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CLINICAL STUDY - PATIENT STUDY

Primary spinal cord glioma: a Surveillance, Epidemiology, and End Results database study

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Abstract To characterize the overall survival (OS) and cause specific survival (CSS), and variables affecting outcome, in patients with primary spinal cord astrocytoma (SCA) and ependymoma (SCE). About 664 patients with SCA and 1,057 patients with SCE were analyzed using the Surveillance, Epidemiology, and End Results database. For grade 1, 2, 3 and 4 SCA, the 5-year OS was 82, 70, 28 and 14%; the 5-year CSS was 89, 77, 36 and 20%. For SCA, lower grade, younger age, and undergoing resection significantly improved OS and CSS; treatment without radiotherapy was favorable for CSS. Smaller tumor size also improved survival. For grade 1, 2, and 3 SCE, the 5-year OS was 92, 97 and 58%; the 5-year CSS was 100, 98 and 64%. For SCE, lower grade, younger age, and undergoing resection significantly improved OS and CSS; treatment without radiotherapy was favorable for OS. Smaller tumor size did not confer a survival benefit. Patients with resected grade 2 spinal cord glioma who did not receive radiotherapy fared well with respect to OS and CSS. For patients with spinal cord glioma, the variables of histology, grade, age and undergoing resection are significant predictors of outcome. Though treatment with radiotherapy was associated with worse outcomes, this may reflect a bias in that patients who underwent radiotherapy were perhaps more likely to have had adverse risk factors. Given the retrospective nature of this study, specific recommendations about which situations warrant radiotherapy cannot be determined.

Keywords Spinal cord ependymoma · Spinal cord astrocytoma · Spinal cord glioma · Radiotherapy

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Introduction

Primary spinal cord tumors are uncommon. Spinal cord glioma (SCG) represents <30% of all spinal cord tumors, with an overall incidence of approximately 0.22 SCG per 100,000 person years [1]. Standard treatment options for SCG include resection, radiotherapy and combined modality resection and radiotherapy [2–39]. Some series show that patients with SCG fare better than those with intracranial gliomas [6, 29, 39, 40] though other studies do not [4, 7, 27]. Several studies demonstrate that spinal cord astrocytomas (SCA) fare worse than spinal cord ependymomas (SCE) [8, 13, 14, 21, 25, 30].

Previously reported adverse risk factors for SCE include: more advanced age [17, 26, 27], younger age [39], poor performance status/neurologic function [6, 17, 19, 27, 36], higher grade [6, 17, 21, 22, 27, 29, 39], less extensive resection [9, 12, 16, 17, 26, 29, 35, 38, 39, 41, 42], and subtherapeutic radiation dose [2, 4, 6, 8, 10, 19, 27]. The variables of age [10, 19, 30], extent of resection [10, 21, 27, 30], and grade [41] were not significant in other studies. Previously reported adverse risk factors for SCA include: poor performance status [34], more advanced age [20, 33, 37, 39, 43], younger age [24], higher grade [3, 13, 18, 24, 25, 33, 34, 37, 39, 43], and less extensive resection [8, 21, 39, 44], though less extensive resection was not an adverse risk factor in most studies [12, 18, 20, 24, 33, 37], with higher grade tumors [12, 18, 37], as well as lower grade tumors [12, 20, 24, 34]. More extensive resection was an adverse risk factor in one recent study [43]. Generally grade 4 SCG has a dismal prognosis, though long-term survivors after aggressive resection and radiotherapy have been reported [25].

Small patient numbers, and differences in patient populations between different studies complicate the interpretation of these findings. With rare exceptions [39], the published outcome on SCG represents single institution retrospective studies with small patient numbers, spanning several decades.

This study offers a descriptive analysis of patients with SCG included in the Surveillance, Epidemiology, and End Results (SEER) database, with the goal of better characterizing the overall survival (OS), cause specific survival (CSS) and risk factors affecting patient outcome.

Methods

Patient database

The SEER database is a longitudinal database that collects information from 17 cancer registries, representing 26% of the United States population (http://seer.cancer.gov/). Serial registry data are de-identified, submitted to the United States National Cancer Institute on a biannual basis, and are available for researchers. The SEER 17 limited-use registry was used [45]. Nine of the registries date back to 1973–1975, four registries date back to 1992, and four registries date back to 2000.

A total of 1,814 patients with primary SCG (excluding primitive neuroectodermal tumors), coded in the SEER database as "Primary site-labeled" = "C72.0-Spinal cord" were included in the present analysis. Patients coded as "Primary site-labeled" = "C72.1-Cauda equina" and "C70.1-Spinal meninges" were not included.

In the SEER database, "Grade" was scored as a measure differentiation, and not meant to reflect grade as scored by any recognized grading system. "Grade" was classified as: "Well differentiated; Grade I," ($n = 175$) "Moderately differentiated; Grade II," ($n = 337$) "Poorly differentiated; Grade III," ($n = 60$) "Undifferentiated; anaplastic Grade IV," ($n = 138$) or "Unknown" ($n = 1,104$), based upon explicit mention of differentiation or grade in the pathology report. From 2004, ependymomas were characterized as 'malignant', 'borderline' or 'benign.' Myxopapillary ependymoma and subependymoma were considered, 'borderline' malignancies. 'Benign' and 'borderline' tumors were not included prior to 2004; however, 'malignant' myxopapillary ependymoma was included in the ICD-O-2 and ICD-O-3 fields as "Myxopapillary ependymoma, malignant" or "Ependymoma, NOS" and 'malignant' subependymal tumors were included as "Subependymal glioma."

