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REVIEW ARTICLE

Prognostic factors in intramedullary astrocytomas: a literature review

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Abstract Astrocytomas affect a significant portion of patients with intramedullary tumors. These infiltratively growing tumors are treated by a variety of methods—biopsy and decompressive surgery, maximal safe resection, adjuvant oncological therapy. Also, numerous prognostic factors are reported in the literature. Better understanding of factors that influence prognosis may help in treatment planning with the goal of prolonging survival. We have thus undertaken an extensive literature review in order to define factors affecting prognosis. A total of 38 articles were studied. Only tumor grade was consistently reported as the major factor affecting prognosis. The influence of other clinical factors (age, gender, history length, functional status, tumor location or extent, syrinx or cyst presence) can be speculated upon, but cannot be assessed adequately from the available literature. For both low- and high-grade (HG) astrocytomas, maximal safe tumor resection should be the primary treatment objective but is often not feasible in contrast to other intramedullary and spinal neoplasms. Since the biological nature of spinal cord HG glioma is identical to that of the brain, the same treatment algorithm of maximal safe resection followed by concomitant radio- and chemotherapy would be sensible to implement.

Keywords Intramedullary tumor · Intramedullary astrocytoma · Survival · Prognostic factor · Literature review

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Abbreviations

IMSCT	Intramedullary spinal cord tumor
LG	Low grade
IMG	Intermediate grade
HG	High grade
WHO	World Health Organization
GTR	Gross total resection
STR	Subtotal resection
PR	Partial resection
Bio	Biopsy
PFS	Progression-free survival
OS	Overall survival
CSS	Cause-specific survival
LC	Local control
EOR	Extent of resection
RT	Radiotherapy
CHT	Chemotherapy
MRI	Magnetic resonance imaging
FU	Follow-up
MM	Morbidity and mortality
NR	Not reported
NS	Not significant
KPS	Karnofsky Performance Status
HR	Hazard ratio
aHR	Adjusted hazard ratio

Introduction

Intramedullary spinal cord tumors (IMSCTs) are relatively rare neoplasms accounting for 2–4% of all central nervous system tumors and for 20–25% of all spinal tumors [4, 23, 68, 69]. Astrocytomas and ependymomas represent approximately 80% of all IMSCTs [23]. Whereas ependymoma is

the most common IMSCT in the middle-aged population, its diagnosis is relatively rare among children. On the other hand, astrocytomas constitute the majority of IMSCTs found in children and adolescents [9, 17, 19, 23, 67]. The majority of IMSCTs are low-grade (LG) neoplasms. On the other hand, high-grade (HG) tumors, e.g. anaplastic astrocytomas (WHO grade III) and intramedullary glioblastomas (WHO grade IV), together account for approximately 8–13% of intramedullary tumors of astrocytic origin [7, 29, 65, 68] and are usually characterized by rapid progression.

Gross total resection (GTR) has been established as the gold standard in the treatment of intramedullary ependymoma, with series reporting 70–100% of ependymomas being radically resected [6, 16, 20, 45, 57] and long-term survival being the rule rather than exception. On the contrary, the therapeutical spectrum in infiltratively growing intramedullary astrocytomas ranges from histological verification and decompressive surgery with subsequent radiotherapy [64] to GTR, with 6–70% of intramedullary astrocytomas undergoing GTR [27, 28, 34, 49, 56, 58, 61, 64].

Besides surgery, radiotherapy is a widely employed therapeutical option in the treatment of intramedullary astrocytoma. Its use varies considerably; some centers use it as a standard part of treatment protocol [24, 30, 37], others irradiate patients according to the rapidity of preoperative disease progression [61] and other institutions irradiate patients depending upon resection extent [34, 64].

Despite advances in diagnostic imaging, microsurgical techniques, surgical adjuncts and adjuvant oncological therapy, the prognosis of intramedullary astrocytoma is not as well known contrary to their intracranial counterparts [63]. Due to its relative rarity, it is very probable that a randomized controlled trial comparing various management strategies in the treatment of intramedullary astrocytoma will never be conducted. Better understanding of factors that influence prognosis may help in treatment planning with the goal of prolonging survival. We have thus undertaken an extensive literature review in order to define factors affecting recurrence rate and survival with the goal of clarifying an optimal therapeutical strategy for intramedullary astrocytoma, since its management is controversial, contrary to ependymoma.

Methods

The Medline database was searched in February 2008 using the keywords “spinal cord neoplasm”, “spinal cord tumor”, “spinal cord astrocytoma”, “intramedullary tumor”, “intramedullary astrocytoma”, “intramedullary glioma”, “spinal cord glioma”, “intramedullary glioblastoma”, “spinal cord glioblastoma”, “surgery”, “radiotherapy”, “prognosis”, “prognostic factor”, “treatment”, “resection”, “chemotherapy” and their combinations. The “What’s new” Medline function was applied for the described search strategy to update the list of articles during the time of manuscript preparation. Full texts of relevant English language articles (review articles included) were studied by two readers and their reference lists searched for additional articles which were in turn studied as well. This traditional approach is more prone to bias than a meta-analysis or systematic review; however, we endeavored to unreservedly include all studies. Such an approach has been successfully used before also in other topics [21, 31, 50]. Moreover, studies of intramedullary astrocytoma report patient characteristics and results in a very varying fashion, practically precluding a meta-analysis or systematic review. Many valuable studies would then be excluded if strict inclusion criteria were applied. Particularly, articles dealing primary with intramedullary tumors, where astrocytomas constitute a varying portion, would have to be excluded, because astrocytoma patients are described as part of the whole group and crude data extraction is not always possible.

The point of our review was factors that influence progression-free (PFS) and overall survival (OS). We concentrated on patient demographics (age, gender, history length, functional status), tumor characteristics (location, extension, syrinx/cyst presence, tumor grade), surgical therapy (extent or resection, EOR) and adjuvant oncological therapy (radiotherapy, RT). Particular attention was turned to studies published after 1980 and reporting 10 or more patients and presenting data in a statistical fashion where the influence of the above described factors proved to be statistically (in)significant. Each article was read by two independent reviewers and assessed both for quality (see bellow) and for presence of relevant information with regard to prognostic factors of interest.

Quality assessment

In order to assess quality of the reviewed studies, we first defined what attributes an ideal single institution study should have (Table 1). Number of patients was assessed as follows: less than 20 patients, 0 points; 21–50 patients, 1 point; more than 51 patients, 2 points. Every other parameter listed was assigned 1 point if clearly reported, 0 if missing or unable to ascertain, and occasionally 0.5 if present, but information incomplete. Such methodology was used successfully before [74]. IMSCT studies were assessed not only by their overall methodology, but also by astrocytoma-specific results. Possible maximum number of points gained is 30. Based on number of points gained, studies were divided into two categories: A, 15 points and more; B, 14 points and less (Tables 1, 2, last column). Two

Table 1 Quality assessment: attributes required for an ideal single institution study [74]

Study attribute	No. of studies reporting (%)
Prospective data collection	0 (0)
No. of patients	38 (100)[a]
Independent assessment of	
Pre- and postoperative MRI or other imaging	1 (3)
Histology	4 (11)
Outcome	0 (0)
Exclusion and inclusion criteria	21 (55)
Study period	37 (97)
Method of long-term follow-up	18 (47)
Length of follow-up	35 (92)
Recurrence definition	15 (39)
Reported data	
Age	37 (97)
Gender	35 (92)
Clinical history	25 (66)
Symptom duration	23 (61)
Previously treated patients	11 (29)
Functional status	24 (63)
Tumor location	33 (86)
Tumor extent	17 (45)
Cyst/syrinx presence	6 (16)
MRI-based extent of resection	9 (24)
Surgical technique	14 (37)
Morbidity + mortality	26 (68)
Histological findings	35 (92)
Radiotherapy technique	17 (45)
Radiotherapy complications	13 (34)
Chemotherapy use	14 (37)
All included patients accounted for	36 (95)
Actuarial analysis	34 (89)
Prognostic factors	27 (71)

Each parameter was assigned 1 point if present, 0 points if missing or unable to ascertain, and occasionally 0.5 if present, but information incomplete

[a] Number of patients was scored as follows: less than 20 patients, 0 points; 21–50 patients, 1 point; more than 51 patients, 2 points. Possible maximum number of points gained is 30

independent readers assigned points to each article, discrepancies were resolved through consensus.

Results

The described search strategy yielded a total of more than 2,400 articles. After excluding clearly irrelevant articles by title, a total of 290 studies dealing with intramedullary astrocytomas or IMSCTs were left for further study. Abstracts of these articles were reviewed and full texts of 170 articles were subsequently obtained. Of these, 19 intramedullary astrocytoma articles reported one or more of the prognostic factors of interest and form the basis of this review (Table 2). Additional 19 articles dealing with IMSCTs also reported one or more prognostic factors of interest for astrocytoma patients and form the basis of this review as well (Table 3). One IMSCT study [2] is a follow-up of a previous one [1], only the latter was used in this review [2].

Quality assessment

There were 21 category A and 17 category B studies. The mean number of point reached was 15.7 (range 9–22.5). Altogether, 7 articles scored 20 points or more [8, 9, 24, 46, 56, 59, 60].

Age

Results of a statistical analysis of age as a prognostic factor were reported in 15 studies [2, 5, 24, 27, 28, 30, 34, 41, 46, 49, 56, 59, 60, 64, 65] (Table 4). Of these, 13 were classified as category A, 8 failed to find a significant relationship between age and prognosis [2, 24, 28, 30, 34, 46, 56, 59], as did one additional category B study [27]. Four category A studies reported increased age to negatively affect prognosis: Sandler et al. [64] found patients with tumor recurrence to be older (mean 38 years, median 31 years) than those without recurrence (mean 19 years, median 17 years), furthermore the oldest three patients in his study all experienced recurrence within 1 year. Similarly, Lee et al. [41] reported that older age adversely affected local control, PFS and OS, finding confirmed by others in terms of both PFS and cause-specific survival (CSS) [60]. A large multicenter review of pediatric patients with intramedullary astrocytomas conducted in France reported age <7 years to correlate with better outcome. Ten-year OS for younger patients was 76% compared with 38% for patients older than 7 years ($p = 0.04$) [5]. Contrary to these four reports, the last category A study [49] reported age over 20 to be associated with increased survival. In addition, one category B study dealing exclusively with malignant astrocytomas reported advanced age to decrease median survival [65].

