Spinal Cord Astrocytomas

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Mirza Pojskić and Kenan I. Arnautović

13.1 Introduction

Astrocytomas are the most common intramedullary tumors in children and occur secondary to ependymomas in adults [1–3]. The great majority of patients with astrocytomas have solitary tumors [3]. However, intramedullary astrocytomas may be encountered together with other spinal tumors in patients with neurofibromatosis type 1 (NF-1) or type 2 (NF-2) [3]. Astrocytomas in adults carry a better prognosis then their pediatric counterparts [4]. They are often infiltrating tumors and radical resection is not always possible [3]. For the purpose of this chapter, we concentrated mostly on low-grade astrocytomas in adults.

Spinal cord astrocytomas have different biomarkers than supratentorial astrocytomas. The 2016 World Health Organization (WHO) classification of tumors of the central nervous system introduced a novel classification for astrocytomas. One characteristic of astrocytomas is a major restructuring of diffuse gliomas with incorporation of genetically defined entities [5, 6]. In the new classification, the diffuse gliomas include WHO grade II and grade III astrocytic tumors, grade II and III oligodendrogliomas, grade IV glioblastomas, as well as the related diffuse gliomas of childhood. WHO grade II diffuse astrocytomas and WHO grade III anaplastic astrocytomas are now each divided into isocitrate dehydrogenase (IDH)-mutant, IDH-wildtype and not otherwise specified (NOS) categories [5].

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-319-99438-3_13) contains supplementary material, which is available to authorized users.

M. Pojskić (✉)
Department of Neurosurgery, University of Marburg, Marburg, Germany

K. I. Arnautović
Semmes Murphey, Memphis, TN, USA

Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, TN, USA

K. I. Arnautović, Z. L. Gokaslan (eds.), *Spinal Cord Tumors*,
https://doi.org/10.1007/978-3-319-99438-3_13

This classification leaves the kinds of astrocytomas that have a more circumscribed growth pattern, and lack IDH gene family alterations and frequently BRAF alterations (pilocytic astrocytoma, pleomorphic xanthoastrocytoma) or TSC1/TSC2 mutations (subependymal giant cell astrocytoma) distinct from the diffuse gliomas [5].

13.2 Epidemiology

Intramedullary spinal cord astrocytomas account for 6–8% of all primary spinal cord tumors [7–11]. Low-grade histologic findings, which include diffuse and pilocytic astrocytomas, are more common (75–90%) than high grade findings, such as anaplastic astrocytomas and glioblastoma [7–11]. Patients present at an average age of 29 ± 18 years with an equal age distribution spanning from 1 week to 69 years [3]. According to the literature, the average patient history can last from 13 to 30 months [3], with a considerably shorter history for malignant astrocytomas compared with benign astrocytomas.

13.3 Molecular Biology and Biomarkers

Astrocytomas arise from glial cell predecessors that infiltrate the spinal cord. These tumors can be divided in subtypes following the new 2016 WHO grading scale: Grade I gliomas (pilocytic astrocytoma and subependymal giant cell astrocytoma), and diffuse astrocytomas (Grade II and Grade III [anaplastic astrocytoma] and Grade IV [glioblastoma multiforme] with their distinct subtypes) [5, 6] The term "low-grade" Astrocytomas is usually reserved for WHO I and II tumors.

Spinal cord diffuse astrocytomas (WHO Grades II and III) are known not to harbor IDH1/2 mutations as do many of their supratentorial counterparts, which suggests mIDH1-IHC may only rarely be of diagnostic help in the context of small biopsies from infratentorial and spinal cord tumors [12]. An H3F3A K27 mutation (histone K27 M-H3.3) was demonstrated in patients with pediatric and adult spinal cord astrocytomas [12, 13].

Spinal pilocytic astrocytomas constitute 90% of intramedullary spinal cord tumors in patients younger than 10 years and 60% of those in adolescent patients [14]. In the spinal cord, BRAF–KIAA1549 fusion genes are common in pilocytic astrocytomas [15]. Deletion of the tumor-suppressor gene cyclin-dependent kinase inhibitor 2A (CDKN2A, also known as p16) was shown as to be a common mutation in pilocytic astrocytomas with loss of heterozygosity (LOH) at 9p21 (which encompasses CDKN2A), or at 10q23 (which encompasses the phosphatase and tensin homologue gene) in 31.6% and 50.0% of pilocytic astrocytomas, respectively [16]. Further genes of interest in the molecular biology of spinal cord astrocytomas are CDKN2A, H3F3A (identified as epigenetic marker of midline or spinal GBM), NF-1, TP-53, ATR-X and PTEN [17].

13.4 Symptoms

Symptoms of astrocytomas of the spinal cord in adults are dependent on the location of the lesion, tumor growth pattern, tumor volume, and histological grade where low-grade lesions have longer history. Most common symptoms of intramedullary tumors are pain, gait ataxia, motor weakness, sensory deficits, dysesthesias, and sphincter problems [2, 4, 9, 18–26]. With malignant tumors, many patients complain about pain, gait ataxia, or motor weakness immediately [3]. A comparison of benign and malignant tumors revealed no significant differences in the clinical picture apart from the considerably shorter history for malignant tumors [3]. Sensory deficits showed negative correlation with survival [27], perhaps because these are less likely to prompt patients to seek medical care, compared with motor deficits, potentially delaying diagnosis and treatment and resulting in worse outcomes.

13.5 Diagnosis

Magnetic resonance imaging (MRI) of the spine with and without gadolinium in axial, coronal, and sagittal projections reveals precise spinal level with the upper and lower border of the tumor, demarcation toward the normal cord, and the orientation of the tumor within the cord, as well as the differentiation between solid tumor and the cyst and syrinx. The resectability of an intramedullary tumor cannot be always predicted by MRI [3]. The extension of the lesion on the sagittal plan calculated on preoperative MRI was reported to be the only predictive factor associated with the immediate postoperative outcome and the short-term follow-up [26]. Presence and pattern of contract enhancement uptake may differentiate between malignant and benign lesions [3]. If a recurrent tumor has to be operated on, functional X-ray may be helpful to evaluate for possible spinal instability, resulting from the previous operation. Furthermore, a computed tomography (CT) scan with bone window, including sagittal and coronal reconstruction, may be helpful to determine exposure of the “healthy virgin” dura, as it demonstrates bony landmarks for the dissection of epidural scar tissue [3].

Astrocytomas often take up contrast inhomogeneously on T1-weighted images. Cysts accompany these tumors less often—42.5% in one series [3]. On axial scans, astrocytomas are often eccentric and may transgress the pia mater to grow exophytically. Astrocytomas may torque the spinal cord and infiltrate spinal nerve roots. Some astrocytomas do not take up gadolinium at all. To determine the exact extension of an astrocytoma, T2-weighted images may be extremely helpful as they tend to show a better demarcation toward normal cord tissue than do T1-weighted images [3]. Specifically, astrocytomas tend to have slightly fewer well-defined margins and are more likely to be eccentrically located within the spinal cord. Lesions on the spinal cord appear as isointense or hypointense when viewed on Tl-weighted imaging, and as hyperintense on T2-weighted imaging; these lesions can be enhanced with contrast despite their low histological grade [7].