The "Histology/behavior," "Histology recode-Brain groupings" and "Grade" fields were used to define tumor grade for the purpose of this study, with the understanding that this "grade" does not reflect a WHO grade. For this study, the following assumptions were made: tumors classified as pilocytic astrocytoma, myxopapillary ependymoma or subependymoma in the SEER database histology fields were scored as grade 1, even if the grade in the SEER database was scored as "Moderately differentiated; Grade II" or "Unknown"; tumors classified as "Benign" or "Borderline malignancy" in the behavior code fields were scored grade 1; tumors classified as fibrillary astrocytoma in the SEER database histology fields were scored as grade 2, even if the grade in the SEER database was scored as "Unknown"; tumors classified as "Anaplastic astrocytoma" or "Anaplastic ependymoma" in the SEER histology fields were scored as grade 3, even if the grade in the SEER database was scored as "Undifferentiated; anaplastic; Grade IV" or "Unknown"; tumors classified as glioblastoma in the SEER database histology fields were scored as grade 4, even if the grade in the SEER database was scored as "Poorly differentiated; Grade III" or "Unknown." Astrocytomas not specifically coded as "Anaplastic astrocytoma" in the SEER database histology fields were scored as grade 3 if categorized as "Poorly differentiated; Grade III" and grade 4 if categorized as "Undifferentiated; anaplastic; Grade IV." Ependymomas not specifically coded as "Anaplastic ependymoma "in the SEER database histology fields were scored as grade 3 if categorized as "Poorly differentiated; Grade III." Cases scored in the SEER database as "Unknown" grade as well as: "Astrocytoma, NOS," "Glioma, malignant," "Mixed glioma," "Oligodendroglioma, NOS" or "Ependymoma, NOS" in the "Histology/behavior" field; and "Astrocytoma, NOS," "Glioma, NOS," "Mixed glioma," "Oligodendroglioma" or "Ependymoma/anaplastic ependymoma" in the SEER database histology fields were considered to have unknown grade for this analysis.

The SEER "Site specific surgery" and "Surgery of primary site" fields describe the extent of surgical resection. Cases in the SEER database categorized as "Unknown if surgery performed" were considered to not have surgery if the "Diagnostic confirmation" field was "Clinical diagnosis only" or "Radiography without microscopic confirmation." Cases in the SEER database categorized as "Unknown if surgery performed" were considered to have had resection if diagnostic confirmation was "Direct visualization without microscopic confirmation." Cases in the SEER database categorized as having undergone surgery, but diagnosed by "Clinical diagnosis only" or "Radiography without microscopic confirmation" were assumed to have undergone the procedure, but without pathologic confirmation. The SEER database has a field describing if radiotherapy was administered, though neither the radiation dose nor extent of field are available. There is no field to describe if chemotherapy was administered. The SEER database does not provide information about the location of the tumor or number of sites within the spine, or whether the cerebral spinal fluid was seeded with metastatic cells.

Statistical analysis

Stata version 9.2 (StataCorp, College Station, TX) was used for data analysis. Actuarial OS and CSS were calculated using the Kaplan–Meier method [46]. The log-rank test was used for univariate analysis (UVA) comparison of survival between subgroups. Cox proportional hazards model was used for multivariate analyses (MVA) [47], performed using variables significant on UVA. Patients with unknown surgery and/or unknown radiation delivery were excluded from the UVAs and MVAs.

The MVAs in which grade is included omit a large number of patients whose grade is unknown. The majority of patients with unknown grade were identified as having ependymoma, and the treatment and outcome of those patients with unknown grade are similar to patients with low grade SCG (see "Results"). It is a reasonable assumption that most of these patients had low grade SCG. In an effort to further explore the variables significant on UVA for OS and CSS, additional MVA models were performed in which unknown grade was re-categorized as grade 2 ("grade unknown → 2" MVA models).

Results

Patient and tumor characteristics

Table 1 summarizes the patient and tumor characteristics. Patient age ranged from <1 to 91 years old. Most patients were white. Close to half were diagnosed in the 2000s (due in part to the addition of four registries in 2000). Most patients with unknown grade had ependymoma. Tumor size was unavailable in 224 patients (diagnosed before 1983) and unknown in 1,104; size ranged from microscopic to 160 mm (median 27 mm).

Table 1 Patient and tumor characteristics

	All[a]	Astrocytoma	Ependymoma
Total number	1,814	664	1,057
Age			
<1–9	148 (8%)	119 (18%)	20 (2%)
10–19	187 (10%)	117 (18%)	61 (6%)
20–39	535 (29%)	180 (27%)	329 (31%)
40–59	674 (37%)	169 (25%)	482 (46%)
≥60	270 (14%)	79 (12%)	165 (16%)
Race			
White	1,539 (85%)	531 (80%)	937 (88%)
Black	158 (9%)	88 (13%)	55 (5%)
Other[b]	105 (6%)	43 (6%)	55 (5%)
Male	1,004 (55%)	375 (56%)	580 (55%)
Female	810 (45%)	289 (44%)	478 (45%)
Year diagnosed			
1970s	145 (8%)	84 (13%)	53 (5%)
1980s	269 (15%)	140 (21%)	110 (10%)
1990s	512 (28%)	195 (29%)	285 (27%)
2000s	888 (49%)	245 (37%)	609 (58%)
Grade			
1	407 (22%)	180 (27%)	221 (33%)
2	323 (18%)	155 (23%)	146 (14%)
3	150 (8%)	117 (18%)	28 (3%)
4	82 (5%)	82 (12%)	–
Unknown	852 (47%)	130 (20%)	662 (63%)

[a] Includes 11 patients with oligodendroglioma and 81 patients with unspecified glioma of whom 54 have unknown grade

[b] Excluding 12 unknown

For the entire cohort, on UVA, SCA fared significantly worse than SCE with respect to OS and CSS ($P < 0.00001$).