Gender

Results of a statistical analysis of gender as a prognostic factor were reported in 11 studies [2, 5, 24, 27, 30, 34, 41, 49, 59, 60, 65] (Table 5). Of these, nine were classified as category A, six failed to find a significant association between gender and prognosis [2, 34, 41, 49, 59, 60], as did two additional category B studies [27, 65]. Two category A

Table 2 Summary of intramedullary astrocytoma studies

Author (reference)	Study period	Study type	Patients	Resection assessment	Histology review	GTR (%)	Radiotherapy (%)	HG tumors (%)	Follow-up [median (range)]	Lost to follow-up	Quality (points)
Kopelson [37]	1962–1980	Retrospective single center	14	NR	Local	0 (0)	14 (100)	5 (36)	NR	2	B (12)
Reimer [58] (p)	1955–1980	Retrospective single center	32	NR	NR	2 (6)	26 (81)	5 (16)	NR	3	B (13)
Cohen [7] (m)	1981–1987	Retrospective single center	19	Intraop. ultrasonography	NR	NR	18 (95)	19 (100)	9.5 (1–28) months	0	A (16.5)
Rossitch [61] (p)	Since 1952	Retrospective single center	12	NR	Local	4 (33)	6 (50)	0 (0)	10.5 (0.5–38) years[a]	0	B (9)
Sandler [64]	1975–1989	Retrospective single center	21	Intraop. ultrasonography	NR	3 (14)	15 (71)	2 (9)	NR	1	A (15)
Epstein [15]	1982–1990	Retrospective single center	25	Intraop. ultrasonography	NR	25 (100)	7 (28)	6 (24)	38 (4–82) months	0	A (16.5)
Huddart [24]	1966–1989	Retrospective single center	27	Surgery	Local	0 (0)	27 (100)	6 (22)	6.5 (0.1–13.5) years	0	A (21.5)
Minehan [49]	1958–1988	Retrospective single center	79	NR	Local	4 (5)	64 (81)	9 or 12 (11 or 15)[b]	NR	NR	A (18)
Innocenzi [27]	1953–1990	Retrospective single center	65	NR	Local	10 (15)	20 (31)	10 (15)	7.3 (0.5–27) years[a]	7	B (14)
Przybylski [56] (p)	1976–1992	Retrospective single center	18	Surgery + MRI	Local	5 (28)	9 (50)	7 (39)	11 (3–18) years	0	A (20.5)
Jyothirmayi [30]	1984–1993	Retrospective single center	29	NR	Local	0 (0)	29 (100)	6 (21)	51 (7–143) months	0	A (19)
Bouffet [5] (p)	1971–1994	Retrospective 13 centers	73	Surgery + MRI	Central	11 (15)	37 (51)	24 (33)	4.2 (0.4–23) years	3	A (17.5)
Kim [34]	1978–1999	Retrospective single center	30	Surgery + MRI	Local	9 (30)	19 (63)	10 (33)	31.9 (0.5–184) months[a]	2	A (19.5)
Jallo [28]	1988–1994	Retrospective single center	17	Surgery + MRI	Local	12 (70)	9 (53)	0 (0)	86.8 (33–158) months	0	A (19)
Santi [65] (m)	1962–2000	Retrospective single center	36	NR	Local	7 (19)	25 (69)	36 (100)	17 (1–84) months	0	B (14)
Lee [41]	1970–1999	Retrospective single center	25	NR	Local	1 (4)	21 (84)	10 (40)	54 (10–313) months	0	A (18)
Robinson [59]	1980–2003	Retrospective single center	14	Surgery + imaging	Local	1 (7)	10 (71)	0 (0)	10.2 (1.3–23.4) years[a]	0	A (22.5)
Nakamura [51]	1986–2002	Retrospective single center	30	NR	Local	7 (23)	19 (63)	12 (40)	5.5 (1–16.5) years[a]	0	B (11)

Table 2 continued

Author (reference)	Study period	Study type	Patients	Resection assessment	Histology review	GTR (%)	Radiotherapy (%)	HG tumors (%)	Follow-up [median (range)]	Lost to follow-up	Quality (points)
McGirt [46] (m)	1990–2002	Retrospective single center	35	MRI	Local	12 (34)	33 (94)	35 (100)	52 ± 28 months[a]	3	A (21)

p: series of pediatric patients, m: series of high-grade tumors

[a] Mean follow-up

[b] Two different histological classifications applied

studies reported female patients to have better prognosis: Huddart [24] found female patients to have statistically better 5-year OS (100%) compared with male patients (34%; $p < 0.01$), even after stratification by grade. Jyothirmayi [30] reported better 5-year PFS for female patients (90%) when compared to male patients (65%; $p = 0.03$), although difference in 5-year OS was not significant (58 vs. 52%, $p = 0.6$). On the other hand, in the already mentioned pediatric French cooperative study, where gender representation was almost equal, boys fared better than girls (10-year OS 79 vs. 39%, $p = 0.04$) [5].

History length

Results of a statistical analysis of history length as a prognostic factor were reported in 10 studies [5, 22, 24, 27, 30, 34, 49, 59, 60, 64] (Table 6). Of these, eight were classified as category A, five failed to identify significant relationship between history length and outcome [24, 30, 34, 59, 64], as did one additional category B study [22]. Three category A studies in agreement reported increased survival in patients with history length longer than 2 months [5] and 6 months [49, 60]. In addition, one category B study reported decreased 5-year OS in patients with history length shorter than 1 year [27].

Functional status

Statistical analysis reporting functional status as a prognostic factor was reported in eight studies [24, 27, 30, 34, 41, 46, 56, 59] (Table 7). All but one [27] were classified as category A, five did not report any significant relationship between functional status and survival [24, 30, 46, 56, 59]. Two category A studies in agreement reported increased survival in patients with favorable functional status: mean and median survivals were increased for patients with higher preoperative functional status (149.5 and 184 vs. 22.5 and 6 months; $p < 0.05$) and functional status was indentified as the only important prognostic factor among LG astrocytomas [34]. Five-year OS was also significantly increased in patients with favorable neurological function (73 vs. 22%, $p = 0.04$), although the difference in local control and PFS was not significant [41]. In addition, one category B study reported increased survival rates for patients with higher Karnofsky Performance Status [27].

Tumor location

Statistical analysis reporting tumor location as a prognostic factor was reported in nine studies [2, 24, 27, 28, 30, 34, 49, 51, 52] (Table 8). Of these, five were classified as category A, four did not report any significant relationship between tumor location and outcome [24, 28, 30, 34], only

Table 3 Summary of intramedullary spinal cord tumor studies dealing with astrocytoma patients

Author (reference)	Study period	Study type	Astrocytoma patients (all patients)	%	Resection assessment	Histology review	GTR (%)	Radiotherapy (%)	HG tumors (%)	Follow-up [median (range)]	Lost to follow-up	Quality (points)
Kopelson [38]	1962–1979	Retrospective single center	11 (23)	48	Surgery	Local	0 (0)	9 (82)	4 (36)	33.3 (6–105) months	0	B (14)
Guidetti [20]	1951–1978	Retrospective single center	58 (129)	45	Surgery	NR	2 (3)	29 (50)	5 (9)	*1–27* years	6	B (9)
Garcia [18]	1954–1979	Retrospective single center	15 (37)	40	Surgery	NR	*1* (*3*)	15 (100)	NR	*11* (*4–29*) years	2	B (12)
Hardison [22] (p)	1970–1984	Retrospective single center	23 (26)	88	NR	NR	*1* (*4*)	16 (69)	6 (26)	*4.6* (*1–14*) years	0	B (12)
Linstadt [42]	1957–1986	Retrospective single center	15 (42)	36	Surgery	NR	0 (0)	15 (100)	3 (20)	11.2 (4.8–28.2) years	0	B (10)
Cooper [10]	1981–1987	Retrospective single center	18 (52)	35	NR	NR	9 (50)	18 (100)	7 (39)	*38* (*2–72*) months[a]	1	A (15)
Hulshof [25]	1970–1990	Retrospective two centers	13 (50)	26	Surgery	No	0 (0)	12 (92)	3 (23)	*5* (*0.25–19*) years[a]	0	B (13)
Cristante [11]	1984–1992	Retrospective single center	23 (86)	27	Surgery	NR	8 (35)	0 (0)	6 (26)	*4.5* (*0.7–9*) years[a]	1	B (14)
O'Sullivan [54] (p)	1959–1990	Retrospective single center	15 (31)	50	Surgery	Local	NR	15 (100)	3 (20)	*11* (*1.2–26*) years	0	B (12)
Samii [62]	1977–1992	Retrospective single center	37 (100)	37	Surgery + MRI	No	3 (8)	NR	NR	24 ± 34 months	NR	A (17.5)
Shirato [66]	1979–1993	Retrospective single center	13 (36)	36	NR	Local	1 (8)	13 (100)	6 (46)	*3.7* (*0.2–12.3*) years	0	A (16)
Constantini [8] (p)	1980–1993	Retrospective single center	15 (27)	56	Intraop. ultrasonography + MRI	Local, 2 reviewers	*19* (*70*)	3 (20)	3 (20)	*76* (*20–143*) months	*2*	A (20)
Innocenzi [26] (p)	1955–1992	Retrospective two centers	29 (45)	64	Surgery	NR	10 (34)	2 (7)	0 (0)	*3–32* years	NR	B (12)
McLaughlin [47]	1969–1991	Retrospective single center	12 (22)	55	NR	Local	1 (8)	12 (100)	4 (33)	NR	0	B (12)
Rodrigues [60]	1960–1997	Retrospective single center	48 (52)	92	NR	Local	*5* (*10*)	48 (100)	*10* (*19*)	*3.7* (*0.2–27*) years	NR	A (20)
Constantini [9] (p)	1980–1994	Retrospective single center	76 (164)	46	Surgery + MRI	Local, 2 reviewers	*126* (*77*)	*20* (*12*)	18 (24)	*85* (*20–191*) months[a]	*9*	A (20.5)
Raco [57]	1972–2003	Retrospective single center	86 (202)	43	Part MRI	NR	27 (31)	NR	18 (21)	6.7 (0.4–18) years[a]	4	A (19.5)
Abdel-Wahab [2]	1953–2000	Retrospective six centers	57 (242)	24	NR	Central	13 (23)	39 (68)	10 (17)	21 (2–164) months	*59*	A (18)
Nakamura [52]	1994–2003	Retrospective single center	23 (68)	34	NR	Local, 2 reviewers	7 (30)	NR	12 (52)	*6.2* (*2.5–11.4*) years[a]	NR	B (13)

