Neuro-Oncology Advances

Astrocytomas of the spinal cord

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Abstract

Tumors of astrocytic origin represent one of the most frequent entities among the overall rare group of spinal cord gliomas. Initial clinical symptoms are often unspecific, and sensorimotor signs localizing to the spinal cord occur with progressing tumor growth. On MRI, a hyperintense intrinsic spinal cord signal on T_2-weighted sequences with varying degrees of contrast enhancement raises suspicion for an infiltrative neoplasm. Blood and CSF analysis serves to exclude an infectious process, nutritional deficits, or metabolic disorders. When such other differential diagnoses have been ruled out, a neuropathological tissue-based analysis is warranted to confirm the diagnosis of a spinal cord astrocytoma and guide further patient management. As such, maximal safe resection forms the basis of any treatment. Meticulous preoperative planning is necessary to weigh the potential improvement in survival against the risk of functional deterioration. Intraoperative neuromonitoring and ultrasound may aid in achieving a more extensive resection. Depending on the assigned WHO tumor grade spanning from grade 1 to grade 4, the use of radiotherapy and chemotherapy might be indicated but also wait-and-scan approaches appear reasonable in tumors of lower grade. Close imaging follow-up is necessary given that recurrence inevitably occurs in astrocytomas of grades 2–4. Prognosis is so far dictated by tumor grade and histopathological findings, but also by age and clinical performance of the patient. Targeted therapies resting upon an in-depth tissue analysis are emerging in recurrent tumors, but no prospective study is available so far given the rarity of spinal cord astrocytomas.

Keywords

astrocytoma | glioma | outcome | spinal cord | surgery | therapy

Definition, Epidemiology, Clinical Findings, and Diagnosis

Among all CNS tumors, astrocytomas of the spinal cord are rare. However, within the group of intramedullary gliomas, nearly 30–40% of all tumors are of astrocytic origin.[1–3] In children, such tumors represent the most frequent intramedullary entity with 40–60% of all pediatric spinal cord neoplasms.[1,4,5] In contrast, intramedullary oligodendrogliomas are extremely rare, with an incidence of 2% of all tumors arising from the spinal cord.[6] Their diagnosis and management do not differ from astrocytomas (with the caveat that due to the paucity of cases, reliable data are lacking) and therefore these tumors are not mentioned separately in this text.

Medullary astrocytomas are classified according to their histological features using the World Health Organization (WHO) classification system (WHO grades 1–4).[7] Pilocytic astrocytomas are being assigned to grade 1, diffuse or fibrillary tumors to grade 2, anaplastic astrocytomas to grade 3, and spinal glioblastomas (GBM) to grade 4.[8,9] The majority of intramedullary astrocytomas are graded as WHO grades 1 and 2, identifying with a far better prognosis than tumors grades 3 and 4 which account for roughly 25% of all cases.[8] As such, pediatric tumors are low-grade pilocytic astrocytomas,

and high-grade lesions are somewhat more frequent in adults.[1,10,11] More recently, updated guidelines incorporate genetic markers into the grading system, in addition to traditional histological features (see below).[7]

Clinical Presentation

Most intramedullary gliomas initially present with nonspecific clinical symptoms (eg axial back pain, unspecific sensations, or radiculopathy) which may direct the diagnostic workup towards more common spinal pathologies.[12] Localizing signs including ataxia, nonradicular paresis, and/or sensory deficits should initiate a more elaborated neurological workup including an MRI of the spine. Despite being often mentioned in textbooks, bowel and bladder dysfunction is rare as an initial symptom.[13,14]

Diagnostic Workup and Imaging Findings

Progressive neurological deficits including ataxia and especially a gradual development of a transverse syndrome should trigger a meticulous neurological workup. At each stage, an MRI is mandatory to reveal or exclude a medullary pathology.[15] In addition, an electrophysiological examination might help to uncover the underlying disease by further confirming the clinical suspicion of an exclusive intramedullary process. Furthermore, when a neuroinflammatory disease might be considered as a differential diagnosis (either due to clinical symptoms, neuroimaging findings, or electrophysiological results), the cerebrospinal fluid should be analyzed prior to any biopsy, especially in cases with profound symptoms and rather small medullary lesions. A blood analysis serves to exclude a systemic inflammatory process, nutritional deficits, metabolic disorders, or an immunocompromised state mimicking an infiltrative intrinsic spinal cord neoplasm.