Spinal cord astrocytoma

Table 2 summarizes the treatment with respect to surgery and radiotherapy for SCA. More patients with low grade SCA, as compared to high grade SCG, underwent resection alone.

For grade 1, 2, 3 and 4 SCA, the 5-year OS was 82, 70, 28 and 14%. The 5-year CSS was 89, 77, 36 and 20%. Table 3 shows the OS and CSS for the entire cohort of patients with SCA as well as subgroups of interest. On UVA, younger age, lower grade, resection and no

Table 2 Treatment summaries

	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade unknown
Astrocytoma						
Surgery alone	230	117 (68%)	48 (32%)	17 (15%)	12 (15%)	36 (29%)
Surgery + radiotherapy	246	31 (18%)	61 (40%)	67 (58%)	49 (62%)	38 (31%)
Radiotherapy alone	105	14 (8%)	31 (21%)	25 (22%)	11 (14%)	24 (19%)
No surgery or radiotherapy	59	10 (6%)	11 (7%)	5 (4%)	7 (9%)	26 (21%)
Ependymoma						
Surgery alone	710	159 (74%)	97 (67%)	10 (36%)	–	444 (69%)
Surgery + radiotherapy	253	46 (21%)	41 (28%)	18 (64%)	–	148 (22%)
Radiotherapy alone	24	5 (2%)	3 (2%)	0	–	16 (2%)
No surgery or radiotherapy	49	6 (3%)	3 (2%)	0	–	40 (6%)

Excluding patients with unknown surgery and/or radiotherapy

radiotherapy delivery were significantly favorable predictors of OS and CSS. There is a non-significant trend towards worse early survival (<4 years) of the 10–19 year group versus older adults. Gender (not shown), race (not shown), and decade of diagnosis did not significantly impact survival. Figure 1 depicts the Kaplan–Meier OS by grade.

The survival outcomes by grade as classified in the SEER database were comparable to survival outcomes by grade as described in the "Methods", with the exception of an appreciably better OS and CSS in patients classified as "Undifferentiated; anaplastic Grade IV" in the SEER database as compared to grade 4 in the present study. Also, patients classified as "Well differentiated; Grade I" in the SEER database experienced a slightly worse long-term survival as compared to patients classified as grade 1 in the present study.

Multivariate analyses of OS and CSS were run, in which age and grade were treated as continuous variables, while radiation delivery and resection were treated as discrete variables (yes/no). Younger age, lower grade and resection were significantly favorable variables. Additional MVA models were performed for OS and CSS, in which unknown grade was reclassified as grade 2. With the "grade unknown → 2" MVA model, age, grade and resection remained significant, while the use of radiotherapy (adverse factor) was significant for CSS.

To explore the potential impact of SCA tumor size, additional MVA models were run in which tumor size was included as a continuous variable. For OS, tumor size was significant ($P = 0.048$) in the MVA models in which unknown grade was excluded (98 patients analyzed) and borderline significant ($P = 0.077$) in the "grade unknown → 2" MVA models (111 patients analyzed); grade ($P < 0.0001$ in both models) and age ($P = 0.005$ and 0.007) were significant, while resection ($P = 0.99$ and 0.89) and use of radiotherapy ($P = 0.41$ and 0.83) were not significant. For CSS, tumor size was not significant in either MVA model ($P > 0.2$); grade ($P < 0.0001$ in both models) and age ($P = 0.015$ and 0.026) were significant, while resection ($P = 0.65$ and 0.92) and use of radiotherapy ($P = 0.50$ and 0.99) were not significant.

Spinal cord ependymoma

Table 2 summarizes the treatment with respect to surgery and radiotherapy for SCE. More patients with low grade SCE, as compared to high grade SCE, underwent resection alone.

For grade 1, 2, and 3 SCE, the 5-year OS was 92, 97 and 58%. The 5-year CSS was 100, 98 and 64%. Table 4 shows the OS and CSS for the entire cohort of patients with SCE as well as subgroups of interest. On UVA, younger age, lower grade, earlier decade of diagnosis, resection and no radiotherapy delivery were significantly favorable predictors of OS and CSS. The 10–19 year old age group experienced a non-significant trend towards worse OS compared to younger children and adults <60 years (5-year OS of 80 vs. 93%, $P = 0.16$). After 15–20 years, the OS of the 10–19 year old subgroup begins to exceed the OS of older adults. Gender and race (not shown) did not significantly impact survival. Figure 2 depicts the Kaplan–Meier OS by grade.

The survival outcomes by grade as classified in the SEER database were comparable to survival outcomes by grade as described in the "Methods". Interestingly, patients classified as having grade 1 SCE experienced a non-significant trend towards worse OS versus those with grade 2 SCE ($P = 0.063$), though CSS was more similar.

