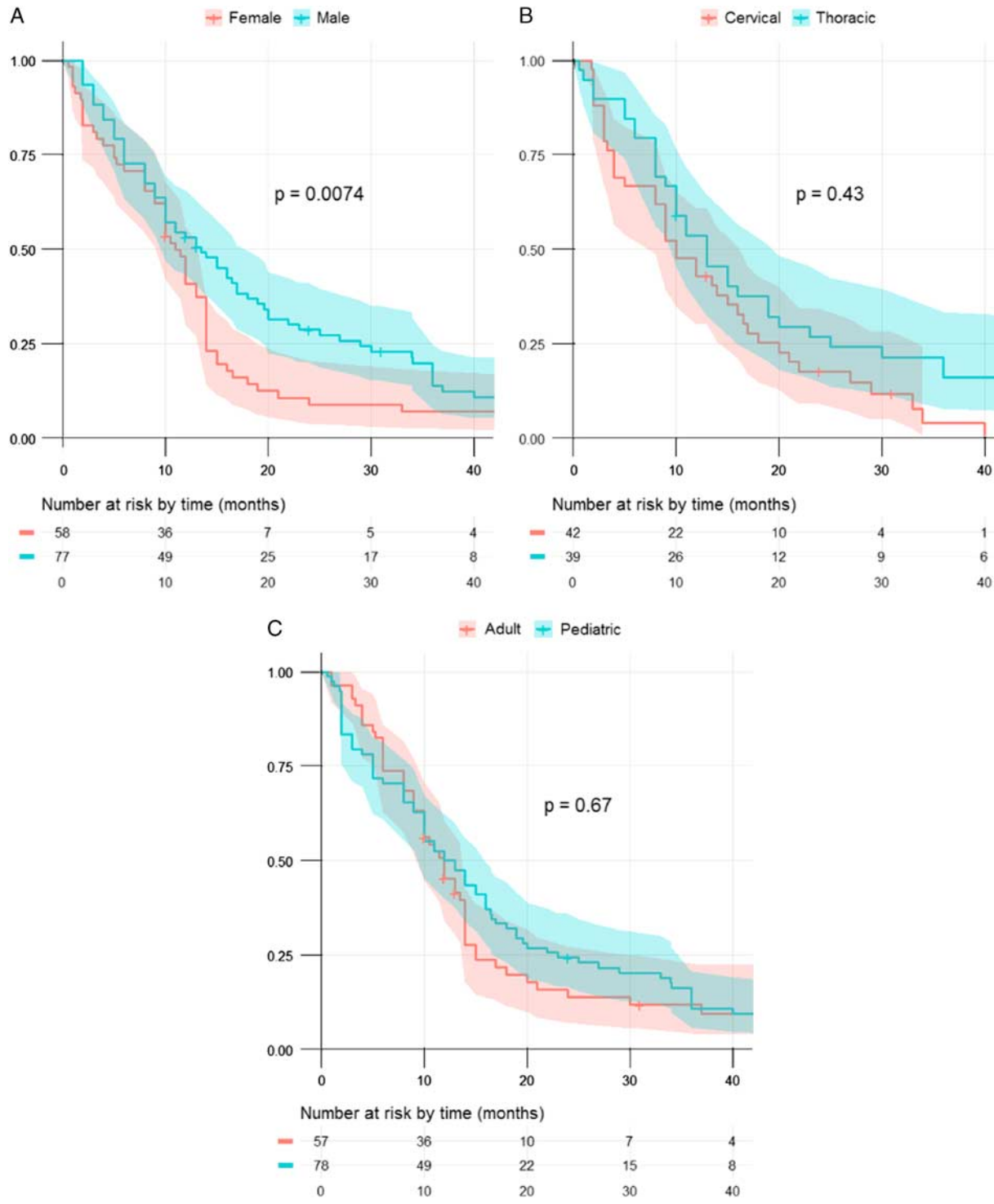

FIGURE 3. Actuarial Kaplan Meier survival curves with log-rank test results reported for comparison of survival outcome. A, Median overall survival for females was 11 months (95% CI, 10-14) versus 13.5 months (95% CI, 10-18) for males; B, 10 months (95% CI, 8-17) for patients with cervical only scGBM versus 13 months (95% CI, 10-20) for patients with strictly thoracic scGBM; C, 12 months (95% CI, 10-14) for pediatric scGBM versus 12.5 months (95% CI, 10-16) for adult scGBM.

dehydrogenase-1 (IDH-1) and O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation only have prognostic significance primarily for supratentorial GBMs.[16] Fewer than 200 scGBM case reports have been published (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/AJCO/A192), which is prohibitive for conducting prospective clinical

trials to test specific therapies. Furthermore, contradictory reports on the benefit of resection, radiation, and chemotherapy limit clinicians' ability to formulate a consensus on optimal treatment strategies. Therefore, retrospective analysis of published reports is the only means available to assess treatment efficacy.