Numbers in italics apply to all patients within the intramedullary tumor series

p: series of pediatric patients

[a] Mean follow-up

Table 4 Age: summary of studies reporting analysis of age as a prognostic factor

Author (reference)	Quality	Year	Patients	Age			Age group	Patients	Outcome studied	Result	Comment
				Median	Mean	Range					
Sandler [64]	A	1992	21	21	NR	0.75–70	Median 31 years	9	Recurrence	Yes (↓)	Advanced age: shorter time to recurrence
							Median 17 years	12		No (↑)	Younger age: no recurrence
Huddart [24]	A	1993	27	31	NR	6–69	<16	5	5-year OS (%)	80	Not significant
							16–39	13		64	
							>39	9		38	
Minehan [49]	A	1995	79	NR	NR	NR	>20	65	Survival	Increased (↑)	p NR
Innocenzi [27]	B	1997	65	NR	34.8	2–68	2–18	12	5-year OS (%)	66	Not significant
							19–50	41		61	
							>50	12		66	
Przybylski [56] (p)	A	1997	18	8.6	9.2	0.6–17.9	NR	NR	Recurrence	No effect	
Jyothirmayi [30]	A	1997	23	NR	31	3–57	<18	5	5-year OS (%)	60	Not significant
							19–39	13		46	
							>40	5		80	
Bouffet [5] (p)	A	1998	73	7	NR	0.25–16	<7	37	10-year OS (%)	76 (↑)	$p = 0.04$
							>7	36		38 (↓)	
Rodrigues [60]	A	2000	48	32	NR	2–76	<18	13	5-year PFS/CSS (%)	100/100 (↑)	$p = 0.03$
							>18	35		43/56 (↓)	
Kim [34]	A	2001	28	36	NR	19–68	19–40	21	Mean/median survival (months)	91.9/–56.2/11.0	$p = 0.209$, not significant
							>40	7			
Jallo [28]	A	2001	17	NR	33	22–61	NR	NR	Recurrence	No effect	
Santi [65] (m)	B	2003	36	26	31.8	3–88	<20	12	Median survival (months)	13 (↑)	$p < 0.001$
							20–40	15		15 (↑)	
							>40	9		3 (↓)	
Lee [41]	A	2003	25	40	28	1–58	"Older age"	NR	5-year LC/PFS/OS	Adverse effect (↓)	"Older age" not defined, increased risk ratio
Robinson [59]	A	2005	14	40.5	40.6	5.2–77.2	NR	NR	5-, 10-, 20-year OS, PFS	No effect	
Abdel-Wahab [2]	A	2006	57	30	NR	1–69	10-year increase	NR	15-year OS/PFS	No effect	
McGirt [46] (m)	A	2008	35	NR	29	2–61	NR	NR	Median survival	No effect	

↑ positive influence on outcome measure, ↓ negative influence on outcome measure, p: series of pediatric patients, m: series of high-grade tumors

Table 5 Gender: summary of studies reporting analysis of gender as a prognostic factor

Author (reference)	Quality	Year	Patients	Gender	*n*	Outcome studied	Result	Comment
Huddart [24]	A	1993	27	M	17	5-year OS (%)	34 (↓)	$p < 0.01$
				F	10		100 (↑)	
Minehan [49]	A	1995	79	M	47	Survival	No effect	
				F	32			
Innocenzi [27]	B	1997	65	M	45	5-year OS (%)	60	Not significant
				F	20		55	
Jyothirmayi [30]	A	1997	23	M	12	5-year PFS/OS (%)	65/52 (↓)	PFS $p = 0.03$
				F	11		90/58 (↑)	OS $p = 0.6$, not significant
Bouffet [5] (p)	A	1998	73	M	37	10-year OS (%)	79 (↑)	$p = 0.04$
				F	36		39 (↓)	
Rodrigues [60]	A	2000	52	M	32	5-year PFS/CSS (%)	No effect	
				F	20			
Kim [34]	A	2001	28	M	19	Mean/median survival (months)	73.5/12	$p = 0.940$, not significant
				F	9		91.8/102	
Lee [41]	A	2003	25	M	13	5-year LC/PFS/OS	No effect	
				F	12			
Santi [65] (m)	B	2003	36	M	23	Median survival (months)	9	$p = 0.410$, not significant
				F	13		11	
Robinson [59]	A	2005	14	M	7	5-, 10-, 20-year OS, PFS	No effect	
				F	7			
Abdel-Wahab [2]	A	2006	57	M	24	15-year OS/PFS	No effect	
				F	33			

M male patients, *F* female patients, p: series of pediatric patients, m: series of high-grade tumors, ↑ positive influence on outcome measure, ↓ negative influence on outcome measure

Minehan [49] found significantly "increased" survival in patients with thoracic spinal cord involvement. In addition, in one category B study, survival of patients with astrocytomas in thoracic location was significantly higher than in cervical location in both LG and HG tumors [51].

Tumor extent

Statistical analysis reporting tumor extent as a prognostic factor was reported in nine studies [2, 5, 24, 27, 28, 34, 41, 46, 59], all but one [27] classified as category A (Table 9). Only Kim et al. [34] found tumor extension of four and more segments to be associated with shorter mean survival (46.1 months) than tumors spanning less than four segments (mean survival 119.6 months; $p < 0.05$). In the other mentioned studies, tumor extent was not associated with prognosis.

Syrinx/cyst presence

Intramedullary peritumoral syrinx or tumor-associated cysts were reported as a prognostic factor in five studies, all were classified as category A [2, 24, 30, 59, 62] (Table 10). The presence of intramedullary cysts was associated with improved 5-year OS (88 vs. 44%, $p < 0.05$) [24] and improved 5-year PFS (100 vs. 70%, $p = 0.03$), although not 5-year OS (67 vs. 43%, $p = 0.06$) [30]. In the other studies, the presence of syrinx was not found to be a statistically significant factor.

Tumor grade

There were 35 studies reporting outcomes for patients according to histological grade, 20 were classified as category A, 15 as category B (Table 11). Comparison between grades was made in 30 articles, 1 study referred to histology as "astrocytoma" [18], 1 study reported outcomes for HG tumors only [7] and 3 for LG tumors only [28, 59, 61]. In 14 studies (10 category A [2, 5, 24, 30, 34, 41, 46, 49, 60, 66], 4 category B [47, 51, 52, 58]), statistical analysis comparing histological grades was performed. Only Shirato et al. [66] did not find statistical significant difference in 3-year OS between LG and HG tumor (80 vs. 40%, $p = 0.0861$). All other articles reported more favorable outcome for LG tumors when compared to HG. One study [46] compared grade III patients with grade IV patients; increased survival rates were found for grade III histology. Results from the remaining studies are summarized in Table 11; LG

Table 6 History length: summary of studies reporting analysis of history length as a prognostic factor

Author (reference)	Quality	Year	Patients	History length			Group	Patients	Outcome studied	Result	Comment
				Median	Mean	Range					
Hardison [22] (p)	B	1987	26	NR	NR	NR	NR	NR	PFS	No effect	
Sandler [64]	A	1992	21	9 months	NR	1 month–4 years	Median 9 months	9	Recurrence	Yes	No effect on recurrence
							Median 8 months	12		No	
Huddart [24]	A	1993	27	1 year	NR	0–25 years	<1 year	14	5-year OS (%)	46	Not significant
							>1 year	13		73	
Minehan [49]	A	1995	79	8 months	NR	1 day–126 months	<60 days	14	Survival	Increased (↑)	p NR
							>180 days	47			
Jyothirmayi [30]	A	1997	23	3 months	NR	2 weeks–6 years	<3 months	10	5-year PFS/OS (%)	68/40	PFS $p = 0.3$
							>3 months	13		92/67	OS $p = 0.3$
Innocenzi [27]	B	1997	65	NR	NR	NR	<1 year	NR	5-year OS (%)	42 (↓)	Significant difference, p NR
							>1 year			71 (↑)	
Bouffet [5] (p)	A	1998	73	2 months	NR	6 days–14 years	<2 months	38	10-year OS (%)	34 (↓)	$p = 0.0003$
							>2 months	35		90 (↑)	
Rodrigues [60]	A	2000	52	9 months	NR	1 week–13 years	>6 months	35	5-year PFS/CSS (%)	63/74 (↑)	PFS $p = 0.02$
							<6 months	17		36/46 (↓)	CSS $p = 0.02$
Kim [34]	A	2001	28	NR	13 months	1 month–6 years	<1 year	23	Mean/median survival (months)	63.8/11	$p = 0.187$
							>1 year	5		143/102	
Robinson [59]	A	2005	14	8 months	NR	0.1–120 moths	NR	NR	5-, 10-, 20-year OS, PFS	No effect	

p: series of pediatric patients, ↑ positive influence on outcome measure, ↓ negative influence on outcome measure

Table 7 Functional status: summary of studies reporting analysis of functional status as a prognostic factor