Multivariate analyses of OS and CSS were run, in which age and year of diagnosis were treated as continuous variables, while grade (1–2 vs. 3), radiation (yes/no) and any resection (yes/no) were treated as discrete variables. Additional MVA models were performed for OS and CSS, in which unknown grade was reclassified as grade 2. Grade 1–2 versus 3 was significant in all MVA models. Younger

Table 3 Patient outcome: astrocytoma

	Overall survival							Cause specific survival				
	1 years (%)	5 years (%)	10 years (%)	MS (months)	*P* value UVA	*P* value MVA	*P* value MVA[a]	1 years (%)	10 years (%)	*P* value UVA	*P* value MVA	*P* value MVA[a]
All patients	79	58	52	133				83	62			
Grade (as outlined in "Methods")												
1	93	82	74	NR @ 360	<0.00001	<0.0001	<0.0001	96	88	<0.00001	<0.0001	<0.0001
2	87	70	62	248				92	73			
3	65	28	23	19				70	30			
4	46	15	11	10				49	17			
?	84	68	64	237				89	73			
Grade (as scored in SEER database)												
Well differentiated; grade I	92	80	68	277	<0.00001	Not run	Not run	95	85	<0.00001	Not run	Not run
Moderately differentiated; grade II	89	71	65	250				93	76			
Poorly differentiated; grade III	72	36	31	22				74	37			
Undifferentiated; anaplastic grade IV	58	23	17	15				64	25			
Unknown	80	64	60	186				84	67			
Age												
<1–9	94	84	80	360	<0.00001	<0.0001	<0.0001	95	88	<0.00001	0.028	0.008
10–19	71	59	54	181				74	60			
20–39	81	56	54	198				84	61			
40–59	81	53	43	66				85	52			
≥60	62	40	24	23				74	53			
Decade diagnosed												
1970s	79	52	44	72	0.38	Not run	Not run	81	52	0.33	Not run	Not run
1980s	74	60	54	135				80	65			
1990s	80	58	53	NR @ 189				86	63			
2000s	82	59	–	NR @ 71				85	–			
Resection												
No resection	70	47	38	52	<0.00001	0.002	0.004	75	47	<0.00001	<0.0001	0.001
Resection	83	63	57	228				86	68			
Radiotherapy												
No radiotherapy	86	75	69	NR @ 366	<0.00001	0.43	0.11	91	82	<0.00001	0.062	0.014
Radiation delivered	75	47	40	53				77	49			

[a] MVA model in which grade unknown is reassigned as grade 2

MS Median survival, *NOS* not otherwise specified, *NR* not reached, *UVA* univariate analyses, *MVA* multivariate analyses

? = unknown

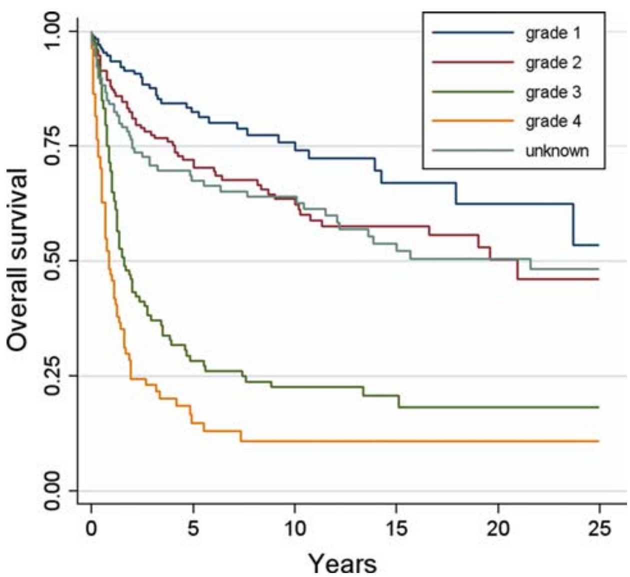

Fig. 1 Kaplan–Meier overall survival of spinal cord astrocytoma by grade. Beyond 25 years, the total number of patients at risk is small (31), so survival is shown only up to 25 years

age was favorable for OS and CSS. No radiation delivery was favorable for OS; resection was significantly favorable for OS and CSS. A more recent year of diagnosis was significantly favorable for OS and CSS in the "grade unknown → 2" MVA models.

To explore the potential impact of SCE tumor size, additional MVA models were run in which tumor size was included as a continuous variable. For OS, tumor size was not significant ($P = 0.56$) in the MVA model in which unknown grade was excluded (154 patients analyzed) or in the "grade unknown → 2" MVA model ($P = 0.24$; 352 patients analyzed). In both MVA models of OS, in which size was included, grade was not significant ($P = 0.20$ and 0.13), while younger age ($P = 0.038$ and <0.0001) and resection ($P = <0.0001$ and 0.001) were significant; radiotherapy delivery was significant ($P = 0.050$) in the "grade unknown → 2" model. For CSS, no variable, including tumor size ($P = 0.91$) was significant ($P > 0.2$ for all variables) in the MVA model in which unknown grade was excluded. For the "grade unknown → 2" CSS MVA model, grade ($P = 0.025$), younger age ($P = 0.017$), more recent year of diagnosis ($P = 0.002$), and resection ($P = 0.010$) were significantly favorable, while smaller tumor size ($P = 0.12$) and radiotherapy ($P = 0.12$) were not.