The existing scGBM data has notable shortfalls. First, a lack of "time-to-treatment" information is systemic. In fixed-covariate, univariate, or multivariate regression analyses for either survival or progression free survival, patients that receive therapies will seem to live longer because of post hoc group assignment—because their inclusion is predicated upon the patients living long enough to receive treatment—that is independent of any correlation with treatment effect.[17] This "immortal time bias" is common to retrospective observational analyses but correctable with time-dependent Cox proportional hazards models.[18,19] Unfortunately, only 3% (4/135) of case reports with treatments had full time-to-treatment information,[10,20–22] and only 2% (3/135) had partial information.[23–25] Furthermore, among patients that received surgery, radiation, and chemotherapy, only 5%, 5%, and 7%, respectively, had time of treatment information (Table 2). For the patients with time-of-treatment information available, all underwent surgical resection within a range of 0 to 1 month, consistent with the 22-day median observed in a single-institutional review of spinal cord astrocytoma.[26] The median treatment time for radiation and chemotherapy was 2 months after diagnosis, but the variance was notably larger: 1 to 4 months for radiation and 1 to 7 months for chemotherapy. It is imperative that future studies of this disease include time-of-treatment information to allow a more thorough retrospective investigation of treatment effects.

In addition, there may be lead-time bias for scGBM patients treated after the widespread adoption of neuroimaging for diagnosis.[27] We partially corrected for this by screening for case reports that used neuroimaging for diagnosis. However, several case series were retrospective, investigating years of patient reports at a single institution,[28,29] so while some patients may have been diagnosed with neuroimaging, others may not (because of the long-term retrospective nature of some case series, we did not investigate case report publication date versus patient survival). Finally, publication bias favoring successful treatments and outcomes may lead to a distortion of survival data.[30,31] In fact, at least three scGBM case reports explicitly characterized their patients' survival as an improvement over the known median OS, suggesting that a sizable portion of published scGBM case reports may be outliers.[22,32,33] This is not unique to scGBM; in a retrospective study, observational clinical research was among the most likely to select for studies with significant results.[31] The end-result is a probable overrepresentation of case reports that perform well against the average; outcomes for scGBM are likely worse than the literature reports.

TABLE 2. Clinical Reporting of Patient Traits and Treatment Information

Metric	Percentage of Patients With Information
Patient symptoms	43
Karnofsky performance status	1
Type of chemotherapy	76
Time of treatment	
Surgery	5
Radiation	5
Chemotherapy	7

Percentage of patient reports that included information on symptoms, KPS, and treatments. "Type of chemotherapy" corresponds to the percentage of case reports with specific details about the type of chemotherapy administered. For example, a generic statement that the patient "received chemotherapy" would not count. "Time of treatment" percentages are from the cohort of patients that were stated as having received that type of treatment. Surgery includes all types of surgical intervention.

Other groups have undertaken analyses for spinal glioblastoma, and there is overlap between their patient cohorts and the one presented here. The two closest in scope are Beyer et al[34] and a study of the Surveillance, Epidemiology and End Results (SEER) program database between 1973 and 2007 by Adams et al.[5] Without this screening, treatments employed more often after the clinical adoption of neuroimaging will seem to improve OS due, in some part, to earlier detection of the disease. Further, unlike Adams et al, we compared outcomes between surgical and chemotherapeutic subgroups rather than between treated and untreated subpopulations to avoid the aforementioned immortal time bias.