Author (reference)	Quality	Year	Patients	Scale used	Grade	Patients	Outcome studied	Result	Comment
Huddart [24]	A	1993	27	Cohen [7]	II and III	17	5-year OS (%)	67	Not significant
					IV	10		44	
Jyothirmayi [30]	A	1997	23	Cohen [7]	II	11	5-year PFS/OS (%)	90/82	PFS $p = 0.4$
					III and IV	12		63/33	OS $p = 0.08$
Przybylski [56] (p)	A	1997	18	McCormick [45]	I and II	16	Recurrence	No effect	
					III and IV	2			
Innocenzi [27]	B	1997	65	Karnofsky [33]	80–100	10	5-year OS (%)	75 (↑)	Significant difference, p NR
					60–70	24		65	
					<60	31		51 (↓)	
Kim [34]	A	2001	28	Cohen [7]	I and II	13	Mean/median survival (months)	149.5/184 (↑)	$p < 0.05$
					III and IV	15		22.5/6 (↓)	
Lee [41]	A	2003	25	McCormick [45]	I and II	NR	5-year LC/PFS/OS (%)	NS/NS/73 (↑)	LC $p = 0.088$
					III and IV			NS/NS/22 (↓)	PFS $p = 0.09$
									OS $p = 0.04$
Robinson [59]	A	2005	14	McCormick [45] Karnofsky [33]	Not stratified		5-, 10-, 20-year OS, PFS	No effect	
McGirt [46] (m)	A	2008	35	Modified McCormick [45]	I and II	16	Median survival	No effect	
					III and IV	19			

↑ positive influence on outcome measure, ↓ negative influence on outcome measure, p: series of pediatric patients, m: series of high-grade tumors

Table 8 Location: summary of studies reporting analysis of tumor location as a prognostic factor

Author (reference)	Quality	Year	Patients	Location	Patients	Outcome studied	Result	Comment
Huddart [24]	A	1993	27	C	16	5-year OS (%)	64	Not significant
				Not cervical	10		51	
Minehan [49]	A	1995	79	Th	26	Survival	Increased (↑)	p NR
Innocenzi [27]	B	1997	65	C	12	5-year OS (%)	58	Not significant
				C–Th and Th	45		60	
				Th-L	8		62	
Jyothirmayi [30]	A	1997	23	C	9	5-year PFS/OS (%)	88/74	PFS $p = 0.9$
				Th–L	14		68/42	OS $p = 0.4$
Jallo [28]	A	2001	17	NR	NR	Recurrence	No effect	
Kim [34]	A	2001	28	C and C–Th	20	Mean/median survival (months)	95.9/102	$p = 0.721$
				Th and Th–L	8		67.8/8	
Nakamura [51]	B	2006	30	C	13	10-year OS (%) LG/HG (estimate from Kaplan–Meier)	21/0 (↓)	LG $p = 0.0251$
				Th	16		78/50 (↑)	HG $p = 0.0125$
				L	1			
Abdel-Wahab [2]	B	2006	57	L-Conus	NR	15-year OS/PFS	No effect	
				Cord proper	NR			
Nakamura [52]	B	2008	23	C	NR	5-year OS	No effect	$p = 0.8$
				Th	NR			

C cervical, *Th* thoracic, *L* lumbar, ↑ positive influence on outcome measure, ↓ negative influence on outcome measure

Table 9 Extent: summary of studies reporting analysis of tumor extent as a prognostic factor

Author (reference)	Quality	Year	Patients	Extent	Patients	Outcome studied	Result	Comment
Huddart [24]	A	1993	27	Single site	13	5-year OS (%)	37	$p = 0.06$
				Multiple	14		77	
Innocenzi [27]	B	1997	65	<3 segments	26	5-year OS (%)	61	Not significant
				>3 segments	39		59	
Bouffet [5] (p)	A	1998	73	<7 segments	37	10-year OS (%)	58	$p = 0.61$
				>7 segments	36		63	
Jallo [28]	A	2001	17	NR	NR	Recurrence	No effect	
Kim [34]	A	2001	28	<4 segments	14	Mean/median survival (months)	119.6/– (↑)	$p < 0.05$
				>4 segments	14		46.1/8 (↓)	
Lee [41]	A	2003	25	NR	NR	5-year LC/PFS/OS	No effect	
Robinson [59]	A	2005	14	NR	NR	5-, 10-, 20-year OS, PFS	No effect	
Abdel-Wahab [2]	A	2006	57	<5 segments	37	15-year OS/PFS	No effect	
				>6 segments	16			
McGirt [46] (m)	A	2008	35	NR	NR	Median survival	No effect	

↑ positive influence on outcome measure, ↓ negative influence on outcome measure, p: series of pediatric patients, m: series of high-grade tumors

histology was predictive of better outcome, although formal statistical analysis was not always performed.

Extent of resection

Results for EOR (as assessed by the authors) regardless of histology were reported in 14 studies, 10 were classified as category A [2, 5, 24, 30, 34, 41, 49, 56, 60, 64], 4 as category B [22, 25, 27, 58] (Table 12). In two category A studies, GTR in comparison to lesser resection was associated with significantly reduced risk of recurrence (0 vs. 69%, $p = 0.029$) [56] and with significant risk reduction of 15-year PFS, although not 15-year OS [2]. One additional category B study reported better 7-year OS in patients with subtotal resection (STR) compared to biopsy (100 vs. 42%, $p = 0.02$) [58].

Table 10 Syrinx/cyst: summary of studies reporting analysis of syrinx/cyst presence as a prognostic factor

Author (reference)	Quality	Year	Patients	Syrinx/cyst	Patients	Outcome studied	Result	Comment
Huddart [24]	A	1993	27	Yes	9	5-year OS (%)	88 (↑)	$p < 0.05$
				No	18		44 (↓)	
Samii [62]	A	1994	37	Yes	8	Recurrence	No effect	
				No	29			
Jyothirmayi [30]	A	1997	23	Yes	5	5-year PFS/OS (%)	100/67 (↑)	PFS $p = 0.03$
				No	18		70/43 (↓)	OS $p = 0.06$
Robinson [59]	A	2005	14	NR	NR	5-, 10-, 20-year OS, PFS	No effect	
Abdel-Wahab [2]	A	2006	57	Yes	16	15-year OS/PFS	No effect	
				No	33			

↑ positive influence on outcome measure, ↓ negative influence on outcome measure

Results for EOR specifically for LG histology were reported in 13 studies, 6 were classified as category A [5, 9, 15, 28, 34, 59], 7 as category B [11, 20, 26, 27, 51, 52, 61] (Table 13, upper part). Only one category A study found significantly increased 10-year PFS for patients receiving GTR or STR when compared to partial resection (PR) defined as less than 80% tumor resection, although no such difference was found when comparing GTR with STR [9]. Also, one category B study reported significantly better 10-year OS in patients receiving GTR or PR when compared to biopsy only [51]. In addition, in the study of Epstein (category A), where all 17 patients received GTR, no recurrence was observed during a mean follow-up of 50 months [15].

Results for EOR specifically for HG histology were reported in nine studies, four were classified as category A [5, 15, 34, 46], five as category B [11, 27, 51, 52, 65] (Table 13, lower part). Only one category A study reported increased 4-year OS in anaplastic astrocytoma (grade III) patients [46]; those receiving GTR had significantly improved survival (78% at 5 years) when compared to patients with STR (38% at 5 years, $p = 0.028$). Likewise, no patient with completely resected tumor developed disseminated disease as compared with nine patients (60%) of those receiving STR ($p = 0.01$). However, after adjusting for multiple comparisons, the difference in surgery extent only trended toward significance ($p < 0.007$). Regarding residual tumor volume, the authors reported that increase in each 10% of tumor residual is associated with a 40% increased risk of mortality. Remarkably, radical resection of anaplastic astrocytoma was not associated with increase in postoperative decline in neurological function [46]. In addition, one category B study reported increased 10-year OS in patients receiving GTR or PR when compared to biopsy (80 vs. 32%, $p = 0.0251$) [51].

Radiotherapy

Results for RT regardless of histology were reported in five studies [2, 5, 18, 56, 64], all but one [18] were classified as category A (Table 14, upper part). Statistical analysis comparing irradiated and non-irradiated patients was performed in the four category A studies. No significant relationship was identified in any of them.

Results for RT specifically for LG histology were reported in 16 studies, 9 were classified as category A [2, 5, 10, 28, 34, 49, 59, 60, 66], 7 as category B [25, 27, 37, 42, 47, 51, 54] (Table 14, middle part). Six category A and one category B study reported statistical analysis comparing irradiated and non-irradiated patients, only one (category A) study found statistical significance. Abdel-Wahab et al. [2] found the addition of RT to surgery to significantly reduce adjusted hazard ratio (0.24, $p = 0.02$) in a multivariate model when compared to surgery alone. This difference was significant only for 15-year PFS and not 15-year OS.

Results for RT specifically for HG histology were reported in 12 studies, 7 were classified as category A [2, 5, 7, 10, 49, 60, 66], 5 as category B [27, 36, 47, 51, 65] (Table 14, lower part). Altogether, five studies (3 category A, 2 category B) reported statistical analysis comparing radiated and non-irradiated patients; only one (category A) found statistically significant advantage in survival for irradiated patients with non-pilocytic astrocytoma [49].