Patient outcome: use of radiotherapy

Table 5 summarize the OS and CSS of patients with grade 2–4 SCG, treated with resection with or without adjuvant radiotherapy. Patients with resected grade 2 SCE treated with radiotherapy experienced a worse OS compared to those not treated with radiotherapy, though CSS was similar. Patients with resected grade 2 SCA treated with radiotherapy experienced a worse OS and CSS compared to those not treated with radiotherapy. In patients with resected high grade SCG, OS and CSS were not significantly impacted by whether or not radiotherapy was delivered.

Discussion

Spinal cord glioma is a rare malignancy, for which the management is challenging due to potentially devastating consequences of the disease as well as paucity of published data. Given the relative rarity, SCG is well-suited for retrospective studies, and the SEER database provides a large study cohort with long follow-up.

Several retrospective studies suggest that grade and histology are significant predictors of survival and disease control, with lower grade tumors and ependymomas having the best prognosis. The present study confirms these findings. Nevertheless, comparing outcomes of like-graded tumors between different studies, and even within the same study, can be a challenge due to the difficulty in accurately and reproducibly assigning a grade. Several factors complicate glioma grading, including: (1) tissue sampling errors; (2) variable levels of pathology expertise; (3) differing criteria with which grade is assigned; (4) availability and use different pathologic staging systems over the course of decades. Database discrepancies, inconsistencies and/or coding errors can also be problematic. Major limitations of this study are (1) a large percentage of patients with unknown grade; and (2) among those who were assigned a grade, a uniform grading system was not used. While after 2004, WHO grading was to be recorded in the optional "CS Site-Specific Factor 1" field, this field was scored as unknown for all patients, even if a grade was assigned in the SEER grade field, suggesting that registries did not opt to use the "CS Site-Specific Factor 1" field and/or used other grading systems.

In our study, greater age was an adverse predictor of OS and CSS for SCA and SCE, a finding which contradicts a recent multi-institutional pooled analysis [39]. Interestingly, the subgroup of patients aged 10–19 experienced a non-significantly worse OS and CSS as compared to younger children and non-elderly adults. These differences do not appear to be attributable to differences in the distribution of grade or histology (data not shown). Possible reasons for these differences are unknown.

Grade was highly significant for OS and CSS of SCG, consistent with innumerable other studies (see "Introduction"). Interestingly, the OS for grade 1 SCE was

Table 4 Patient outcome: ependymoma

	Overall survival							Cause specific survival				
	1 years (%)	5 years (%)	10 years (%)	MS (months)	*P* value UVA	*P* value MVA	*P* value MVA[a]	1 years (%)	10 years (%)	*P* value UVA	*P* value MVA	*P* value MVA[a]
All patients	97	90	81	300				99	93			
Grade (as outlined in "Methods")												
1	98	92	73	NR @ 315	0.002	*	*	100	93	<0.00001	*	*
2	100	97	91	NR @ 375				100	98			
3	96	58	51	NR @ 264				96	56			
?	96	90	81	298				98	93			
Grade 1–2 versus 3					0.0001	<0.0001	<0.0001			<0.00001	<0.0001	<0.0001
Grade (as scored in SEER database)												
Well differentiated; grade I	96	91	73	NR @ 315	<0.00001	Not run	Not run	100	92	<0.00001	Not run	Not run
Moderately differentiated; grade II	100	97	91	222				100	98			
Poorly differentiated; grade III	100	38	–	32				100	<50			
Undifferentiated; anaplastic grade IV	94	54	45	72				94	48			
Unknown	97	90	81	298				98	93			
Age												
<1–9	100	100	100	NR @ 294	<0.00001	<0.0001	<0.0001	100	100	0.002	0.070	0.002
10–19	95	80	73	NR @ 390				96	84			
20–39	100	95	90	NR @ 386				100	94			
40–59	98	92	84	278				100	94			
≥60	89	78	49	119				94	85			
Decade diagnosed												
1970s	98	81	69	215	0.002			98	78	<0.00001		
1980s	95	87	77	280				96	89			
1990s	96	90	82	NR @ 190				98	94			
2000s	98	92	–	NR @ 71				99	–			
Year of diagnosis						0.11	0.013				0.11	0.003
Resection												
No resection	86	71	65	292	0.002	0.005	0.001	94	77	0.003	0.011	0.003
Resection	98	92	82	296				99	94			
Radiotherapy												
No radiotherapy	97	92	84	NR @ 390	0.002	0.056	0.045	99	96	0.001	0.66	0.17
Radiation delivered	98	89	75	249				99	87			

[a] MVA model in which grade unknown is reassigned as grade 2

*When grade was included as a continuous variable, grade was not significant for OS ($P > 0.1$), while it was significant for CSS ($P \leq 0.001$). The MVA models shown include grade as a discrete variable (1–2 vs. 3)

MS Median survival, *NOS* not otherwise specified, *NR* not reached, *UVA* univariate analyses, *MVA* multivariate analyses