Cysts usually accompany high-grade astrocytomas [10]. In contrast to this, syrinx is more specific for low-grade astrocytomas. This could be due to the fact that low-grade tumors have fewer infiltrates than high-grade tumors, resulting in a greater impact on cerebrospinal fluid (CSF) flow [10]. Presence of syrinx and cyst has also been viewed as positive prognostic parameter by some authors [19, 21, 22, 28, 29].

Zhao et al. divided spinal cord astrocytomas according to axial diffusion tensor tractography (DTT) in 2 types [30]: Type I (infiltrative; stage IA with infiltration and stage IB with destruction) and Type II (with displacement; with cysts). Axial diffusion tensor tractography (DTT) showed reliable prediction of resectability in patients with cervical spinal cord astrocytomas with type II tumors being gross totally resected [30].

13.6 Treatment

For treating low-grade primary spinal cord gliomas, gross total resection is considered the best treatment and has an excellent local control rate [3, 31]. The "ideal" goal of treatment should be radical gross total resection of tumor while preserving and improving neurological function to normal. Figures 13.1, 13.2, 13.3, 13.4 and 13.5 show clinical examples of patients with low-grade astrocytomas treated by the senior author (KIA) with radical resection and improved and resolved neurological deficit. There is currently no gold standard treatment for malignant primary spinal cord glioma [10, 20, 32].

Table 13.1 summarizes the available literature on surgically treated spinal cord astrocytomas in adults (1992–2017). We included all studies reporting spinal cord astrocytomas with significant numbers of cases in the series (n > 20) and/or all studies with intramedullary spinal cord tumors that had a significant number of

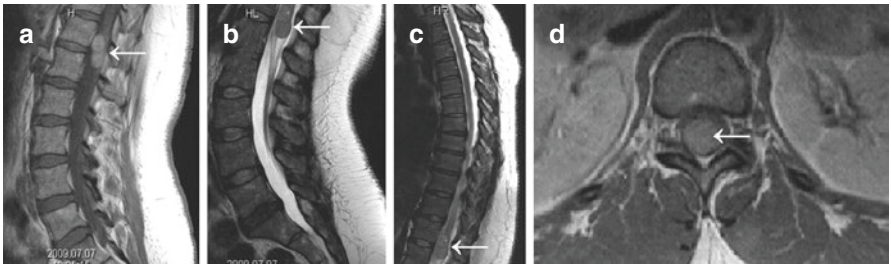

Fig. 13.1 Imaging of a 45-year-old female patient with severe low back pain, weakness of lower extremities, and perineal numbness. MRI of the total spine with and without contrast showed intramedullary lesion in T12–L1. (**a**) Sagittal T1-weighted post-contrast MRI of the lumbar spine shows well-demarcated homogenously enhanced intramedullary lesion (arrow). (**b**) Sagittal T2-weighted MRI of the lumbar spine. (**c**) Sagittal T2-weighted MRI of the lumbar and thoracic spine. (**d**) Axial post-contrast T1-weighted MRI showing the intramedullary tumor at T12. The lesion was resected and the pathohistological diagnosis showed the diagnosis of anaplastic astrocytoma (Grade III)

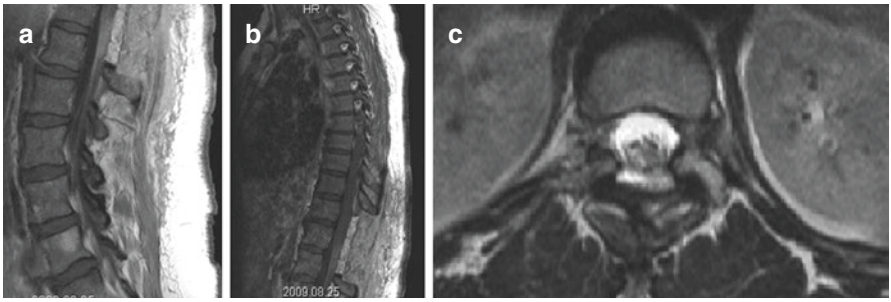

Fig. 13.2 Postoperative MRI of the spine with and without contrast showing the complete lesion resection. (**a**) T1-weighted post-contrast sagittal MRI of the lumbar spine. (**b**) T1-weighted post-contrast sagittal MRI of the thoracic spine. (**c**) T2-weighted axial MRI of the resection cavity at T12

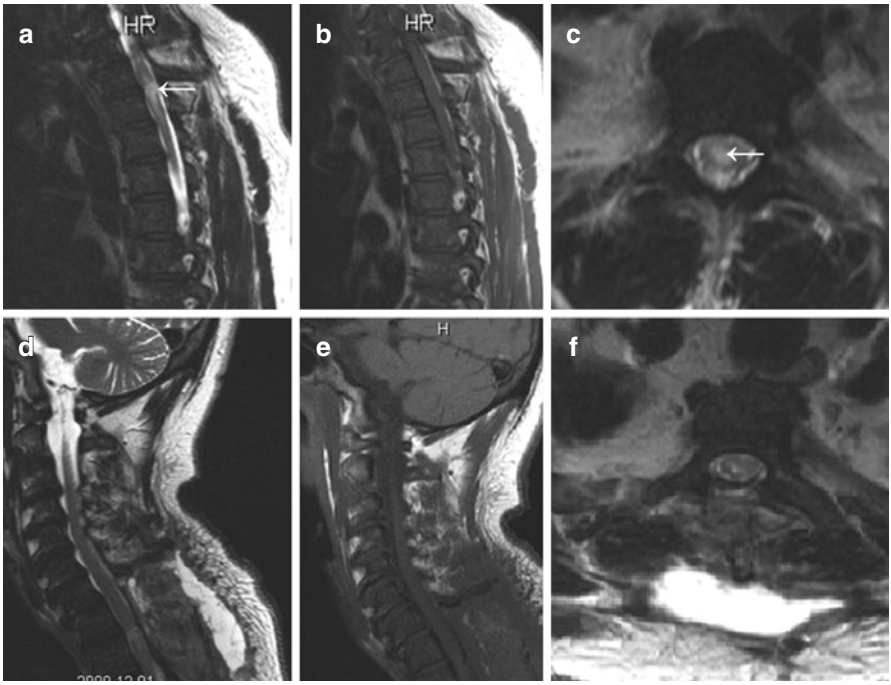

Fig. 13.3 Imaging of a 58-year-old male patient with history of weakness of lower extremities and sensory level at T1. MRI of the total spine with and without contrast showed intramedullary lesion in T1–T2 (arrow). (**a**) Sagittal T2-weighted MRI of the thoracic spine. (**b**) Sagittal post-contrast T1-weighted MRI of the thoracic spine. (**c**) Axial T2-weighted MRI of the intramedullary lesion at T1. The lesion was resected and the pathohistological diagnosis showed the diagnosis of low grade astrocytoma. (**d**) Sagittal T2-weighted MRI showing complete resection of the tumor. (**e**) Sagittal post-contrast T1-weighted MRI of the cervicothoracic spine. (**f**) Axial T2-weighted MRI showing the resection cavity