Intramedullary astrocytomas grades 2–4 typically present as hypo or isointense lesions on T_1-weighted, hyperintense on T_2-weighted MRI, and can include syrinx formation.[14] These tumors are often asymmetrical and located off-center with a preponderance to cervical and cervicothoracic localizations. Juxta-lesional hemorrhage is rather rare in astrocytomas of adulthood and may therefore raise suspicion for an ependymoma, an intramedullary metastasis, or a cavernoma. The typical intramedullary astrocytoma in adulthood has no clear demarcation indicating its invasive growth. Contrast enhancement of varying degrees might be seen, but selected cases may also present as exclusively nonenhancing lesions. In children, pilocytic astrocytomas grade 1 are the most frequent entity. They present with a rather sharp delineation, often cystic components and may also have small areas of (previous) hemorrhage (Figure 1). PET—imaging utilizing radiolabeled amino acids in medullary lesions is, up to now, is limited regarding spatial resolution. Nevertheless, small series report an additional benefit in some cases with difficult differential diagnoses.[16,17] This may get better with the evolving use of PET–MRI technology.[18] Machine learning techniques can be applied to classify the tumor's malignant status or automatically segment the spinal cord to quantify the tumor morphology.[19,20]

Such technologies may aid in the visualization of metabolic hotspots extending beyond the contrast-enhancing
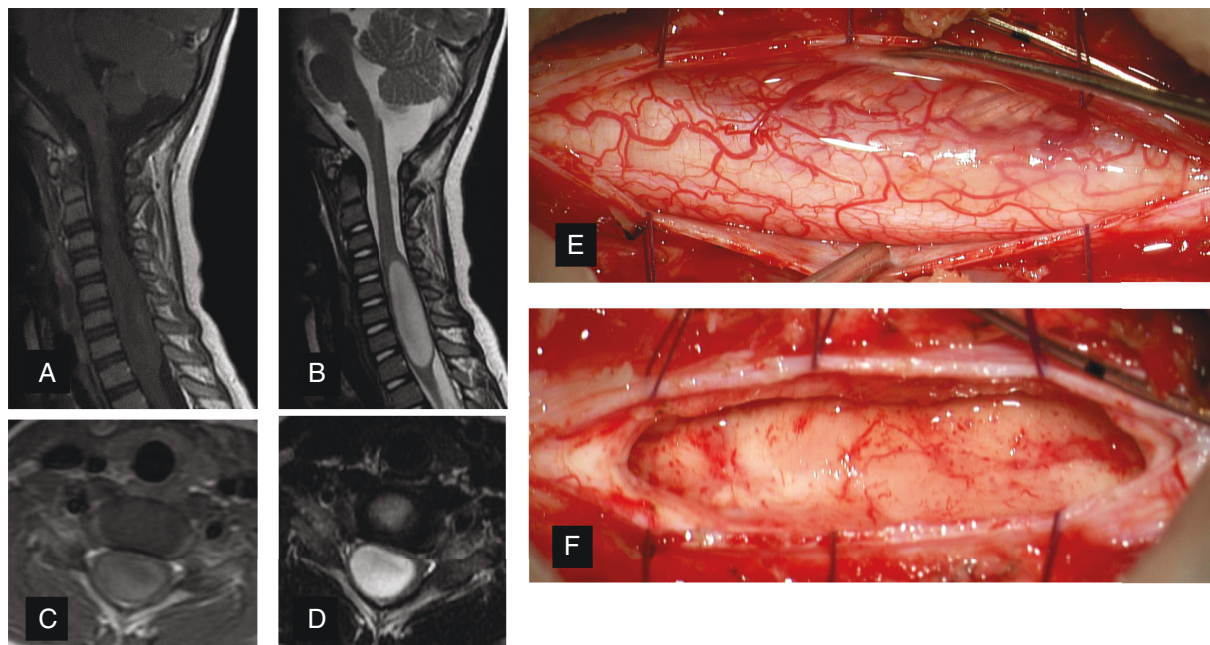
Figure 1.   Infant with intramedullary pilocytic astrocytoma CNS WHO grade 1. A/C: Axial and sagittal contrast enhanced T_1-weighted MRI, B/D: Axial and sagittal T_2-weigthed MRI, E: spindle-shaped bulging of the myelin, F: complete resection within clear margins after midline myelotomy.