? = unknown

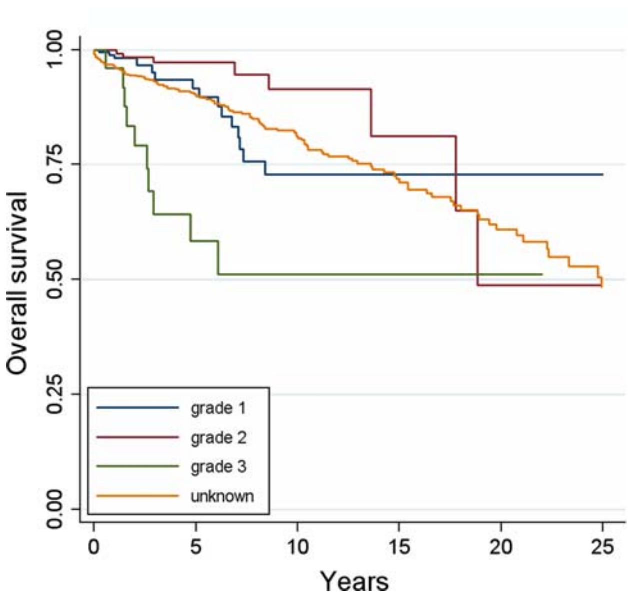

Fig. 2 Kaplan–Meier overall survival of spinal cord ependymoma by grade. Beyond 25 years, the total number of patients at risk is small (25), so survival is shown only up to 25 years

non-significantly worse than grade 2 SCE, which resulted in grade being non-significant when treated as a continuous variable in the MVA for SCE (Table 4). Low grade (grade 1–2) versus grade 3 SCE was highly significant in MVA models for OS and CSS.

Grade 1 myxopapillary ependymomas can be characterized by early progression, and relatively poor OS [48], perhaps contributing to the relatively worse OS of grade 1 SCE. Most (>95%) of the patients identified as having myxopapillary ependymoma in the SEER database were diagnosed after 2000, and thus a meaningful comparison could not be made in our analysis. Grade as a continuous variable was significant in MVA models for CSS, suggesting that the worse OS of grade 1 SCE in this study may also reflect confounding variables. This discrepancy may also reflect the difficulty in grading gliomas (as described above), as well as the manner in which grade was assigned in this study. As described in the "Methods", from 2004, ependymomas were characterized as 'malignant', 'borderline' or 'benign', while prior to 2004, only 'malignant' ependymomas were included. While tumors which would have been scored as 'borderline' or 'benign' after 2004, may have been included as grade 1 'malignant' tumors prior to 2004 (since the classification of grade 1 ependymomas as 'malignant', 'borderline' or 'benign' is a matter of semantics), perhaps many of these tumors were not included in the SEER database prior to 2004. This would potentially create a different patient population of grade 1 tumors after 2004. The long-term survival of patients in this study reflects patients registered when registries were instructed to include only 'malignant' gliomas. In our study, <35% of grade 1 tumors were diagnosed prior to 2004 (data not shown).

Tumor size was explored as a variable potentially affecting outcome. For SCA, smaller tumor size appears to favorably impact OS, but not CSS. Interestingly, whether patients underwent resection or radiotherapy were not significant when SCA tumor size was included in the MVA. For SCE, tumor size did not appear to impact survival outcomes; whether patients underwent resection remained significant when SCE tumor size was included in the MVA models. Because many patients did not have tumor size recorded (111 patients with SCA and 352 patients with SCE were analyzed for tumor size), and because tumor size, in general, is not a reliable variable, caution should be used in interpreting these results.

The role of adjuvant radiotherapy after resection of SCG is not well understood. For high grade SCG, given the relative rarity and generally poor prognosis, the incremental benefit radiotherapy offers in terms of tumor control and survival is not well characterized. In our retrospective analysis, the OS and CSS of patients with grade 3–4 SCG

Table 5 Radiotherapy

	Number	10-year OS (%)	*P* value	10-year CSS (%)	*P* value
Grade 2 ependymoma s/p resection					
No radiotherapy	97	99	0.041	99	0.88
Radiotherapy	41	80		100	
	Number	5-year OS (%)	*P* value	5-year CSS (%)	*P* value
Grade 2 astrocytoma s/p resection					
No radiotherapy	48	86	0.042	92	0.083
Radiotherapy	61	74		79	
Grade 3–4 astrocytoma s/p resection					
No radiotherapy	29	29	0.94	47	0.50
Radiotherapy	116	21		28	

were not significantly impacted by radiation delivery, albeit perhaps partially attributable to biases inherent in retrospective analyses. Nevertheless, radiotherapy is known to be effective against gliomas and remains a standard adjuvant treatment for high grade SCG.

For grade 2 SCG, the benefit of adjuvant radiotherapy is more controversial. Several retrospective studies have shown that after gross total resection of grade 2 SCG, post-operative radiotherapy is not needed [16, 18, 19, 25, 32]. Certainly, with modern surgical and imaging techniques, total resection of grade 2 SCG is more readily attainable, and close observation with serial imaging is reasonable [15, 16, 19, 25, 28, 29, 31–33, 39].

After subtotal resection of low grade SCG, several studies advocate post-operative radiotherapy [2, 12, 16, 17, 21, 23, 25, 34, 35] and/or treated all (or nearly all) patients in their series with radiotherapy (and therefore cannot assess the efficacy of withholding radiation) [4, 6–8, 10, 11, 13, 14, 22, 29, 30, 33, 38]. However, it is not known which patients might benefit from close observation, reserving radiotherapy or additional surgery for salvage, as opposed to upfront radiotherapy [26]. At least one study demonstrates no benefit from radiotherapy after subtotal resection of low grade SCE [26]. A modern pooled analysis has advocated deferring radiotherapy in patients with subtotally resected low grade SCE, while offering upfront radiotherapy for low grade SCA (which yielded a significantly improved progression-free survival) [39]. In a recent retrospective study, post-operative radiotherapy for all infiltrative (grade 2–4) SCA yielded a significantly improved OS [43].