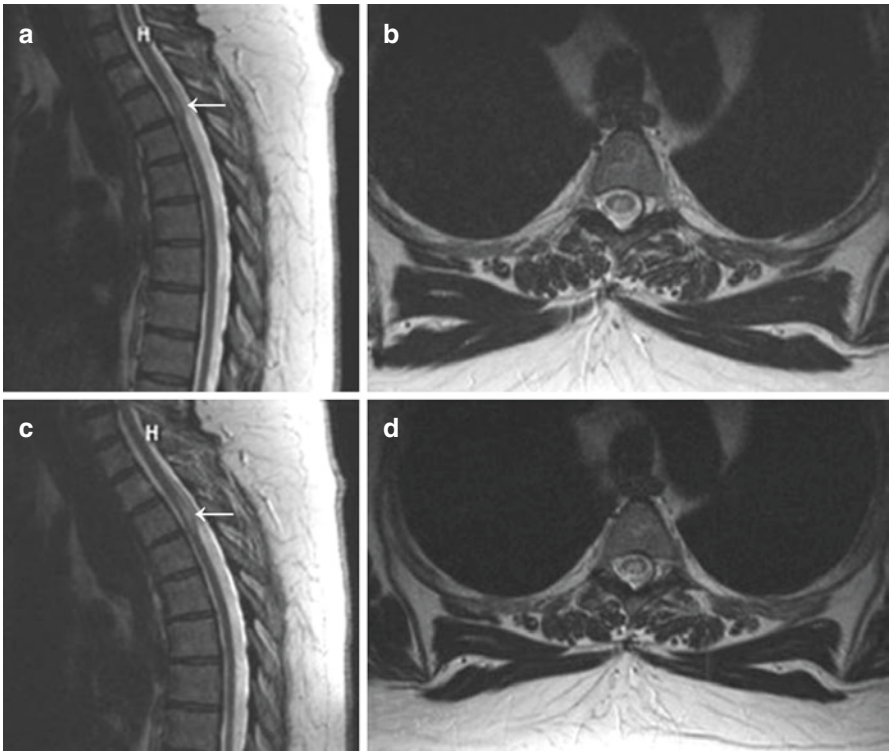

Fig. 13.4 Imaging of a 61-year-old female patient with diabetes and worsening gait. The patient was followed for years with an intramedullary lesion at T1. (**a**) Sagittal T2-weighted MRI of the thoracic spine showing the hyperintense intramedullary lesion at T1 (arrow). (**b**) Axial T2-weighted MRI of the thoracic spine at the same level. (**c**) Six-year follow-up showing growth of the lesion at T1 in sagittal T2-weighted MRI of the thoracic spine (arrow). (**d**) Axial T2-weighted MRI of the thoracic spine

astrocytoma cases. We also included studies with mixed pediatric and adult cohort of patients with spinal cord astrocytomas in which a significant percentage of adult cases were available.

We identified 20 large studies that evaluated surgical results of adult low-grade spinal cord astrocytoma treatment. There is not a single study that evaluated patients with only low-grade pathology; our literature review therefore includes studies that included more than 50% of patients with pilocytic astrocytomas and WHO Grade I and II tumors. Three of these studies included mixed cohorts of adult patients with intramedullary spinal cord tumors that included a significant number of astrocytoma cases [2, 11, 24, 31], and 1 study that evaluated a mixed cohort of adult and pediatric astrocytomas [3].

All of the studies were retrospective. The number of cases ranged from 23 to 136 [29, 33]. The largest study by Minehan et al. included 136 cases of adult spinal cord astrocytomas with mean age of presentation of 34.7 years [33]. This was also the

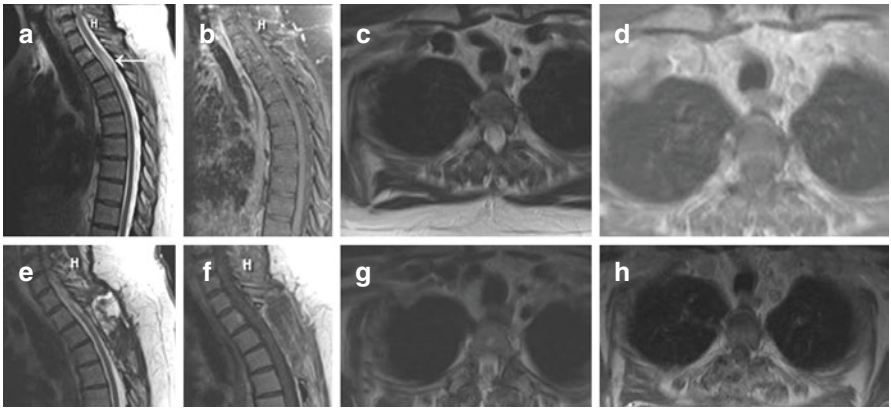

Fig. 13.5 Preoperative post-contrast MRI of the cervical and thoracic spine showing the intramedullary lesion at T1 (arrow). (**a**) Sagittal T2-weighted MRI of the cervicothoracic spine. (**b**) Sagittal T1-weighted post-contrast MRI of the cervicothoracic spine. (**c**) Axial T2-weighted MRI of the cervicothoracic spine. (**d**) Axial T1-weigted MRI of the thoracic spine, post-contrast. The lesion was resected, the pathohistological diagnosis showed low grade astrocytoma WHO Grade II. Post-operative MRI showed the complete resection of the tumor. (**e**) Sagittal T2-weighted MRI of the cervicothoracic spine. (**f**) Sagittal T1-weighted post-contrast MRI of the cervicothoracic spine. (**g**) Axial T2-weighted MRI of the cervicothoracic spine. (**h**) Axial T1-weigted MRI of the thoracic spine, post-contrast

only study with more than 100 cases. Mean age of presentation ranged from 28.3 years to 41 ± 17 years [27, 31]. Younger age was found to be associated with longer progression free survival and local control in 2 studies [34, 35]. There was no significant gender predisposition. There is a slight tendency toward tumor occurrence in the cervical and thoracic region compared with the lumbar spine.

There are currently no prospective studies that evaluate the outcome in patients with spinal cord astrocytomas. However, the current retrospective data allows for several conclusions to be made about surgical treatment. Although gross total resection is considered to be a gold standard for low-grade spinal astrocytomas and extent of surgical resection showed significant association with survival and reduces risk of disease progression [1, 4, 21, 24], studies of low-grade spinal cord astrocytomas are very heterogeneous concerning the treatment modality. In the largest study by Minehan et al., only 16% of patients underwent gross total resection, and only a further 25% underwent subtotal resection [33]. Gross total resection rates vary between 5 and 67% [36] with only 1 study that reported 100% gross total resection [8]. Ardeshiri et al. report 72.7% [37] and Fakhreddine et al. reported a 55% [27] rate of gross total resection, whereas remaining the studies report rates between 12% [18] and 30% [26].