foci and guide the neurosurgeon toward areas of the most active tumor growth. In turn, this may enhance diagnostic accuracy as the final diagnosis always rests upon a neuropathological tissue-based diagnosis. Workup should not only include histopathology, but also the most recent WHO classification also requires analysis of molecular markers including IDH status in order to establish an accurate diagnosis.[7] In cases of remaining uncertainty, epigenetic analyses such as DNA methylation-based classification systems are available to allow for a more detailed tumor categorization.[21]

Treatment Options

Surgical Resection

Surgical intervention of any kind is usually the first step in patients suspected to harbor an intramedullary astrocytoma. In uncertain cases, especially when an inflammatory lesion cannot be ruled out, a biopsy might be indicated to clarify the histology and guide further management. The same applies to very diffusely growing, infiltrating lesions where no dissection plane can be intraoperatively identified.

In general, as soon as a symptomatic tumor has been diagnosed the indication for treatment should be made early since neurological outcome and functional prognosis have been reported to be more favorable in patients with better performance at the time of treatment.[22,23] Whenever the lesion is large with considerable local mass effect and neurological deficits or myelopathy, a more pronounced debulking should be aimed at. However, although gross total resection (GTR) is believed to improve local tumor control, it is accompanied by the risk of significant postoperative morbidity, given the infiltrative nature of astrocytomas and lack of clear margins.[24–26] Hence, the potential improvement in survival from more extensive resections must be considered to outweigh the risk of functional deterioration.[13,27–30] Critical discussions with the patient and his caregivers are therefore indicated prior to the operation, especially as individuals with high-grade tumor face a very limited prognosis even when surgical resection is being maximized. Tumors without clear dissection planes or suggestive of a high-grade lesion on MRI should therefore be considered for near total or subtotal resection (STR).[31] The same applies to elderly patients with severe comorbidity or those with severe preoperative deficits and reduced potential for neurorehabilitation. In contrast to diffuse astrocytomas, pilocytic astrocytomas (even very large ones extending into the lower brainstem), often display a dissection plane with the potential of gross total resection and a subsequent good prognosis (Figure 1). Intraoperative pathology using frozen section technique can help to distinguish astrocytoma from ependymoma. In the case of the latter (or a pilocytic astrocytoma), a more meticulous search for a dissection plane may be warranted to improve radicality.

Intraoperative ultrasound can be used to visualize the lesion, intraoperatively delineate the tumor margins, and might help to guide myelotomy. Usually, astrocytomas appear hyperechoic on ultrasound, but very infiltrative astrocytomas often present blurry margins which hamper proper identification of the potential resection area.[32]

Studies on intraoperative neuromonitoring (IONM) have reported improved functional outcomes for patients with monitoring compared to those without.[33,34] Somatosensory evoked potentials (SSEP), motor evoked potentials (MEP), and transcranial motor evoked potential monitoring are used most frequently.[13,34–36] MEP were reported to have a sensitivity of 84% for detecting surgery-related functional impairment.[37] A more robust and very specific monitoring technique is D-wave monitoring, which can be applied either epidural or intradural. It provides reliable and fast feedback; however, in patients with severe preoperative deficits, the reliable detection of feedback signals might not be feasible from a technical standpoint.[13,34,35,38–40]