In our analysis, patients with resected grade 2 SCG, specifically SCA, who underwent radiotherapy fared worse than patients who did not undergo radiotherapy. This most likely reflects a bias in that patients who were offered therapeutic radiotherapy perhaps had more adverse risk factors (i.e. larger tumor, close or positive margins, multifocal disease), a notion confirmed by a large multi-institutional pooled analysis [39]. Therefore retrospectively comparing the outcome of those treated with upfront radiotherapy versus those not undergoing upfront radiotherapy is likely impacted by this bias.

Conclusions

For patients with SCG, age, histology and grade are significant predictors of outcome. Though treatment with radiotherapy was associated with worse outcomes, this likely reflects a bias in that patients who received radiotherapy were perhaps more likely to have had adverse risk factors (i.e. larger tumor, close or positive margins). Patients with grade 2 SCG who did not undergo radiotherapy after resection fared quite well with respect to OS and CSS. Given the retrospective nature of this study, specific recommendations about which situations warrant radiotherapy cannot be derived from our analyses.

References

1. Schellinger KA, Propp JM, Villano JL, McCarthy BJ (2008) Descriptive epidemiology of primary spinal cord tumors. J Neurooncol 87(2):173–179
2. Kopelson G, Linggood RM, Kleinman GM, Doucette J, Wang CC (1980) Management of intramedullary spinal cord tumors. Radiology 135(2):473–479
3. Kopelson G, Linggood RM (1982) Intramedullary spinal cord astrocytoma versus glioblastoma: the prognostic importance of histologic grade. Cancer 50(4):732–735
4. Marks JE, Adler SJ (1982) A comparative study of ependymomas by site of origin. Int J Radiat Oncol Biol Phys 8(1):37–43
5. Peschel RE, Kapp DS, Cardinale F, Manuelidis EE (1983) Ependymomas of the spinal cord. Int J Radiat Oncol Biol Phys 9(7):1093–1096
6. Garrett PG, Simpson WJ (1983) Ependymomas: results of radiation treatment. Int J Radiat Oncol Biol Phys 9(8):1121–1124
7. Read G (1984) The treatment of ependymoma of the brain or spinal canal by radiotherapy: a report of 79 cases. Clin Radiol 35(2):163–166
8. Garcia DM (1985) Primary spinal cord tumors treated with surgery and postoperative irradiation. Int J Radiat Oncol Biol Phys 11(11):1933–1939
9. Sonneland PR, Scheithauer BW, Onofrio BM (1985) Myxopapillary ependymoma. A clinicopathologic and immunocytochemical study of 77 cases. Cancer 56(4):883–893
10. Shaw EG, Evans RG, Scheithauer BW, Ilstrup DM, Earle JD (1986) Radiotherapeutic management of adult intraspinal ependymomas. Int J Radiat Oncol Biol Phys 12(3):323–327
11. Di Marco A, Griso C, Pradella R, Campostrini F, Garusi GF (1988) Postoperative management of primary spinal cord ependymomas. Acta Oncol 27(4):371–375
12. Cooper PR (1989) Outcome after operative treatment of intramedullary spinal cord tumors in adults: intermediate and long-term results in 51 patients. Neurosurgery 25(6):855–859
13. Linstadt DE, Wara WM, Leibel SA, Gutin PH, Wilson CB, Sheline GE (1989) Postoperative radiotherapy of primary spinal cord tumors. Int J Radiat Oncol Biol Phys 16(6):1397–1403
14. Chun HC, Schmidt-Ullrich RK, Wolfson A, Tercilla OF, Sagerman RH, King GA (1990) External beam radiotherapy for primary spinal cord tumors. J Neurooncol 9(3):211–217
15. McCormick PC, Torres R, Post KD, Stein BM (1990) Intramedullary ependymoma of the spinal cord. J Neurosurg 72(4):523–532
16. Wen BC, Hussey DH, Hitchon PW et al (1991) The role of radiation therapy in the management of ependymomas of the spinal cord. Int J Radiat Oncol Biol Phys 20(4):781–786
17. Whitaker SJ, Bessell EM, Ashley SE, Bloom HJ, Bell BA, Brada M (1991) Postoperative radiotherapy in the management of spinal cord ependymoma. J Neurosurg 74(5):720–728
18. Epstein FJ, Farmer JP, Freed D (1992) Adult intramedullary astrocytomas of the spinal cord. J Neurosurg 77(3):355–359
19. Ferrante L, Mastronardi L, Celli P, Lunardi P, Acqui M, Fortuna A (1992) Intramedullary spinal cord ependymomas—a study of 45 cases with long-term follow-up. Acta Neurochir (Wien) 119(1–4):74–79