Median overall survival for low-grade astrocytomas was reported between 91 and 156 months (7.58–13 years). Five-year survival for low-grade lesions (WHO Grades I and II) was between 54–78%, whereas the pilocytic astrocytomas examined in 3 studies had a longer median overall survival and 5-year survival up to

Table 13.1 Surgical series on spinal cord astrocytomas in adults 1992–present

Author and year	Patients (No.)	Age	Location	Histology	Resection	Adjuvant treatment	Neurological outcome	Surgical complications	Survival	Prognostic factors favorable for survival and neurological outcome
Epstein et al. 1992 [8]	25	30.2 mean age men, 29.6 mean age women	6 cervical, 11 thoracic, 10 cervico-thoracic	Group A: 19 low grade astrocytoma Group B: 6 anaplastic astrocytoma	Gross total resection in all cases	None	Group A: 12 unchanged, 3 improved, 2 worsened Group B: 4 declined, two remained unchanged	Not specified	Group A: 5/6 died; group B: 2/19 died Rest survived for mean of 50.6 months	Low grade histology
Huddart et al. 1993 [28]	27	Not specified	Not specified	Low grade and high grade astrocytomas	10 partial resection, 17 biopsy	Radio-therapy all patients	8 patients functional improvement, 15 were unchanged and 2 deteriorated	Not specified	Overall 5- and 10-year survival was 59 and 52%, and progression free survival was 38 and 26% at 5 and 10 years	Favorable functional status Low grade histology Female gender Presence of intramedul-lary cysts

Jyothirmayi et al. 1997 [29]	23	31 years	Cervical 5, cervicothoracic 4, thoracic 8, thoracolumbar 6	15 low grade, 6 high grade	Near total excision in 3, partial excision in 10 and biopsy in 10	Radiotherapy all patients	12 had improvement of neurologic status, 9 had stable status, and 2 deteriorated	Not specified	5-year overall survival was 79% for low grade tumors, 10 months for high grade tumors	Favorable functional status Low grade, female sex and intramedullary cyst correlate with PFS
Innocenzi et al. 1997 [38]	65	Median age 34.8 years	Cervical (12) 58% 72 Cervicothoracic and thoracic (45) Thoracic-lumbar (8)	WHO I 29, WHO II 26, WHO III 10 cases	GTR 10, STR 22, biopsy 23	Radiotherapy 20 patients	Not specified	Not specified	Grade I (pilocytic) median survival was 98 months with an actuarial survival at 5 years of 76%. Grade II median survival was 68 months and actuarial survival at 5 years was 68%. Grade III median 15 months	GTR longer survival compared to STR/partial resection Low histological grade and good preoperative and postoperative general condition favorable

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Table 13.1 (continued)

Author and year	Patients (No.)	Age	Location	Histology	Resection	Adjuvant treatment	Neurological outcome	Surgical complications	Survival	Prognostic factors favorable for survival and neurological outcome
Rodrigues et al. 2000 [34]	52	32 mean age	Cervical and/or thoracic spinal cord in 39 (75%) cases, and the cauda equina was involved in another 13 (25%) cases. The average extent of tumor was 4 vertebral bodies	Low-grade in 37 (71%) cases, intermediate-grade in 5 (10%) cases, and high-grade in 10 (19%) cases.	27 biopsy, 20 subtotal and 5 total resection	All patients radiotherapy, 6 chemotherapy	Stable functional status for 48 (92%) patients, improvement in 2 (4%) patients, and decline in 2 (4%) patients	Not specified	Five-year overall, cause-specific, and progression-free survivals were 54%, 62%, and 58%	Low grade histology age < 18 years, length of symptoms prior to diagnosis >6 months

Samii et al. 2007 [22]	65, 38 in adults with 42 operations	29 ± 18 years	18 tumors were located in the cervical cord, 32 in the thoracic, and 15 in the conus area; 31% had an associated syrinx.	27 grade I, 3 grade II, 9 grade III, 3 grade IV	18% complete resection 62% subtotal resection	9 underwent postoperative radiotherapy, 1 patient received chemotherapy, and 1 patient a combination of both.	Improvement 25%, stable and unchanged 58%, worsening of neurological status 17%	Permanent surgical morbidity in 14% of patients	Overall, 87% survived for 1 year and 63% and 57% survived for 5 and 10 years	Most important factor determining long-term outcome was the preoperative level of neurological function survival rates were influenced by local recurrences, histological grade (fig. 3.75), and patient age
Kim et al. 2001 [20]	28	36 years	The cervical cord was involved in 15patients, cervicothoracic in5, thoracic in 6 and thoracolumbar in 2	Low grade 18, anaplastic 3, GBM 7 cases	GTR in 3 patients, STR 6, partial removal in 14 and biopsy only in 5	19 radiotherapy	Not specified	Not specified	The median survivals of patients with low- and high-grade astrocytoma were 184 months and 8 months, respectively	Favorable functional status histological grade predictive of survival

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Table 13.1 (continued)

Author and year	Patients (No.)	Age	Location	Histology	Resection	Adjuvant treatment	Neurological outcome	Surgical complications	Survival	Prognostic factors favorable for survival and neurological outcome
Lee et al. 2003 [35]	25	40 years	6 cervical, 6 cervicothoracic, 24 thoracic and thoracolumbar	15 low grade (WHO I or II), 4 WHO III, and 6 specimens as high grade (WHO IV)	19 biopsy, 5 STR, and 1 had a GTR	22 radiotherapy, 13 chemotherapy	9 patients favorable and 13 unfavorable NF	Not specified	The actuarial OS rate at 5 years for favorable NF at diagnosis was 73%, compared to 22% for patients with unfavorable preoperative NF	PFS and LC were significantly better for young patients and those with lower tumor grade
Raco et al. 2005 [2]	202 patients with intramedullary tumor, 86 astrocytomas (42%)	Not specified	Not specified	27 grade I 41 grade II 18 grade III-IV	Grade I, 22 (81%) total and 5 (19%) partial resection Grade II 5 (12%) complete resection Grade III to IV no complete resection 61% (11 of 18 patients)	Not specified	Grade I: 26% (6 of 23 patients) had improved, 9% (2 of 23 patients) had worsened, and 66% (15 of 23 patients) remained 10% of grade II improved 61% (11/18) grade III-IV worsened	Not specified	Not specified	Low grade histology Complete resection Preoperative neurological status

Nakamura et al. 2006 [23]	30	Mean age 35 years	Cervical level in 13 patients, at the thoracic level in 16 patients, and at the conus medullaris in one patient.	18 low grade, 12 high grade	7 total, 8 partial resection, 15 biopsy	19 patients radiotherapy	Low grade 5 remained fair or better, high grade no change in all except two patients	5/18 low grade fair or better, 10/12 high grade aggravated or no change	The survival rate for all 30 patients with spinal cord astrocytoma was 68% at 5 years and 36% at 10 years	Low grade histology Thoracic region favorable
Abdel-Wahab et al. 2006 [21]	57	30 radiation group, 29 surgery-only group (mean age)	18 cervical, 16 thoracic, 1 conus, 22 overlapping, 2 not specified	Only 42% had review of grade by WHO criteria	13 patients complete resection	39 patients radiotherapy	Unknow for 34 patients; improved in 14, stable in 5 and worse in 4	Not specified	5-, 10 and 15 year survival: 59,53 and 32% Median PFS 44 months	Low grade histology Complete resection reduces risk of disease progression Radiation significantly reduced the risk of disease progression in low- and moderate-grade astrocytomas
Yang et al. 2009 [11]	174 patients, 62 astrocytomas		32 cervical, 30 thoracic	56 low grade, 6 high grade	Total 24, subtotal 22, 16 partial	39 radiotherapy	30 unchanged, 28 improved, 4 deteriorated	1 wound infection, 2 CSF fistulas with revision surgery	96 months follow up: 2/56 and all high grade died	Low grade histology