Additionally, the analysis by Adams and colleagues includes case reports of both anaplastic astrocytoma and GBM, whereas our focus here is on GBM alone, but the study benefits from the diverse geographic sampling of its cancer registry. Our systematic review differs from others because we are the first to screen for the use of neuroimaging with diagnosis to avoid lead-time bias, which is highly relevant in a retrospective analysis such as this.[35]

Within the patient population we found that all long-term survivors of scGBM, who lived at least 40 months from the time of diagnosis, had an affliction of the thoracic region. This is explainable by the possibility for more aggressive treatment in the lower regions of the spinal cord, as we later discuss. We also observed that females have significantly worse OS than males ($P = 0.0074$; Fig. 1). This is in opposition to Beyer et al,[34] who found no difference ($P = 0.311$) between the two sexes, but consistent with the findings of Adams et al[5] ($P = 0.048$).

There have been conflicting reports on the benefit of surgical resection for cytoreduction as compared to biopsy for diagnosing scGBM since most patients proceed to receive adjuvant radiation. Therefore, a larger benefit from radiation may mask a small survival advantage from resection. Among reports on spinal cord astrocytoma, some authors have reported that resection benefited patients by prolonging their OS, including the SEER analysis by Adams et al,[5,36,37] while others have found no such survival benefit.[6,38] In fact, Raco et al[10] suggested that surgical intervention worsened neurological performance without improving survival. In addition to its questionable survival benefit, resection is often avoided because of the infiltrative nature of scGBM, the absence of a distinct tissue plane between the tumor and adjacent spinal cord parenchyma, and the likelihood of neurological worsening because of aggressive neurosurgical intervention.[39,40] Our analysis suggests that there is no significant difference in survival between subtotal and total resection cohorts ($P = 0.10$; Fig. 3). We did not investigate resection versus nonresection subgroups because of probable immortal time bias and surgical selection bias.

Although temozolomide chemoradiation is the standard of care for intracranial GBM, the use of radiation and chemotherapy on scGBM is controversial because their benefit is unknown.[41–43] In clinical practice, radiation has been administered as an adjuvant therapy shortly after neurosurgical resection,[43,44] at the time of first recurrence or dissemination,[45] or both.[7] Isaacson et al[44] recommended that high-grade astrocytomas of the spinal cord receive a total does of 5400 cGy in 180 cGy per fractions, though there have been encouraging outcomes with higher doses as Shirato et al[46,47] reported a

patient who lived an additional 4.8 years after receiving 6500 cGy of radiation in 26 fractions. Like a surgical cordectomy reported by Marchan et al,[39] Shirato et al[47] pointed out such high doses of radiation should only be applied to patients with already compromised motor function and scGBM located in the lower thoracic or lumbar segment of the spinal cord because it may result in "radiocordectomy." Neither Adams et al[5] nor Mineham et al[13] found radiation predictive of OS by multivariate analysis, though neither group separated patients by tumor grade according to the World Health Organization classification. Adams and colleagues did find a trend towards improved survival from radiation in a log-rank analysis of patient survival curves ($P = 0.068$), but the results are difficult to interpret for lack of correction for immortal time bias.

In a head-to-head comparison between primary scGBM patients who received temozolomide versus those who did not, Hernández-Durán et al[12] did not find temozolomide to be associated with prolonged survival. Similarly, we find no significant difference between patients who received temozolomide versus those that were known to have received other types of chemotherapy ($P = 0.11$; Fig. 3), though many patients, 16% (21/135), received some form of unspecified chemotherapy, precluding a more in-depth analysis.

CONCLUSIONS

Spinal cord glioblastoma is a deadly disease that is so rare it is unlikely there will ever be a clinical trial. We have reported trends, such as significantly worse outcomes for female patients, a lack of survival difference between temozolomide and other chemotherapies, and the apparent lack of survival benefit from total resection. But more thorough case reporting is vital for future investigations. For example, only 5% (7/135) of case reports included time-of-treatment information, and 16% (21/135) of patients received an unspecified form of chemotherapy. We urge future authors of case reports to thoroughly document their patient characteristics and treatment information so that future researchers may perform a better retrospective analysis of prognostic factors and treatment outcomes. Furthermore, we encourage all clinicians to publish their case reports documenting patients with scGBM to offset publication bias that clouds understanding of the disease.