Results for RT specified for EOR were reported in six studies, three were classified as category A [5, 24, 30], three as category B [20, 25, 42] (Table 15). Two studies (one category each) reported comparison for radiated and non-irradiated patients. Guidetti et al. [20] (category B) did not find any relationship. Bouffet (category A) found the addition of RT to be associated with decreased

Table 11 Histology: summary of studies reporting outcome according to tumor histology and grade

Author (reference)	Quality	Year	Patients	Histology	Patients	Outcome studied	Result	Comment
Kopelson [38]	B	1980	11	LG	4	5-year/10-year OS (%)	58/23	p NR
				HG	4	All patients		
				Undetermined	3			
Kopelson [37]	B	1982	14	LG	9	5-year OS (%)	89 (↑)	p NR, "grade major factor"
				HG	5		0 (↓)	
Garcia [18]	B	1985	15	Astrocytoma	15	Estimate 5-year/10-year OS (%)	60/50	p NR
						All patients		
Reimer [58] (p)	B	1985	32	LG	27	5-year/10-year OS (%)	80/55 (↑)	$p < 0.001$
				HG	5		0 (↓)	
Hardison [22] (p)	B	1987	23	LG	17	18 months PFS (%)	53	p NR
				HG	6		0	
Cohen [7] (m)	A	1989	19	HG	19	Median survival (months)	6 (1–28)	
Linstadt [42]	B	1989	15	LG	12	5-year/10-year/15-year PFS (%)	66/53/53	p NR
				HG	3	Survival (months)	<8	
Cooper [10]	A	1989	18	LG	11	Deaths	4/11	p NR
				HG	7		7/7	
Rossitch [61] (p)	B	1990	12	LG	12	10-year OS (%)	81.8	
Sandler [64]	A	1992	21	LG	18	5-year OS (%)	68	p NR
				HG	2	All patients		
				Unknown	1			
Epstein [15]	A	1992	25	LG	19	Recurrence (mean FU, months)	0 (50.2)	2 unrelated deaths: 2, 27 months
				HG	6	Death, progression (years)	6 (2)	1 alive, progression at 8 months
Huddart [24]	A	1993	27	LG	19	5-year OS (%)	69 (↑)	$p < 0.05$
				HG	6		33 (↓)	
				Unknown	2			
Hulshof [25]	B	1993	13	LG	10	5-year/10-year OS (%)	58/43	p NR
				HG	3			
Cristante [11]	B	1994	23	LG	17	Recurrence (%)	12	p NR
				HG	6		100	
O'Sullivan [54] (p)	B	1994	15	LG	12	10-year/20-year PFS, OS (%)	83/71	p NR
				HG	3	Survival (years)	16, 10, 1	
Minehan [49]	A	1995	79	Pilocytic gr. I	33	Estimate 5-year OS (%)	82 (↑)	$p < 0.001$
				Pilocytic gr. II	10		75 (↓)	
				Non-pilocytic gr. I–II	24		28 (↑)	$p = 0.05$
				Non-pilocytic gr. III–IV	12		0 (↓)	
Shirato [66]	A	1995	13	LG	7	3-year OS (%)	80	$p = 0.0861$, NS
				HG	6		40	
Innocenzi [26] (p)	B	1996	65	gr. I	29	5-year OS (%)	76	p NR, "significant role"
				gr. II	26		68	
				gr. III	10	5-year OS (%)/ median survival (months)	0/15	

Table 11 continued

Author (reference)	Quality	Year	Patients	Histology	Patients	Outcome studied	Result	Comment
Constantini [8] (p)	A	1996	15	LG	12	Recurrence (%)	25	Statistical analysis not performed
				HG	3		67	
Przybylski [56] (p)	A	1997	18	LG	11	5-year/10-year/15-year OS (%)	88/83/63	5 HG patients alive more than 12 years
				HG	7	All patients		
Jyothirmayi [30]	A	1997	23	LG	15	5-year PFS/OS (%)	81/79 (↑)	PFS $p = 0.03$
				HG	6		33/0 (↓)	OS $p = 0.006$
Bouffet [5] (p)	A	1998	73	LG	49	10-year OS (%)	76 (↑)	$p = 0.00008$
				HG	24		32 (↓)	
McLaughlin [47]	B	1998	12	LG	8	5-year OS (%)	83 (↑)	$p = 0.0001$
				HG	4		25 (↓)	
Rodrigues [60]	A	2000	52	LG	37	5-year PFS/CSS (%)	64/73 (↑)	$p = 0.01$
				IMG or HG	15		20/30 (↓)	$p = 0.004$
Constantini [9] (p)	A	2000	76	LG	58	Estimate 5-year PFS (%)	80	p NR
				gr. III	14		35	
				gr. IV	4		0	
Kim [34]	A	2001	28	LG	18	Median survival (months)	184 (↑)	$p < 0.05$
				HG	10		8 (↓)	
Jallo [28]	A	2001	17	LG	17	5-year/10-year OS (%)	82/82	
Santi [65] (m)	B	2003	36	gr. II → IV	2	Median survival (months)	33	$p = 0.482$
				gr. III	13		10	
				gr. IV	21		10	
Lee [41]	A	2003	25	LG	15	5-year LC/PFS/OS (%)	48/43/78 (↑)	$p = 0.001$
				gr. III	4		0/0/67 (↓)	$p < 0.001$
				gr. IV	6		0/0/17 (↓)	$p < 0.001$
Robinson [59]	A	2005	14	LG	14	5-year/10-year/20-year OS (%)	100/75/60	
						5-year/10-year/20-year PFS (%)	93/80/60	
Raco [57]	A	2005	86	gr. I	27	5-year PFS (%)	91	p NR
				gr. II	41		63	
				HG	18	Mean survival (months)	15.5	
Nakamura [51]	B	2006	30	LG	18	Estimate 5-year OS (%)	88 (↑)	$p = 0.0011$
				HG	12		32 (↓)	
Abdel-Wahab [2]	A	2006	57	LG	40	15-year PFS; HR HG vs. LG	2.67 (↑)	$p = 0.02$
				HG	10	15-year OS; HR HG vs. LG	Univariate: 4.06 (↓)	$p < 0.01$
				Unknown	7	15-year OS; aHR HG vs. LG	Multivariate: 4.86 (↓)	$p < 0.01$
McGirt [46] (m)	A	2008	35	gr. III	27	1-year/5-year OS (%)	85/59	$p = 0.0001$
						Median survival (months)	72 (↑)	
				gr. IV	8		31/0 (↓)	
							9	

Table 11 continued

Author (reference)	Quality	Year	Patients	Histology	Patients	Outcome studied	Result	Comment
Nakamura [52]	B	2008	23	LG	11	5-year OS (%)	64 (↑)	$p = 0.001$
				HG	12		25 (↓)	

↑ positive influence on outcome measure, ↓ negative influence on outcome measure

Table 12 Resection extent: summary of studies reporting influence of resection extent on outcome regardless of histology

Author (reference)	Quality	Year	Patients	EOR	Patients	Outcome studied	Result	Comment
Reimer [58] (p)	B	1985	32	GTR	2	7-year OS (%)		
				STR	22		100 (↑)	$p = 0.02$
				Bio	8		42.7 (↓)	
Hardison [22] (p)	B	1987	25	STR/PR	8	18-month PFS (%)	38	p NR
				Bio	17		41	
Sandler [64]	A	1992	21	GTR	3	Recurrence (%)	0	p NR
				STR	7		43	
				Bio	11		36	
Huddart [24]	A	1993	27	PR/STR	10	5-year OS (%)	73	p NS
				Bio	17		53	
Hulshof [25]	B	1993	13	PR	5	Recurrence (%)	0	p NR
				Bio	8		75	
Minehan [49]	A	1995	79	STR/GTR	24	5-year/10-year OS (%)	NR	$p = 0.081$ in favor of Bio
				Bio	55			
Innocenzi [27]	B	1997	65	GTR	10	5-year OS (%)	80	p NR
				STR	Unclear		59	
				Bio	Unclear		56	
Przybylski [56] (p)	A	1997	18	GTR	5	Recurrence (%)	0 (↑)	FU 5-14 years
				STR/Bio	13		69 (↓)	$p = 0.029$
Jyothirmayi [30]	A	1997	23	GTR/STR	13	5-year PFS/OS (%)	91/68	PFS $p = 0.07$
				Bio	10		58/38	OS $p = 0.09$
Bouffet [5] (p)	A	1998	73	GTR	11	10-year OS (%)	90 (↑)	Univariate $p = 0.08$
				Other	62		64 (↓)	Multivariate NS
Rodrigues [60]	A	2000	52	GTR	5	5-year PFS/CSS (%)	NR	EOR not significant
				STR	20			
				Bio	27			
Kim [34]	A	2001	28	GTR/STR	9	Median survival (months)	113	$p = 0.468$
				PR/Bio	19		102	
Lee [41]	A	2003	25	GTR	1	LC/PFS/OS	NR	LC $p = 0.64$
				STR	5			PFS $p = 0.32$
				Bio	19			OS $p = 0.52$
Abdel-Wahab [2]	A	2006	57	GTR	13	15-year PFS; HR reduction	84% GTR	$p = 0.01$
				Other	40			
				Unknown	4	15-year OS	NS	$p = 0.25$

↑ positive influence on outcome measure, ↓ negative influence on outcome measure

10-year OS for patients receiving GTR or STR (39 vs. 100%, $p = 0.02$). However, no such relationship was found for irradiated/non-irradiated patients receiving PR or biopsy [5].