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Table 13.1 (continued)

Author and year	Patients (No.)	Age	Location	Histology	Resection	Adjuvant treatment	Neurological outcome	Surgical complications	Survival	Prognostic factors favorable for survival and neurological outcome
Minehan et al. 2009 [33]	136	34.7 20.7 years mean age	All but 2 lesions involved either cervical or thoracic level	69 had pilocytic and 67 had infiltrative astrocytoma	Incisional biopsy only (59%), subtotal resection (25%), and gross total resection (16%)	RT was administered to 102 (75%) of the 136 patients,	Not specified	Not specified	Patients with pilocytic tumors survived significantly longer than those with infiltrative astrocytomas (median overall survival, 39.9 vs. 1.85 years;	Pilocytic histologic type, diagnosis after 1984, longer symptom duration, younger age, minimal surgical extent, and postoperative radiotherapy
Fakhreddine et al. 2013 [27]	83	Mean age 28.3 years	56.1% cervical, 69.5% thoracic, 14.6% lumbar	Pilocytic group: 31 WHO grade I infiltrative group: 14 had grade II, 18 had grade III, and 18 had grade IV; 2 patients high-grade (III or IV)	Subtotal or total resection in 55.5%, rest biopsy	Chemotherapy 41.8% Radiotherapy 69.5%	Not specified Patients with infiltrative tumors were also more likely to present with motor deficits		5-year survival times for pilocytic 85.4% and infiltrative patients 36.4%	Tumor grade (pilocytic histology improved OS and grade II improved compared to III compare to IV) Chemotherapy improved PFS in infiltrative astrocytomas

Ardeshiri et al. 2013 [37]	22	16–75, one patient 7 years old	10 cervical 4 cervicothoracic, 5 thoracic, 3 thoracolumbar	15 WHO I 3 WHO II 4 WHO III	16 (72.7%) complete resection	None	Functional and neurological score unchanged in 13 and worse in 9 patients (Frankel score)	None	Follow up 21 months: 25% progression,15% progression, 60% unchanged, 1 died, 1 lost to follow up	Low grade histology cervical location
Klekamp et al. 2013 [31]	225 intramedullary tumors; type B (infiltrating; astrocytomas and gangliogliomas) 80	41+/−17 years	Not specified	Not specified	22.5% were classified as GTRs and 25.0% as STRs	Not specified	Permanent surgical morbidity 21%, 19.3% syringomyelia, 29.5% tumor hemorrhage,	15.9% in entire cohort, CSF fistula most common	Recurrence rate for benign in 10 years 28.8%, malignant 78.2%; GTR/STR 6.3%, partial resection+ biopsy 42.5%; survival not specified	Low grade histology Extent of resection Age correlate to postoperative morbidity

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Table 13.1 (continued)

Author and year	Patients (No.)	Age	Location	Histology	Resection	Adjuvant treatment	Neurological outcome	Surgical complications	Survival	Prognostic factors favorable for survival and neurological outcome
Babu et al. 2014 [18]	46	High grade 27.5, low grade 18.8 mean	Thoracic (47.8%), cervical (28.3%), cervicothoracic (15.2%), thoracolumbar (8.7%)	41.3% had pilocytic astrocytoma (WHO grade I), 21.7% WHO II, 19.6% WHO grade III), and 17.4% (GBM; WHO grade IV).	67.4% resection, of those 12.5% gross total; rest biopsy	Low-grade tumors: 34.5% and 51.7% received radio- or chemotherapy, respectively. High-grade: Adjuvant therapy94.1% and 88.2% being treated with radio- or chemotherapy	45.7% experienced new neurological deficits such as weakness, neuropathic pain, paresthesia/dysesthesia, ataxia, and bladder dysfunction; higher incidence of new deficits in resection cases than those who received biopsy only (54.8% vs. 26.7%); 37% worse than baseline	Number of complications increases with extent of resection	High-grade astrocytoma had a worse median survival time than those with low-grade tumors (28.1 mo vs. median not reached, $P < 0.0001$	High grade histology, tumor dissemination und multiple levels worse prognosis

Seki et al. 2016 [41]	33	Low grade 38.9 years, high grade 42.6 years	Low-grade SCAs cervicothoracic spinal cord (40%), high-grade SCAs occurred most frequently in the thoracic spinal cord (38.5%)	20 low grade, 13 high grade	9 low grade GTR (27.3%)	Low-grade SCA, 15% chemotherapy and 25% All high-grade radiation therapy, nine following chemotherapy	51.5% showed deteriorated neurological status compared to preoperative baseline	Not specified	Median overall survival low grade 91 months, 78% at 5 years vs. high grade 15 months, 31% at 5 years	Low grade: GTR/STR related to better OS High grade histology and neurological status in final follow-up to be significant predictors of poor survival
Ryu et al. 2016 [10]	26	38.9 years mean age	11 cervical 8 thoracic 5 thoracolumbar 2 cervicothoracic	14 high grade 8 low grade 2 cases of malignant transformation	High grade biopsy or partial resection Low grade gross total or total resection	Radiotherapy for high grade tumors	Nurick grade: 58.3% of low-grade patients had a Nurick grade of 1, 2, or 3 85.7% of high-grade patients had a neurological grade of 4 or 5.	None	OS: Low grade 156.38 months High grade 12 months PFS: Low grade 138.85 months High grade 6.64 months	Low grade histology Ki-67 index

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Table 13.1 (continued)

Author and year	Patients (No.)	Age	Location	Histology	Resection	Adjuvant treatment	Neurological outcome	Surgical complications	Survival	Prognostic factors favorable for survival and neurological outcome
Parker et al. 2017 [26]	95 patients	35.6 years	Thoracic in 40%, purely cervical in 28.4%	Grade 1 in 35%; grade 2 in 35%; grade 3 in 22% and grade 4 in 8%	Complete removal in 29.5%	Not specified	During the early postoperative period (3 months) a worsening of functional capacity was observed in 18.4%	Not specified	Probability of survival at 5 years of 78.6% Survival at 10 years is to 76.8%	The preoperative neurological status is the only predictive factor for long-term follow-up

AA anaplastic astrocytoma, *Bx* Biopsy, *CSF* cerebrospinal fluid, *GBM* glioblastoma, *GTR* gross total resection, *KPS* Karnofsky Performance Score, *NF* Neurofibromatosis, *OS* overall survival, *PFS* progression free survival, *SCA* spinal cord astrocytoma, *STR* subtotal resection, *WHO* World Health Organization.

85.4% compared with infiltrative astrocytomas [27, 33, 38]. The strongest predicting factor of functional outcome is the preoperative neurological condition. Pathological grade (i.e., low-grade vs. high-grade), as well as favorable functional outcome, are the strongest predictors of increased survival. Most studies showed that more than 50% of the patients either remain unchanged or worsened following surgery. Adjuvant therapy was performed in most of the patient cohorts with rate of postoperative radiotherapy of 23–100% [3, 34], whereas most patients with higher grades underwent adjuvant radiotherapy or combined radiochemotherapy.