REFERENCES

1. Adamson C, Kanu OO, Mehta AI, et al. Glioblastoma multiforme: a review of where we have been and where we are going. *Expert Opin Investig Drugs*. 2009;18:1061–1083.
2. Asano N, Kitamura K, Seo Y, et al. Spinal cord glioblastoma multiforme with intracranial dissemination–case report. *Neurol Med Chir (Tokyo)*. 1990;30:489–494.
3. Medhkour A, Chan M. Extremely rare glioblastoma multiforme of the conus medullaris with holocord and brain stem metastases, leading to cranial nerve deficit and respiratory failure: a case report and review of the literature. *Surg Neurol*. 2005;63:576–582; discussion 582–583.
4. Morais N, Mascarenhas L, Soares-Fernandes JP, et al. Primary spinal glioblastoma: a case report and review of the literature. *Oncol Lett*. 2013;5:992–996.
5. Adams H, Avendano J, Raza SM, et al. Prognostic factors and survival in primary malignant astrocytomas of the spinal cord: a population-based analysis from 1973 to 2007. *Spine (Phila Pa 1976)*. 2012;37:E727–E735.
6. Wong AP, Dahdaleh NS, Fessler RG, et al. Risk factors and long-term survival in adult patients with primary malignant spinal cord astrocytomas. *J Neurooncol*. 2013;115:493–503.
7. McGirt MJ, Goldstein IM, Chaichana KL, et al. Extent of surgical resection of malignant astrocytomas of the spinal cord: outcome analysis of 35 patients. *Neurosurgery*. 2008;63:55–60; discussion 60–61.
8. Sandler HM, Papadopoulos SM, Thornton AF Jr, et al. Spinal cord astrocytomas: results of therapy. *Neurosurgery*. 1992;30:490–493.
9. Raco A, Esposito V, Lenzi J, et al. Long-term follow-up of intramedullary spinal cord tumors: a series of 202 cases. *Neurosurgery*. 2005;56:972–979; discussion 979–981.
10. Raco A, Piccirilli M, Landi A, et al. High-grade intramedullary astrocytomas: 30 years' experience at the Neurosurgery Department of the University of Rome "Sapienza". *J Neurosurg Spine*. 2010;12:144–153.
11. Guss ZD, Moningi S, Jallo GI, et al. Management of pediatric spinal cord astrocytomas: outcomes with adjuvant radiation. *Int J Radiat Oncol Biol Phys*. 2013;85:1307–1311.
12. Hernández-Durán S, Bregy A, Shah AH, et al. Primary spinal cord glioblastoma multiforme treated with temozolomide. *J Clin Neurosci*. 2015;22:1877–1882.
13. Minehan KJ, Brown PD, Scheithauer BW, et al. Prognosis and treatment of spinal cord astrocytoma. *Int J Radiat Oncol Biol Phys*. 2009;73:727–733.
14. A Package for Survival Analysis in S [computer program]. Version 2.38. Terneau TM; 2015.
15. Dinse GE, Lagakos SW. Nonparametric estimation of lifetime and disease onset distributions from incomplete observations. *Biometrics*. 1982;38:921–932.
16. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131:803–820.
17. Beyersmann J, Gastmeier P, Wolkewitz M, et al. An easy mathematical proof showed that time-dependent bias inevitably leads to biased effect estimation. *J Clin Epidemiol*. 2008;61:1216–1221.
18. van Walraven C, Davis D, Forster AJ, et al. Time-dependent bias was common in survival analyses published in leading clinical journals. *J Clin Epidemiol*. 2004;57:672–682.
19. Fisher LD, Lin DY. Time-dependent covariates in the Cox proportional-hazards regression model. *Annu Rev Public Health*. 1999;20:145–157.
20. Strik HM, Effenberger O, Schafer O, et al. A case of spinal glioblastoma multiforme: immunohistochemical study and review of the literature. *J Neurooncol*. 2000;50:239–243.
21. Mayer RR, Warmouth GM, Troxell M, et al. Glioblastoma multiforme of the conus medullaris in a 28-year-old female: a case report and review of the literature. *Clin Neurol Neurosurg*. 2012;114:275–277.
22. Varghese SS, Sebastian P, Joseph V, et al. An unusually long survival of a patient with glioblastoma of spinal cord: a case report. *J Clin Diagn Res*. 2014;8:QD01–QD03.
23. Elsamaloty H, Zenooz NA, Mossa-Basha M. Glioblastoma multiforme (GBM) of the conus medullaris with brain and brain stem metastases. *Eur J Radiol Extra*. 2006;83:59–62.
24. Viljoen S, Hitchon PW, Ahmed R, et al. Cordectomy for intramedullary spinal cord glioblastoma with a 12-year survival. *Surg Neurol Int*. 2014;5:101.
25. Konig SA, Roediger T, Spetzger U. Treatment of recurrent primary spinal glioblastoma multiforme—case report. *J Neurol Surg A Cent Eur Neurosurg*. 2012;73:256–261.
26. Kim MS, Chung CK, Choe G, et al. Intramedullary spinal cord astrocytoma in adults: postoperative outcome. *J Neurooncol*. 2001;52:85–94.
27. Johnson DR, O'Neill BP. Glioblastoma survival in the United States before and during the temozolomide era. *J Neurooncol*. 2012;107:359–364.
28. Santi M, Mena H, Wong K, et al. Spinal cord malignant astrocytomas. Clinicopathologic features in 36 cases. *Cancer*. 2003;98:554–561.
29. Ononiwu C, Mehta V, Bettegowda C, et al. Pediatric spinal glioblastoma multiforme: current treatment strategies and possible predictors of survival. *Childs Nerv Syst*. 2012;28:715–720.
30. Dafni U. Landmark analysis at the 25-year landmark point. *Circ Cardiovasc Qual Outcomes*. 2011;4:363–371.
31. Easterbrook PJ, Berlin JA, Gopalan R, et al. Publication bias in clinical research. *Lancet*. 1991;337:867–872.