Dose response

Dose–response relationship was analyzed in 11 studies, 7 were classified as category A [2, 24, 30, 34, 49, 60, 64], 4

Table 13 Resection extent for LG and HG tumors: summary of studies reporting influence of resection extent on outcome for LG tumors (upper part) and HG tumors (lower part)

Author (reference)	Quality	Year	Patients	EOR	Patients	Outcome studied	Result	Comment
Guidetti [20]	B	1981	53	GTR	2	Mean survival (months)	25	p NR
				PR	17		98	
				Bio + myelotomy	29		72	
				Bio + decompression	5		45	
Rossitch [61] (p)	B	1990	12	GTR	4	Recurrence (%)	25	p NR
				STR/Bio	8		37.5	
Epstein [15]	A	1992	17	GTR	17	Recurrence (%)	0	Mean FU 50.2 months
Cristante [11]	B	1994	17	GTR	8	Recurrence (%)	0	p NR
				quasi-GTR	3		0	
				PR	6		33	
Innocenzi [26] (p)	B	1996	29	GTR	10	Mean survival (months)	114	p NR, NS
				STR	11		109	
				Bio	8		84	
Innocenzi [27]	B	1997	29	GTR	10	Median survival (months)	114	gr. I patients
				STR	NR		110	p NR
				Bio	NR		84	
			26	STR	NR	Median survival (months)	72	gr. II patients
				Bio	NR		62	p NR
Bouffet [5] (p)	A	1998	49	GTR/STR	21	10-year OS (%)	67	$p = 0.57$
				PR/Bio	28		76	
Constantini [9] (p)	A	2000	58	GTR	NR	10-year PFS	NR	NS GTR v. STR
				STR				GTR/STR v. PR: $p = 0.0017$
				PR				PR < 80%
Kim [34]	A	2001	18	GTR/STR	NR	Median survival (months)	NR	$p = 0.65$
				PR/Bio	NR		NR	
Jallo [28]	A	2001	17	GTR	12	5-year/10-year OS (%)	82/82	"GTR + STR equally efficacious for long-term survival"
				STR	5	All patients		
Robinson [59]	A	2005	14	GTR/STR	7	10-year PFS/OS (%)	100/100	PFS $p = 0.0746$
				Bio	7		60/60	OS $p = 0.0979$
Nakamura [51]	B	2006	18	GTR/PR	9	Estimate 10-year OS (%)	80 (↑)	$p = 0.0251$
				Bio	9		32 (↓)	
Nakamura [52]	B	2008	11	GTR/STR	6	Survival (%)	100	Not significant
				PR/Bio	5		NR	Small sample size
Epstein [15]	A	1992	6	GTR	6	Recurrence (%)	100	Mean survival 8.6 moths
Cristante [11]	B	1994	17	quasi-GTR	3	Recurrence (%)	100	p NR
				PR	3		100	
Innocenzi [27]	B	1997	10	STR	NR	Median survival (months)	18	gr. III patients
				Bio	NR		14	p NR
Bouffet [5] (p)	A	1998	24	GTR/STR	10	10-year OS (%)	38	$p = 0.63$
				PR/Bio	14		26	
Kim [34]	A	2001	10	GTR/STR	NR	Median survival (months)	NR	$p = 0.91$
				PR/Bio	NR		NR	
Santi [65] (m)	B	2003	36	GTR	7	Median survival (months)	14	$p = 0.118$
				STR	11		18	
				Bio	16		12	

Table 13 continued

Author (reference)	Quality	Year	Patients	EOR	Patients	Outcome studied	Result	Comment
Nakamura [51]	B	2006	12	GTR/PR	5	Estimate 5-year OS (%)	68 (↑)	$p = 0.0342$
				Bio	7		0 (↓)	
McGirt [46] (m)	A	2008	27	GTR	12	4-year OS (%)	78 (↑)	Univariate $p = 0.028$
				STR	15		38 (↓)	Multivariate p NS
								gr. III patients
Nakamura [52]	B	2008	12	GTR/STR	4	Death (%)	50	Not significant
				PR/Bio	8		86	Small sample size

↑ positive influence on outcome measure, ↓ negative influence on outcome measure

as category B [18, 38, 42, 47] (Table 16). Only the study of Garcia et al. (category B) found decreased recurrence rates in patients treated with more than 40 Gy (2 recurrences out of 10) in comparison to patients treated with lesser dose (5 recurrences in 5 patients). Although no formal statistical analysis was performed, the authors recommend dose greater than 45 Gy for radiotherapy of intramedullary astrocytoma [18]. The other studies did not report any statistical significant dose–response relationship.

Discussion

We are forced to admit that the ultimate goal of defining an optimal therapeutic strategy for intramedullary astrocytoma was not answered by our literature review. Natural history of intramedullary astrocytoma is believed to be slowly progressive, although no studies to support this have been conducted. Contemporary treatment of intramedullary astrocytoma starts with surgery which plays several crucial roles. Representative histological sample is obtained allowing a detailed analysis (including genetical tumor characteristics in the near future). Tumor debulking relieves possible mass effect on the surrounding spinal cord tissue allowing functional recovery [8, 9, 15, 28, 34]. Additional dura- and laminoplasty provide space for possible subsequent tumor growth. Smaller residual tumor is present for adjuvant oncological treatment. Intuitively, it seems reasonable to believe that more extensive resection would bring about extended survival; however, more radical resection must not be achieved at the cost of neurological function. Since histological studies have shown the presence of normal neurons within the tumor itself, the possibility of radical resection in infiltratively growing intrinsic tumors is at best dubious [15]. A parallel situation exists in intracranial gliomas, where more or less well-conducted trials have shown that prolonging life expectancy with more radical resection is an achievable goal [63]. On the other hand, intracranial gliomas need not be surrounded by such an eloquent tissue as those in spinal cord, where the concentration of functionally important tracts and cells is much higher per unit of tissue. Thus, no "safety margin" of non-eloquent tissue is available. Decreased functional status as a tax for more extensive resection is associated with decreased quality of life, and even shorter survival [27, 34, 41]. In such context, the advantage gained by more extensive tumor removal is lost. Radical resection can be safely pursued when the tumor shows clearly delineated margin. Further safety from intraoperative neurological injury is brought by the addition of neurophysiological monitoring into the surgical armamentarium [39, 75]. More extensive resection was not associated with neurological decline after surgery [9, 11, 34, 46] (Table 17), preoperative neurological function was the most important parameter for favorable functional outcome [6, 8, 9, 11, 13–15, 26, 41, 51, 52, 57, 62].

Another problem encountered with surgery is the assessment of EOR and definition of GTR. Obviously, pre-MRI studies had to rely on intraoperative impression, sometimes supplemented by ultrasound. Nowadays, only "clean" early postoperative MRI scan should be the standard of GTR assessment, as it is in intracranial glioma surgery. Intraoperative MRI may be the promise of near future in centers with such capability.

One reason why few studies support the advantage of GTR is small number of patients within this treatment group. For statistical purposes, these patients are frequently grouped together with those undergoing less extensive resection (STR or PR) [5, 9, 22, 30, 34, 49, 51, 52, 59] to increase sample size and statistical power. Clearly, treatment efficacy of GTR cannot be detected this way, although inferior results of less extensive resection or biopsy may be proven [51]. Similarly, combining patients with less extensive resection together may overestimate the importance of GTR [2], because the non-radical cohort contains a wide spectrum of surgical results [63]. Obviously, large cohorts of patients where postoperative residual tumor volume would be assessed by MRI may answer this question.

Table 14 Radiotherapy: summary of studies reporting influence of radiotherapy on outcome regardless of histology (upper part), for LG tumors (middle part) and for HG tumors (lower part)

Author (reference)	Quality	Year	Patients	RT	Patients	Outcome studied	Result	Comment
Garcia [18]	B	1985	15	Yes	15	Estimate 5-year/10-year OS (%) all patients	60/50	
Sandler [64]	A	1992	21	Yes	15	10-year PFS/OS (%)	30/57	
				No	6	Survival (%)	100	Median FU 56 months (6-150)
Przybylski [56] (p)	A	1997	18	Yes	9	Estimate 5-year/10-year PFS (%)	45	No analysis performed
				No	9		90	
Bouffet [5] (p)	A	1998	70	Yes	37	10-year OS (%)	61	$p = 0.52$
				No	33		68	
Abdel-Wahab [2]	A	2006	57	Yes	39	15-year PFS HR	0.89	Univariate $p = 0.75$
				No	18	15-year OS HR	2.08	Univariate $p = 0.15$
						15-year OS aHR	1.64	Multivariate $p = 0.38$
Kopelson [37]	B	1982	9	Yes	8	5-year OS (%)	89	
Linstadt [42]	B	1989	12	Yes	12	5-year/10-year/15-year PFS (%)	66/53/53	
Cooper [10]	A	1989	11	Yes	11	Deaths	4/11	
Hulshof [25]	B	1993	10	Yes	10	5-year/10-year OS (%)	58/43	
O'Sullivan [54] (p)	B	1994	12	Yes	12	10-year/20-year PFS, OS (%)	83/71	13% of 2nd malignancy at 20 years
Minehan [49]	A	1995	42	Yes	33	Estimate 5-year OS (%)	85	Pilocytic tumors
				No	9		75	$p = 0.14$
Shirato [66]	A	1995	7	Yes	7	3-year OS (%)	80	
Innocenzi [27]	B	1997	3	Yes	3	Median survival (months)	68	10 patients excluded
McLaughlin [47]	B	1998	8	Yes	8	5-year OS (%)	83	
Bouffet [5] (p)	A	1998	49	Yes	21	10-year OS (%)	93	$p = 0.17$
				No	28		70	
Rodrigues [60]	A	2000	37	Yes	37	5-year PFS/5-year CSS (%)	64/73	
Kim [34]	A	2001	18	Yes	10	Median survival (months)	184	$p = 0.056$
				No	8		102	
Jallo [28]	A	2001	17	Yes	9	OS, PFS	NR	Not significant
				No	8			
Robinson [59]	A	2005	14	Yes	10	OS, PFS	NR	Not significant
				No	4			
Nakamura [51]	B	2006	18	Yes	7	Estimate 5-year OS (%)	80	$p = 0.8855$
				No	Unclear		75	
Abdel-Wahab [2]	A	2006	40	Yes	27	15-year PFS aHR	0.24 (↑)	$p = 0.02$
				No	13	15-year OS aHR	NR	Not significant
Kopelson [37]	B	1982	5	Yes	5	5-year OS (%)	0	
Cohen [7] (m)	A	1989	19	Yes	18	Median survival (months)	6 (1–28)	
Cooper [10]	A	1989	7	Yes	7	Deaths	7/7	
Minehan [49]	A	1995	34	Yes	31	Estimate 5-year OS (%)	22 (↑)	Non-pilocytic tumors
				no	3		0 (↓)	$p = 0.001$
Shirato [66]	A	1995	6	Yes	6	3-year OS (%)	40	
Innocenzi [27]	B	1997	7	Yes	7	Median survival (months)	18	10 patients excluded