Postoperative neurological decline was reported in 21–57% of patients who underwent resection of the tumor [18, 19, 23, 35, 39]. Interestingly, the majority of series examining adult spinal cord astrocytomas do not specify operative complications, whereas postoperative worsening of deficits is more attributed to the infiltrative growth of the lesion or progression of the disease rather than to surgical events. It has been argued whether neurological decline in astrocytoma cases was a function of surgical resection or tumor growth. However, if the majority of neurological decline was observed at the patient's last clinic follow-up visit and not in the immediate postoperative period, tumor progression may be a possible mechanism of neurological decline [40]. Late morbidity was commonly observed in the form of neuropathic pain syndromes and rarely as a postoperative myelopathy [31].

13.7 Surgical Technique

The details of the surgical resection of a low-grade astrocytoma are demonstrated in our surgical videos (see online edition of this chapter). For the prone position, the patient is first anesthetized in the supine position on a bed or stretcher. To move the patient into the prone position, we use a log roll maneuver. Once the patient has been successfully turned, the head will face down in a head support device. The eyes should be gently taped shut and protected from any pressure. The patient's chin must be free of the table and frame. We prefer to use chest rolls in form of rolled sheets, as they are less traumatic to the breasts in female patients. The arms are positioned at the patient's side with the palms facing the patient and the thumbs down for the cervical and upper thoracic spine location. Anteroposterior cervical spine X-rays are helpful to determine levels in thoracic spine while lateral X-rays illustrate cervical and lumbar locations.

For lower thoracic and lumbar spine locations, we use a Jackson ("Carbon") table and arm-rests with paddings for elbows and axilla areas. To prevent nerve compression, appropriate supportive padding should be used as a general rule under bony surfaces where superficial nerves are known to travel. The armpits, elbows, and hands are padded. The patient's feet should be kept off the bed surface to prevent pressure sores. Padding should be placed under each patella of the knee joints. A pillow should be placed under the ankle joints to elevate the foot to relieve tension on the sciatic nerve and to prevent the toes from resting on the operating room table mattress. Once the positioning is completed, we determine the correct spinal level under fluoroscopic control [3]. Lateral views are more helpful in cervical and

lumbar locations, while anterior-posterior views are more commonly used in thoracic spinal locations. Electrodes for spinal neurophysiologic monitoring are usually placed before turning the patient prone.

We utilize Yasargil bipolar forceps with different progressive lengths and different tip sizes, which we use commensurate with intraoperative distances and surgical situation. Also, we use Yasargil controlled suctions of different sizes with which we can dial the strength of the suction according to intraoperative needs. Micro scissors of different sizes—straight and curved with blunt and sharp tips in different lengths—are used according to intraoperative situation and tactic.

The exposure of an intramedullary tumor is done usually from the posterior-dorsal aspect of the spinal cord with the patient in the prone position. A midline incision is performed in the fascia and the paravertebral spinal muscles are usually split bilaterally from spinous processes and laminas of spine. Small laminotomy [3] or conventional laminectomy can be performed. We recommend laminectomy in the thoracic and lumbar spine when the tumor is confined to 1 or 2 segments. In the cervical spine, a classical or open-door laminoplasty may be the method of choice, particularly if dealing with 3 or more levels or in younger patients. In tumors extending on more than 2 segments, especially in transitional areas (e.g., between cervical and thoracic spine, or thoracic and lumbar spine), additional stabilization may be considered.

The dura is opened in the midline and tacked to the surrounding muscle tissue with dural tacking sutures, usually 4-0 Nurolon (Ethicon, Somerville, NJ). The arachnoid is opened separately with micro scissors or micro knife, and delicately freed from the posterior or lateral spinal cord, keeping it intact for closure at the end of surgery. Ligaclips are applied to hold the arachnoid membrane to the dura. In most instances, the myelotomy is done in the midline. One exception from this rule may be when the lesion is located in 1 dorsal column and is apparent on the surface without any cortical mantle on one side of the spinal cord. Recognition of the midline to perform the myelotomy may be difficult because the spinal cord is frequently rotated and enlarged with loss of definition of the posterior median sulcus. In that situation, recording of sensory-evoked potentials or utilization of the intraoperative ultrasound is helpful to ensure staying on the median sulcus when separating both posterior columns.

If the tumor is located laterally, the dorsal root entry zone may be used for entry. We recommend opening through the posterior median sulcus over the entire length of the tumor (retraction and opening of the dorsal columns as if they were “pages of a book”) as the first step of dissection. This can be done with micro knife or micro scissors to cut the pia mater with the remainder of the cord splitting between the dorsal columns performed usually with blunt instruments, such as utilizing opening spring of Yasargil bipolar forceps. This maneuver is continued to expose the rostral and caudal aspects of the tumor. Next, we use 6-0 Prolene sutures (Ethicon, Somerville, NJ), which we anchor to the edges of the pia mater and suspend to the dura in order to keep the cord open (i.e., “like the book”) and reduce the micro trauma to the cord due to repeated dissection. This maneuver minimizes manipulation of the spinal cord during tumor removal, protects the lateral spinal cord

surfaces from micro injury, and may later facilitate the determination of tissue planes considerably after the tumor has been debulked. The tumor micro dissection in latero-lateral direction rather than superior-inferior direction minimizes micro trauma to the spinal cord and enables easier creation of the tumor-spinal cord margin by sharp dissection. Micro dissectors can also be used for this purpose.

Tumor size reduction may be achieved by either coagulation or debulking of the tumor. Tumor debulking relieves possible mass effect on the surrounding spinal cord tissue, allowing a certain degree of functional recovery. Any lateral dissection attempted at the beginning of debulking carries the risk of applying a lot of pressure to the surrounding cord. Debulking can be done with tumor forceps, sharp dissection, or ultrasound aspiration.

Once sufficient debulking or shrinking of the tumor has been achieved, the tumor margins should be dissected toward the surrounding cord. Often, the tumor infiltrates the spinal cord and searching for a plane that does not exist may represent a risk. In that case, preoperative recording of motor-evoked potentials (MEPs) compared with intraoperative MEPs may be essential for preserving neurological functioning and patient quality-of-life. With infiltrating tumors, debulking is continued as long as the surgeon can remain safely inside the tumor, assess the interface between the tumor and the normal spinal cord tissue, and then attempt to create a sharp margin between the two. Fine forceps, micro-dissectors, or sharp dissection with micro scissors or micro knife can be used to create a margin at the interface between the tumor and the normal spinal cord tissue. However, astrocytomas may be diffusely infiltrating tumors. Therefore, the identification or creation of cleavage planes may be difficult and should be done with the aid of intraoperative use of neuro-monitoring and ultrasound and substantial clinical and operative experience and judgement. The intraoperative finding of a clear tumor plane of resection carries positive prognostic significance. In tumors with ill-defined margins and/or the inability to create them, an ultrasonic aspirator can be used to debulk the mass. Tumor feeding vessels may come from all angles and will not originate from the anterior spinal artery as regularly as in the case of ependymomas. As long as the tissue appears pathologic, debulking can be continued. In some cases, a clear dissection plane can be followed all around the tumor or in most places.

Hemostasis is achieved using bipolar coagulation and surgically as well. Pial closure is done with 7-0 Prolene sutures, and arachnoid closure is done by approximating the edges with bipolar coagulation. Dural closure is performed with 4-0 Neurolon stitches with application of previously harvested fat graft in prevention of cerebrospinal fluid-leak [42].