20. Sandler HM, Papadopoulos SM, Thornton AF Jr, Ross DA (1992) Spinal cord astrocytomas: results of therapy. Neurosurgery 30(4):490–493
21. Hulshof MC, Menten J, Dito JJ, Dreissen JJ, van den Bergh R, Gonzalez Gonzalez D (1993) Treatment results in primary intraspinal gliomas. Radiother Oncol 29(3):294–300
22. Waldron JN, Laperriere NJ, Jaakkimainen L et al (1993) Spinal cord ependymomas: a retrospective analysis of 59 cases. Int J Radiat Oncol Biol Phys 27(2):223–229
23. Clover LL, Hazuka MB, Kinzie JJ (1993) Spinal cord ependymomas treated with surgery and radiation therapy. A review of 11 cases. Am J Clin Oncol 16(4):350–353
24. Minehan KJ, Shaw EG, Scheithauer BW, Davis DL, Onofrio BM (1995) Spinal cord astrocytoma: pathological and treatment considerations. J Neurosurg 83(4):590–595
25. Shirato H, Kamada T, Hida K et al (1995) The role of radiotherapy in the management of spinal cord glioma. Int J Radiat Oncol Biol Phys 33(2):323–328
26. Sgouros S, Malluci CL, Jackowski A (1996) Spinal ependymomas—the value of postoperative radiotherapy for residual disease control. Br J Neurosurg 10(6):559–566
27. Stuben G, Stuschke M, Kroll M, Havers W, Sack H (1997) Postoperative radiotherapy of spinal and intracranial ependymomas: analysis of prognostic factors. Radiother Oncol 45(1):3–10
28. Lee TT, Gromelski EB, Green BA (1998) Surgical treatment of spinal ependymoma and post-operative radiotherapy. Acta Neurochir (Wien) 140(4):309–313
29. Schild SE, Nisi K, Scheithauer BW et al (1998) The results of radiotherapy for ependymomas: the Mayo Clinic experience. Int J Radiat Oncol Biol Phys 42(5):953–958
30. Abdel-Wahab M, Corn B, Wolfson A et al (1999) Prognostic factors and survival in patients with spinal cord gliomas after radiation therapy. Am J Clin Oncol 22(4):344–351
31. Hoshimaru M, Koyama T, Hashimoto N, Kikuchi H (1999) Results of microsurgical treatment for intramedullary spinal cord ependymomas: analysis of 36 cases. Neurosurgery 44(2):264–269
32. Constantini S, Miller DC, Allen JC, Rorke LB, Freed D, Epstein FJ (2000) Radical excision of intramedullary spinal cord tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults. J Neurosurg 93(2 Suppl):183–193
33. Rodrigues GB, Waldron JN, Wong CS, Laperriere NJ (2000) A retrospective analysis of 52 cases of spinal cord glioma managed with radiation therapy. Int J Radiat Oncol Biol Phys 48(3):837–842
34. Kim MS, Chung CK, Choe G, Kim IH, Kim HJ (2001) Intramedullary spinal cord astrocytoma in adults: postoperative outcome. J Neurooncol 52(1):85–94
35. Chang UK, Choe WJ, Chung SK, Chung CK, Kim HJ (2002) Surgical outcome and prognostic factors of spinal intramedullary ependymomas in adults. J Neurooncol 57(2):133–139
36. Hanbali F, Fourney DR, Marmor E et al (2002) Spinal cord ependymoma: radical surgical resection and outcome. Neurosurgery 51(5):1162–1172; discussion 1172–1174
37. Santi M, Mena H, Wong K, Koeller K, Olsen C, Rushing EJ (2003) Spinal cord malignant astrocytomas. Clinicopathologic features in 36 cases. Cancer 98(3):554–561
38. Gomez DR, Missett BT, Wara WM et al (2005) High failure rate in spinal ependymomas with long-term follow-up. Neuro Oncol 7(3):254–259
39. Abdel-Wahab M, Etuk B, Palermo J et al (2006) Spinal cord gliomas: a multi-institutional retrospective analysis. Int J Radiat Oncol Biol Phys 64(4):1060–1071
40. McGuire CS, Sainani KL, Fisher PG (2009) Both location and age predict survival in ependymoma: a SEER study. Pediatr Blood Cancer 52(1):65–69
41. Cervoni L, Celli P, Fortuna A, Cantore G (1994) Recurrence of spinal ependymoma. Risk factors and long-term survival. Spine 19(24):2838–2841
42. Asazuma T, Toyama Y, Suzuki N, Fujimura Y, Hirabayshi K (1999) Ependymomas of the spinal cord and cauda equina: an analysis of 26 cases and a review of the literature. Spinal Cord 37(11):753–759
43. Minehan KJ, Brown PD, Scheithauer BW, Krauss WE, Wright MP (2009) Prognosis and treatment of spinal cord astrocytoma. Int J Radiat Oncol Biol Phys 73(3):727–733
44. McGirt MJ, Goldstein IM, Chaichana KL, Tobias ME, Kothbauer KF, Jallo GI (2008) Extent of surgical resection of malignant astrocytomas of the spinal cord: outcome analysis of 35 patients. Neurosurgery 63(1):55–60; discussion 60–61
45. Surveillance, Epidemiology and End Results (SEER) Program. SEER*Stat Database: incidence—SEER 17 Regs limited-use þ Hurricane Katrina impacted Louisiana cases, Nov 2007 Sub (1973–2005 varying)—linked to county attributes—total U.S., 1969–2005 counties. National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2008, based on the November 2007 submission. www.seer.cancer.gov
46. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53(282):457–481
47. Cox D (1972) Regression models and life tables. J R Stat Soc B 34(2):187–220
48. Pica A, Miller R, Villa S et al (2009) The results of surgery, with or without radiotherapy, for primary spinal myxopapillary ependymoma: a retrospective study from the rare cancer network. Int J Radiat Oncol Biol Phys 74(4):1114–1120