Table 14 continued

Author (reference)	Quality	Year	Patients	RT	Patients	Outcome studied	Result	Comment
Bouffet [5] (p)	A	1998	21	Yes	16	10-year OS (%)	31	$p = 0.56$
				No	5		50	
McLaughlin [47]	B	1998	4	Yes	4	5-year OS (%)	25	
Rodrigues [60]	A	2000	15	Yes	15	5-year PFS/CSS (%)	20/30	
Santi [65] (m)	B	2003	34	Yes	9	Median survival (months)	12	$p = 0.856$
				Yes + CHT	7		13	
				No	18		10	
Nakamura [51]	B	2006	12	Yes	5	Estimate 5-year OS (%)	80	$p = 0.3961$
				No	Unclear		0	
Abdel-Wahab [2]	A	2006	10	Yes	8	15-year PFS aHR	1.42	$p = 0.67$
				No	2	15-year OS aHR		

↑ positive influence on outcome measure, ↓ negative influence on outcome measure

Table 15 Radiotherapy and resection extent: summary of studies reporting outcome for radiotherapy specified for resection extent

Author (reference)	Quality	Year	Patients	EOR	RT	Patients	Outcome studied	Result	Comment
Guidetti [20]	B	1981	15	PR	Yes	8	Median survival (months)	101	p NR
					No	7		94	
			24	Bio + myelotomy	Yes	13	Median survival (months)	76	p NR
					No	11		68	
Linstadt [42]	B	1989	12	Conservative	Yes	12	5-year/10-year/15-year PFS (%)	66/53/53	
Huddart [24]	A	1993	27	Conservative	Yes	27	5-year/10-year OS (%)	59/52	
Hulshof [25]	B	1993	10	STR/Bio	Yes	10	5-year/10-year OS (%)	58/43	
Jyothirmayi [30]	A	1997	29	Conservative	Yes	29	5-year/10-year OS (%)	55/39	
Bouffet [5] (p)	A	1998	31	GTR/STR	Yes	16	10-year OS (%)	39 (↓)	$p = 0.02$
					No	15		100 (↑)	
			39	PR/Bio	Yes	21	10-year OS (%)	75	$p = 0.19$
					No	18		43	

↑ positive influence on outcome measure, ↓ negative influence on outcome measure

The addition of radiotherapy to the treatment protocol of LG astrocytoma is controversial. Its application can be rationalized because the predominant pattern of failure is local [60]. A dose–response relationship was identified for patients receiving more than 40 Gy [18], whereas no significant advantage was demonstrated for patients receiving more than 50 Gy (Table 16) [2, 24, 30, 49]. Radiotherapy after non-radical resection in intracranial astrocytomas was shown to prolong PFS, although not OS [32, 70]. Progression of an intramedullary tumor is associated with clinical deterioration and decreased quality of life, thus prolonging disease-free interval is an appealing endeavor. On the other hand, LG astrocytomas are slow growing tumors and radiotherapy may not be as effective on tumor cells which are currently not undergoing mitosis [26]. Furthermore, radiation tolerance of spinal cord is limited, particularly in the presence of an intrinsic tumor, which makes the tissue more vulnerable to injury [35, 44, 71]. Long-term survivors treated with mere biopsy and external decompression were reported in some studies [20, 27, 56]. Following radical resection, reserving radiotherapy for recurrent disease may be a reasonable option [15, 28]. Withholding radiation for infants where spinal cord and skeleton are still developing is also necessary [9]. Long-term survivors after radiotherapy may also be exposed to increased risk of development of a second malignant tumor; 13% risk at 20 years as reported [54]. Some studies also reported decreased survival rates for irradiated patients [56, 64]; referral bias for patients in poorer condition to RT may play a role. Currently, there is no sufficient data in the literature to soundly support or discourage radiotherapy in LG intramedullary astrocytomas and resolve this dilemma.

Adjuvant radiotherapy in HG tumors could be viewed as a necessity in the setting of a known highly malignant and

Table 16 Dose response: summary of studies reporting dose–response relationship

Author (reference)	Quality	Year	Patients[a]	Total median dose/fraction (Gy)	Dose range (Gy)	Dose divide (Gy)	Patients	Outcome studied	Result	Comment
Kopelson [38]	B	1980	9	NR	35–43	NR	NR	Survival	No effect	
Garcia [18]	B	1985	15	NR		<40	10	Recurrence	2/10 (↓)	p NR, deemed important
						>40	5		5/5 (↑)	
Linstadt [42]	B	1989	15	NR	32.5–51.8	NR	NR	5-, 10-, 20-year OS, PFS	No effect	$p > 0.25$
Sandler [64]	A	1992	15	NR/1.8–2	35.2–60	Median 50.25	8	Recurrence	No	Not significant
						Median 55.20	7		Yes	
Huddart [24]	A	1993	27	50/NR	39–55	<50	18	5-year OS (%)	65	Not significant
						>50	9		44	
Minehan [49]	A	1995	64	49.8/1.8	13–66.6	<50	38	Survival	No effect	
						>50	26			
Jyothirmayi [30]	A	1997	23	45/1.8	40–55	<50	15	5-year PFS/OS (%)	52/72	PFS $p = 0.3$
						>50	8		60/87	OS $p = 0.7$
McLaughlin [47]	B	1998	12	50/1.8	30–65	NR		5-, 10-year OS, PFS	No effect	
Rodrigues [60]	A	2001	52	50/2	20–60	50	NR	5-year PFS/CSS	No effect	
Kim [34]	A	2001	19	NR	14.4–55.8	NR	NR	Mean, median survival	No effect	
Abdel-Wahab [2]	A	2006	39	50/1.8	6.7–56	<50	13	15-year OS/PFS	No effect	
						>50	22			

[a] Patients receiving radiotherapy

↑ positive influence on outcome measure, ↓ negative influence on outcome measure

progressive tumor, where the treating physician is trying to extend survival by all possible and available means. Best example is patients treated with radiocordectomy, in which case spinal cord function is sacrificed for extended survival [7, 66]. Although some studies of HG astrocytomas did not find benefit for radiotherapy [2, 5, 51, 65], this can be explained by the aggressive nature of HG astrocytoma rather than as a lack of treatment efficacy.

Chemotherapy in the treatment of intramedullary astrocytoma is not widely used. Few case series reported anecdotal long-term survivors [3, 12, 43, 53, 73]. Chemotherapy was used as a part of a complex oncological treatment regimen after surgery and radiotherapy, not infrequently for recurrent tumor. In the setting of extensive or unresectable tumor, chemotherapy can be considered as a first line of treatment and may avoid or delay the use of radiotherapy for young children and infants [12]. For HG astrocytomas, additional chemotherapy did not lead to extended survival [46, 65]. Hopefully, new chemotherapeutical agents will show more promise in the future.

Despite the wealth of literature concerning IMSCTs, only a small portion reports prognostic factors, while the majority of studies are concerned with functional outcome following more or less radical surgery. Among the factors studied, some findings need to be addressed or emphasized.

As expected, higher tumor grade was consistently reported to be associated with poorer prognosis in nearly all studies reviewed. Likewise, short history length correlated with decreased survival in some studies [5, 27, 49, 60], finding best explained by short history in HG tumors [7]. McGirt [46] also found patients with grade III tumors to have longer symptom duration than those with grade IV tumors. Quite the opposite situation can be found in children presenting with spinal deformities. These take considerable time to develop, with symptoms spanning several years, suggesting slow and indolent tumor growth. Since 10-year survival was reported to be 87% in these patients, aggressive and risky management may not be justified in this patient subgroup [5].

Tumor location in the thoracic spinal cord [49] was associated with increased survival when compared to cervical location [51]. Tumors growing from the thoracic spinal cord take longer time to reach respiratory center leading to respiratory failure (common cause of death

Table 17 Morbidity and mortality: summary of morbidity and mortality in 26 studies reporting this parameter

Author (reference)	Year	Patients	Transient morbidity (%)	Permanent morbidity (%)	Mortality (%)	Function same or better (%)	Comment
Guidetti [20]	1981	58	NR	10 (17)	2 (4)	Unclear	
Reimer [58] (p)	1985	32	NR	NR	2 (6)	NR	
Cooper [10]	1989	18	3 (17)		1 (5)	NR	
Epstein [15]	1992	25	10 (40)	2 (8)	2 (8)	17 (68)	
Hulshof [25]	1993	13	4 (30)		0	8 (62)	
Huddart [24]	1993	27	NR	4 (15)	0	23 (85)	After RT
Cristante [11]	1994	23	88/86%[a]	31/29%[a]	1 (4)	Unclear	[a]From all IMSCT patients, upper/lower extremities similar MM regardless of EOR
Samii [62]	1994	15	Not specified for astrocytoma patients		0	NR	
Minehan [49]	1995	76	NR	NR	3 (4)	NR	
Shirato [66]	1995	13	8 (61)		0	NR	Includes deterioration due to tumor growth
Constantini [8] (p)	1996	15	2 (7)[a]		0	25 (93)[a]	[a]From all IMSCT patients
Innocenzi [26] (p)	1996	29	5 (17)	2 (7)	0	Unclear	
Innocenzi [27]	1997	65	NR	NR	4 (5)	NR	Excluded patients
Przybylski [56] (p)	1997	18	4 (22)	2 (11)	0	12 (67)	Trend for deterioration after GTR ($p = 0.069$)
Jyothirmayi [30]	1997	29	0	7 (24)[a]	0	18 (62); 21 (72)[b]	[a]2 after RT; [b]all after RT
Bouffet [5] (p)	1998	73	NR	NR	3 (4)	NR	
Rodrigues [60]	2000	52	2 (4)		0	50 (96)	
Constantini [9] (p)	2000	76	39 (24)[a]		0	125 (76)[a]	[a]From all IMSCT patients EOR independent of functional decline
Kim [34]	2001	30	4 (13)	2 (7)	0	26 (87)	EOR independent of functional decline
Jallo [28]	2001	17	1 (6)	2 (12)	0	12 (70)	
Lee [41]	2003	25	4 (16)	8 (32)[a]	0	15 (60)	[a]2 after RT
Robinson [59]	2005	14	6 (43)[a]	3 (21)	0	11 (79)	[a]1 after RT
Raco [57]	2005	86	41 (48)		3 (4)	39 (45)	Late follow-up
Nakamura [51]	2006	30	12 (40)		0	18 (60)	
McGirt [46] (m)	2008	35	14 (40)		0	21 (60)	EOR independent of functional decline (GTR vs. STR, $p = 0.957$)
Nakamura [52]	2008	23	12 (52)		0	11 (48)	Late follow-up

among intramedullary astrocytoma patients) than tumors initially located in the cervical spinal cord [51]. On the other hand, thoracic spinal cord has been reported to be more susceptible to radiation damage [40, 55], which may be a cause of considerable morbidity in long-term survivors.