13.8 Surgical Complications

Complications of the surgery may include cerebrospinal fluid fistula, pseudomeningocele, intraoperative bleeding, spinal cord infarction, epidural hematoma, operative spinal cord injury and edema, immediate postoperative worsening of the neurological deficits, respiratory failure, and wound infection [11, 40]. An overall

rate of permanent surgical morbidity in intramedullary tumors ranges between 18% and 34.6% [31, 36]. It has been reported that the incidence of acute perioperative neurological decline in patients with intramedullary spinal cord tumors increases with patient age, but improves to baseline in nearly half of patients within 1 month. Long-term improvement in motor, sensory, and bladder dysfunction may be achieved in a slight majority of patients, and occurs more frequently in patients in whom a surgical plane can be identified [43].

Cerebrospinal fluid fistulas are a common complication [31]. These fistulas may be avoided by using a tight running suture of the dura and fat graft, and tight sutures of the muscular layers, which appear to be the strongest barrier against cerebrospinal fluid [31, 42]. We use 4-0 Nurolon stitches for dural closure, checking for possible cerebrospinal fluid leak by using a Valsalva maneuver exercised by an anesthesiologist and applying previously harvested fat graft from the abdomen for watertight suture [42]. This fat graft utilization helps prevent pseudomeningocele and also epidural hematoma formation by eliminating the "dead space" created after laminectomy and also negative pressure that may favor cerebrospinal fluid leak.

In patients undergoing a second operation on a tumor, the muscles may be atrophic from the previous operation and may no longer provide a good barrier against leakage. Transient neurological deficits are not uncommon. Postoperative sensory deficits may be a consequence of the myelotomy required to reach an intramedullary tumor [31]. The longitudinal extent and, thus, the length of the myelotomy were found to correlate with postoperative sensory dysfunctions in several studies [31, 44]. Postoperative tethering can be seen in up to 37% of postoperative MRIs [31], but only about 5% of these patients developed clinical signs of myelopathy unrelated to tumor progress [31]. Nine out of 15 patients in one series experienced immediate worsening of neurological status postoperatively with an increased paresis and aggravated sensory deficit in which MRI was uneventful in all of these cases [44]. New neurological deficits, especially ataxia, could improve over time [42]. In their series, Klekamp et al. reported that long-term morbidity affected 3.7% patients with a postoperative myelopathy related to cord tethering at the level of surgery, and 21.9% in the form of neuropathic pain syndromes [31]. The rate of postsurgical cord tethering could be lowered significantly by using pial sutures after tumor resection. Neuropathic pain syndromes were more common after surgery for tumors with associated syringomyelia or those located in the cervical cord [31].

Complications associated with prone position may include ophthalmic injury and pressure injuries [45]. Ophthalmic injuries include retinal artery occlusion, corneal abrasion, and ischemic optic neuropathy with postoperative visual loss [46]. Pressure injuries include pressure necrosis of the skin, contact dermatitis, tracheal compression, salivary gland swelling, mediastinal compression, visceral ischemia, peripheral vessel occlusion, and limb compartment syndromes. Deep venous thrombosis (DVT) with venous air embolism (VAE) may also occur in patients in the prone position with the reported range of 10–25% [47]. Complications due to anesthetic technique include dislodgement of the endotracheal tube, which can be prevented with use of non-kinking endotracheal tube [48].

13.9 Extent of Resection

Gross total resection is a gold standard in surgery of low-grade astrocytomas. Extent of surgical resection shows a significant association with survival and reduces risk of disease progression [1, 4, 21, 24]. It is mainly reserved for pilocytic and for WHO Grade II tumors [3, 22]. Low-grade astrocytoma complete resection rates vary between 5% and 67% [36] (Table 13.1). One large study on surgical treatment of intramedullary spinal cord tumors showed that an intraoperatively identifiable tumor plane and decreasing tumor size were associated with gross total resection independent of histological tumor type [43].

Various studies reported postoperative neurological decline in 21% to 57% of patients who underwent resection of the tumor [18, 19, 23, 35, 39]. The most important factor in predicting gross total resection are preoperative neurological status or high preoperative McCormick grade [31]. Other strong predictors were adult age, a high spinal level, presence of a syrinx, and first surgery on the tumor. The remaining factors predicting gross total resection were benign histological grade, no arachnoid scarring, a short preoperative history, and an experienced surgeon [31].

Increasing rates of complete resection in patients with intramedullary astrocytomas might be the result of a combination of increased surgical experience, refinements in surgical techniques and the routine use of electrophysiological monitoring during surgery, which encourage the surgeon to a more radical approach [37].

13.10 Specific Surgical Aspects

13.10.1 Management of Blood Pressure during Spinal Surgery

Keeping normovolemia is mandatory to avoid intraoperative hypotension [49]. The prone position during spinal surgery is associated with reduced stroke volume, cardiac index, raised central venous pressure, and low blood pressure [46]. It is important to maintain euvolemia and monitor fluid responsiveness by pulse pressure variation and stroke volume variation [50]. An arterial line is also recommended as a means to monitor real-time blood pressure as well as monitor of intravascular volume (central venous or pulmonary artery catheter). Moderate degrees of hypotension (80–90 mmHg systolic, 20–30% below baseline) are efficacious at reducing blood loss in patients with major spinal surgery, and safe in any patient without specific risk factor [51].

13.10.2 Intraoperative Ultrasonography and Ultrasound-Based Neuronavigation

The first reports on the application of US-based neuronavigation systems in spinal cord surgery showed good utility of this method in guiding the surgical resection [52, 53]. However, its application has been shown to be useful only in resecting extramedullary tumors as the implementation of 3D sonography in intramedullary

tumors would be possible after the elimination of motion artifacts caused by respiration [54]. Use of non-navigated intraoperative ultrasonography with use of high-frequency linear probes (10–12 MHz) was beneficial in confirmation of tumor location and extension, planning myelotomy, and estimation of degree of resection of the intramedullary tumors. They were particularly helpful in guiding the approach to redo surgeries for recurrent spinal cord tumors [55].

13.10.3 Intraoperative Monitoring

Modern surgery of spinal cord astrocytomas is performed with neuro-monitoring. The preservation of MEPs correlates closely with postoperative motor function. A decline of 50% or more in MEPs amplitude is a warning sign that the tumor is almost infiltrative [56]. Setting the critical point to loss of MEP waveform and a 50% reduction of the D-wave yields better surgical outcomes compared with changes in SSEPs, which means surgery should be abandoned when these values are reached [57]. Suspending surgery when the waveform becomes aggravated and recontinuing later when the waveform has improved or abandoning the resection altogether when the waveform becomes multiphasic again or is lost leads to better postoperative outcomes in gait of patients with intramedullary spinal cord tumors [58]. Furthermore, neuro-monitoring assists in various steps of the surgical resection, even at the beginning of the surgery in finding the midline, which can be displaced by large and cystic tumors [56]. Real-time monitoring with constant free-running electromyography is also performed intraoperatively, which is useful for monitoring nerve root irritation and compression [58, 59]. Again, neuro-monitoring is a great and important intraoperative tool, but the final judgement on the extent of surgical resection, intraoperative maneuvers, and tactics rests on shoulders of an operative neurosurgeon.