32. Allen JC, Aviner S, Yates AJ, et al. Treatment of high-grade spinal cord astrocytoma of childhood with "8-in-1" chemotherapy and radiotherapy: a pilot study of CCG-945. Children's Cancer Group. *J Neurosurg*. 1998;88:215–220.
33. Kim WH, Yoon SH, Kim CY, et al. Temozolomide for malignant primary spinal cord glioma: an experience of six cases and a literature review. *J Neurooncol*. 2011;101:247–254.
34. Beyer S, von Bueren AO, Klautke G, et al. A systematic review on the characteristics, treatments and outcomes of the patients with primary spinal glioblastomas or gliosarcomas reported in literature until march 2015. *PLoS One*. 2016;11:e0148312.
35. Black WC, Welch HG. Advances in diagnostic imaging and overestimations of disease prevalence and the benefits of therapy. *N Engl J Med*. 1993;328:1237–1243.
36. Constantini S, Miller DC, Allen JC, et al. Radical excision of intramedullary spinal cord tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults. *J Neurosurg*. 2000;93:183–193.
37. Jallo GI, Kothbauer KF, Epstein FJ. Intrinsic spinal cord tumor resection. *Neurosurgery*. 2001;49:1124–1128.
38. Bouffet E, Pierre-Kahn A, Marchal JC, et al. Prognostic factors in pediatric spinal cord astrocytoma. *Cancer*. 1998;83: 2391–2399.
39. Marchan EM, Sekula RF Jr, Jannetta PJ, et al. Long-term survival enhanced by cordectomy in a patient with a spinal glioblastoma multiforme and paraplegia. Case report. *J Neurosurg Spine*. 2007; 7:656–659.
40. Ciappetta P, Salvati M, Capoccia G, et al. Spinal glioblastomas: report of seven cases and review of the literature. *Neurosurgery*. 1991;28:302–306.
41. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987–996.
42. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10:459–466.
43. Tendulkar RD, Pai Panandiker AS, Wu S, et al. Irradiation of pediatric high-grade spinal cord tumors. *Int J Radiat Oncol Biol Phys*. 2010;78:1451–1456.
44. Isaacson SR. Radiation therapy and the management of intramedullary spinal cord tumors. *J Neurooncol*. 2000;47:231–238.
45. Chamberlain MC, Tredway TL. Adult primary intradural spinal cord tumors: a review. *Curr Neurol Neurosci Rep*. 2011;11:320–328.
46. McLaughlin MP, Buatti JM, Marcus RB Jr, et al. Outcome after radiotherapy of primary spinal cord glial tumors. *Radiat Oncol Investig*. 1998;6:276–280.
47. Shirato H, Kamada T, Hida K, et al. The role of radiotherapy in the management of spinal cord glioma. *Int J Radiat Oncol Biol Phys*. 1995;33:323–328.