On the first sight, controversial results were found for the prognostic importance of age. Minehan et al. reported age over 20 years at diagnosis to be associated with increased survival contrary to other studies (Table 4). The authors also report better survival for patients with pilocytic astrocytoma when compared to diffuse fibrillary astrocytoma or astrocytoma not otherwise specified. However, only 5 of 14 patients (36%) younger than 20 years had pilocytic astrocytoma, whereas 38 of 65 older patients (58%) had this histological finding. The difference in survival may then be influenced by the greater proportion of more favorable histology among older patients [49].

The French multicenter review of pediatric patients also reported adverse effect of age over 7 years when compared to younger patients. The study did not report histological composition or specified therapy within each age group which could have possibly introduced bias [5]. Other studies that did not find age to be of importance did not report separate results for pediatric and adolescent patients [24, 27, 30] owing to small numbers of patients in this age

Table 18 Best scoring seven studies: summary of significant and not significant prognostic factors as well as conclusions for extent of resection and radiotherapy in studies scoring more than 20 points on quality assessment

Author (reference)	Points	Population	Factors not significant	Favorable significant factors	Conclusion EOR	Conclusion RT
Huddart [24]	21.5	Overall	Age, symptom duration, location, extent, bowel/bladder fct., neurological fct., EOR (Bio vs. PR/STR), Rx dose (50 Gy)	LG, female gender, syrinx/cyst presence	Inconclusive	Helps to achieve LC
Constantini [8] (p)	20	Age less than 3 years	Age, LG glioma vs. ganglioglioma	LG	GTR possible with reasonable MM	Not recommended: infant population
Przybylski [56] (p)	20.5	Children	Age, year of diagnosis, degree of anaplasia	GTR	GTR achieves survival free of relapse	Less than GTR—achieves long-term survival at the expense of frequent relapse
Rodrigues [60]	20	Overall	Gender, EOR, RT dose	Younger age, longer history length, LG	Inconclusive	Should be given to delay progression After GTR may not be necessary
Constantini [9] (p)	20.5	Children and young adults	NR for astrocytoma	LG	GTR and STR (80%+) equally efficacious for 10-year PFS in LG	Not recommended for LG after radical surgery
Robinson [59]	22.5	LG tumors	Age, gender, syrinx/cyst, extent, symptom duration, KPS, neurological fct., EOR, RT use	Trend Bio vs. more extensive resection	Inconclusive	LG: if GTR, RT not necessary Anything less, recommended
McGirt [46] (m)	21	HG tumors	Number of resections, extent, age, CHT use (all for gr. III tumors)	Grade III vs. IV, no tumor dissemination	gr. III: GTR superior to STR	Not stated: HG tumor study

group. Instead, these patients were compared to adults. This comparison obviously cannot detect subtle difference within the youngest group, particularly when sample is small. In addition, pediatric male patients also had significantly better 10-year survival than females in the French study [5], contrary to others [24, 30] where adult female patients fared better. Other authors also reported long-term survival in children with HG tumors (over 10 years) [5, 9, 46, 48, 54, 56] which is rather unusual among adult patients [7, 15, 27, 30, 34, 35, 46, 49, 51, 65]. Thus, it may be possible that pediatric astrocytomas are biologically diverse and the large French study [5] reflected this phenomenon.

Our search strategy and subsequent exclusions yielded 38 articles for detailed study and analysis. Limiting our search to articles published in English inadvertently lead to exclusion of some studies published in other languages. However, we do not believe that these excluded studies would shed any more light on the controversial topic of intramedullary astrocytoma. If a fundamentally important article was missed in the initial search, it would surely be encountered in the reference lists of the reviewed papers and as such would be cited extensively. In fact, articles not found on Medline were discovered by this strategy [19, 48, 72] and neither proved to substantially influence the resulting review. Any newly published article is today most likely to appear on Medline, we used the "What's new" function to ascertain that no such article [46] escaped our attention. The classic work of Slooff et al. [68], although thoroughly studied, was not included in the review, since most of the patients were treated in the first half of previous century, not reflecting modern management methods. This was also the reason why we chose to concentrate on articles published after 1980. In addition, statistical analysis before this date was not as elaborate, and rarely performed, as it is in the recent articles. Furthermore, our intent was to reflect contemporary management of intramedullary astrocytoma, just as did others in intracranial glioma surgery [63]. Performing a historical comparison would be beyond the scope of this article and of limited value to present clinical practice anyway.

Other problem encountered was populations overlapping among numerous articles. For example, we included eight papers from New York University Medical Center or Beth Israel Institute for Neurology and Neurosurgery reporting patients treated by F.J. Epstein and his group [7–10, 15, 19, 46]. Study periods in all of the papers were different and overlapping, numerous patients had to be included in more than one article. Similar situation came around with

University of Rome [20, 26, 27, 57] and Massachusetts General Hospital [37, 38]. We were able to ascertain that all patients reported by Abdel-Wahab et al. [1] were included in the follow-up enlarged study [2], allowing us to concentrate on the more recent study only (Abdel-Wahab, personal communication). The overlapping articles were also the reason why we chose not to perform a systematic meta-analysis, patient double (or perhaps multiple) counting would be unavoidable. Another problem was the inclusion of IMSCTs studies, astrocytoma patients were in many instances not reported as a separate group. Whenever possible, we included these papers, because the reported results were deemed important. The alternative would be inclusion of astrocytoma studies only, such strategy would inadvertently lead to limiting the number of studied articles by half. Our suggestion for future articles dealing with IMSCTs is to report survival and recurrence rates separately for each histological diagnosis and grade, which is of utmost importance for this outcome measure. Surgical results with regard to resection extent, morbidity–mortality and long-term functional outcome may be reported across the whole histological spectrum of all IMSCTs. Surgical technique would be better reflected and comparison across histology is valuable in the context of expected postoperative deterioration and long-term functional outcome (Table 17).

The presented review can only be as good as the studies that form its basis. We have been unable to identify a study with prospective data collection. Moreover, patient exclusion because of incomplete chart review was not infrequent. Such an approach is obviously prone to bias. Thus, the best available level of evidence derived from the presented review is level III. The above statement is not meant as a critique of the reviewed papers, rather it is a reflection of the rarity of intramedullary astrocytoma where series usually span decades and treatment strategies and surgical techniques evolve making comparison in patient subgroups particularly difficult and subject to bias. We have thus adopted and slightly modified (to better reflect nature of intramedullary astrocytoma) previously successfully used methodology [74] to further assess the quality of the reviewed articles. The usually applied levels of evidence would not allow for more detailed discrimination. This approach is not without its failing. The division between category A and B studies was chosen arbitrary at the middle of the scale. We could have chosen more "severe" limit for category A studies (e.g. 20), this would limit the number of articles in this category to 7. To control for this, we summarize major conclusions drawn from these "top" articles in Table 18. Of note, of these seven articles, five dealt with homogenous population—LG or HG tumors, pediatric or infant patients only. Such homogenous population was subject of study in 17 articles, 11 classified as category A (52%) and 6 classified as category B (35%), although this difference was not statistically significant ($p = 0.36$, Fisher exact test).

In order to obtain a larger cohort of patients, the obvious answer is a multicenter cooperation which would ideally, but unlikely, result into a randomized controlled trial. This could evaluate, e.g., the addition of radiotherapy after appropriate patient stratification with regard to resection extent. Results of such a trial would not be available for years (maybe decades) and until that time we have to counsel and treat our patients according to the best knowledge available. An interim solution could be the creation of an international registry of intramedullary astrocytic tumors, where patient and tumor characteristics, surgical complications, resection extent based on MRI, central histology review and survival would be reported in a standardized fashion.

Conclusion

Successful treatment of intramedullary astrocytoma remains a formidable and elusive task. Although patients with LG tumors may enjoy long years without disease progression, recurrence and tumor progression are almost unavoidable. Maximal safe resection as guided by intraoperative neurophysiological monitoring helps to prolong disease-free interval but must not be achieved at the cost of neurological function. Withholding adjuvant radiotherapy after MRI-confirmed radical resection is a reasonable option. Radiotherapy is likely to prolong disease-free interval after non-radical resection; however, there is insufficient data in the literature to further clarify its role in the treatment of LG intramedullary astrocytoma.

Treatment of HG intramedullary astrocytomas is unsatisfactory. More extensive resection possibly delays disease progression. Adjuvant oncological therapy fails to control this aggressive tumor, with the possible exception of a subset of pediatric patients. Since the biological nature of spinal cord HG glioma is identical to those of the brain, it would probably be sensible to implement the same treatment algorithm—maximal safe resection followed by concomitant radiotherapy and chemotherapy.

Although many prognostic factors are reported in the literature, the one and only truly important is tumor grade.

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Note added in proof

Concurrently with revision submission (and subsequent acceptance) of this article, the largest series of intramedullary astrocytomas to date appeared on Medline (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: 727–733). Although the authors are aware of this study, due to this unfortunate timing, this series was not included in the review and readers are kindly asked to turn their attention to it.