13.10.4 Fluorescein Guided Surgery

Several studies suggested that the use of 5-ALA (5-aminolevulinic acid) fluorescence could be beneficial, especially in intramedullary gliomas [60]. Bright intraoperative fluorescence marking the border between the tumor and the spinal cord tissue was shown with use of fluorescein in pilocytic astrocytomas but was absent in Grade II astrocytomas [61]. This study showed that gadolinium uptake in T1-weighted MRI sequences could be shown intraoperatively as a fluorescent mass, using SF (salt mass of fluorescein) with a dedicated filter in the surgical microscope [61].

13.10.5 Postoperative Instability of the Spine

Laminoplasty is a safe method that preserves spinal stability and can be used in patients with tumor extension of 2 or more levels [44, 62]. Laminoplasty and

laminectomy were associated with similar functional outcome scores in one study [44]. It has been assumed that adult patients with astrocytomas are at low-risk for postoperative kyphoscoliosis following laminectomy [7]. Laminoplasty for the resection of intradural spinal tumors was not associated with a decreased incidence of short-term progressive spinal deformity or improved neurological function [63]. However, it may be associated with a reduction in incisional cerebrospinal fluid leak [63].

13.11 Surgical Outcome and Survival

We differentiate 2 types of outcome in the surgery of spinal cord astrocytomas: *surgical outcome* and *overall outcome.* Surgical outcome assesses the following: A) The neurological status after the surgery by noting deficits, or using Nurick Grade, McCormick Scale, or Frankel scale), B) Extent of resection, and C) complication rate. *Overall survival* is influenced mainly by the histological type of the tumor. Table 13.1 summarizes the most important surgical series of the spinal cord astrocytomas.

13.11.1 Surgical Outcome

Over the course of the past 30 years preoperative diagnostics, surgical technique, and intraoperative neuro-monitoring has significantly developed so that the reported results of surgical outcome show significant positive trends. Permanent surgical morbidity has now been reported between 14 and 21%, and most studies show that more than 50% of patients either remain unchanged or worsen following surgery (Table 13.1). The strongest predicting factor of functional outcome is the preoperative neurological condition [36, 64]. The timing of surgery is one of the crucial points for good outcome; these lesions should be operated before neurological deterioration occurs [56, 65].

13.11.2 Survival

Survival rates were shown to be influenced by histological grade, local recurrences, and patient age [3, 66]. One study reported a median survival time for pilocytic astrocytomas of 39.9. years [33]. Median overall survival for low-grade astrocytomas was reported between 91 and 156 months (7.58–13 years). Five-year survival for low-grade lesions was between 54–78%, whereas high-grade astrocytomas had overall survival between 9 months and 1.85 years (Table 13.1).

Pathologic grade is the strongest prognostic factor of overall survival and progression free survival in spinal cord astrocytoma [9, 10, 20, 21, 28, 29, 39]; however, it is not always concordant with biologic behaviors [10, 21]. Studies have shown more favorable outcome for low-grade tumors when compared with high-grade tumors,

one of which showed increased survival rates for Grade III tumors compared with Grade IV tumors [39]. Furthermore, increased survival was shown in patients with favorable functional neurological outcome [19, 20, 28, 29, 35, 39].

Some studies stated that neither progression-free intervals nor survivals were influenced significantly by the amount of resection, provided that a "good" reduction of tumor volume to decompress the spinal cord was achieved [3, 8, 19, 20, 43, 67]. Given that low-grade astrocytomas were more likely to be grossly or totally resected than high-grade astrocytomas, surgical extent of resection alone may be a too simplistic as a prognostic factor [10].

Gender and race seem not to significantly influence survival [9, 19–21, 34, 35]. Female sex was found to influence 5-year overall survival and progression-free survival in two studies [28, 29]. In contrast, one population-based analysis showed male sex to be predictive of favorable outcome [4, 68]. Most studies so far fail to find correlation of age to survival [21], although Sandler et al. found patients with tumor recurrence to be older [69], and Lee et al. reported that older age adversely affects local control, progression free survival and overall survival [35]. Only one series showed correlation of cervical location of the tumor with better functional outcome [37] while two studies have shown positive correlation of thoracic region with survival [9, 23]. Increased survival in patients with longer history was reported only in two studies [9, 34].

13.12 Recurrence and Malignant Transformation

Evaluation of tumor recurrence rates for astrocytomas revealed low spinal level, malignant grade, and adult age as important independent predictors. Recurrence rate of astrocytomas after 10 years is between 42 and 48% [31, 40]. The rates correlated with the histological grade and the amount of tumor resection. One series showed the recurrence rate of 6.3% after gross total resection or subtotal resection within 10 years, whereas partially resected or biopsied tumors recurred at a rate of 42.5% over the same time period [31]. Malignant transformation to anaplastic astrocytoma or to glioblastoma with extraneural metastases has been described [10, 28, 70].

We recommend postoperative follow-up after 3, 6, and 12 months post-surgery with MRI of the spine with and without contrast followed by yearly MRI evaluations. A postoperative regular follow-up for low-grade lesions is mandatory for at least 10 years due to the risk of recurrence [26].

13.13 Adjuvant Treatment

13.13.1 Radiation Therapy

The value of postoperative radiotherapy for low-grade astrocytomas remains controversial. The postoperative course of incompletely removed low-grade astrocytomas is considered by most neurosurgeons as being so benign that radiotherapy

could be withheld and repeated surgeries undertaken [4, 27, 70]. A great number of low-grade astrocytomas remain stable over years, if not decades, without any adjuvant therapy [56]. Samii et al. advise radiotherapy for patients with WHO Grade III and IV tumors only [3]. Following radical resection, reserving radiotherapy for recurrent disease may be a reasonable option [8, 67]. In some series [69], overall survival of high-grade patients who had undergone radiation therapy was shorter than that of those who had not [10, 69]. The major factor influencing long term clinical course and survival is the histological grade and not the mode of treatment [28]. Addition of radiotherapy can be can be rationalized because the predominant pattern of failure is local [34]. Postoperative radiotherapy for intramedullary astrocytomas may be recommended for temporary local control [28] since radiation has been shown to significantly reduce the risk of disease progression in low and moderate-grade astrocytomas [21] and to improve survival in infiltrative astrocytomas [33].

13.13.2 Chemotherapy

As malignant tumors in this localization are very rare, hardly any single institution acquires enough patients to perform an appropriate prospective study [28, 32]. Survival benefits of temozolomide (TMZ) after radiotherapy in patients with malignant primary spinal cord tumors were shown in small series with fewer than 25 patients [32, 71]. Chemotherapy was significantly associated with improved progression free survival, yet not overall survival [27]. Chamberlain et al. showed that TMZ, when has modest efficacy as reflected in progression free survival (18-month progression free survival, 41%, 24-month progression free survival, 27%) and median survival (23 months) for recurrent adult spinal cord astrocytoma who already underwent surgery and radiotherapy [71]. One study showed that in patients with infiltrative astrocytomas, chemotherapy was significantly associated with improved progression free survival but not overall survival [27]. Other studies showed that additional chemotherapy did not lead to extended survival in high grade astrocytomas [39, 70].

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