Radiotherapy

Radiation therapy (RT) is used in patients with high-grade lesions after diagnosis, or patients with low-grade lesions and progressive disease.[41] In grade 2 tumors with STR the value of adjuvant RT is not convincingly proven[41,42]; and in pilocytic astrocytomas, adjuvant RT is usually postponed until progression of a nonresectable recurrency. Altogether, there is still a debate revolving around the additional benefit of early RT after surgery.[43] A recent meta-analysis reported RT to worsen outcomes for low-grade lesions but to improve overall survival in high-grade astrocytomas.[43] In line with this assumption, Minehan et al.[44] described a survival benefit for infiltrative tumors but not pilocytic astrocytomas. Given this uncertainty, RT is mostly offered in cases with high-grade infiltrative lesions and a poor prognosis or in unresectable recurrent tumors. Whether proton therapy might be more beneficial compared to "classical" RT has to be shown in prospective studies.[45,46]

Chemotherapy

Similar to RT, the efficacy of chemotherapy (Cx) is unclear.[47] Main indications were recurrent/progressing tumors after previous surgery or RT, or else in pediatric patients below 3 years since these infants are no candidates for RT.[13,24,43,48–51] In a multi-institutional series, the combination of radio and chemotherapy showed response or stable disease in 4/8 patients.[47] Up to now, there is no consistent recommendation for a specific chemotherapeutic regimen; however, most often temozolomide is administered in analogy to malignant intracranial gliomas.[24,52]

Follow-Up and Surveillance

In pilocytic astrocytomas as well in grade 2 astrocytomas, clinical and imaging follow-up should be scheduled every 6 months within the first 3 years, thereafter annually for another 3 years and then biannually. In grades 3 and 4 tumors, clinical workup should be done every 3 months and MRI every 6 months throughout the first 5 years.

Prognosis

Factors Affecting Prognosis and Long-Term Outcome

The main prognostic factor is tumor histology and the resulting WHO grading. Survival for patients with intramedullary astrocytomas is less favorable compared to ependymomas, with reported overall survival rates ranging from 40% to 65% over 15 years.[13,53] Grade 3 and even more so grade 4 tumors (the latter being often termed as "spinal glioblastoma") have a grim prognosis in terms of progression-free survival (PFS) and overall survival (OS) with average overall survival of only a few months,[4,13,48,54,55] and a 5-year overall survival rate of approximately 14% for histological grade 4 astrocytomas.[13,56] Although the WHO grading is an important prognosticator, additional features eg the degree of infiltration (reflecting also surgical resectability) may lead to different prognoses even within the same WHO grade. This suggests that molecular and genetic differences may exist which might account for differences in tumor biology and clinical prognosis.

The recent 2021 WHO classification of central nervous tumors not only updated the classification criteria but also put a very strong focus on (clinically relevant) genetic, epigenetic, and molecular markers in addition to traditional histology.[7,57] As such, there is abundant literature about these markers and their respective clinical relevance in cranial gliomas. Due to the low incidence of intramedullary astrocytic tumors and the lack of respective large tissue biobanks, comparable studies are yet missing for intramedullary astrocytomas. Few molecular markers have been described so far for intramedullary astrocytomas with at least some clinical annotation, with the most common mutations being found in *p53*, *H3F3A p.K27M*, and *ATRX*. In high-grade tumors, *H3F3A p.K27M* was the most frequent mutation showing a significant association with OS and PFS after multivariate analysis. Grade 1 pilocytic astrocytomas frequently harbor KIAA1549-BRAF fusions.[58–60] Several more subclassifications are presently emerging.[61] More in-depth knowledge about these factors might also pave the road for more specific, "targeted" and thereby personalized therapies (see below).

In contrast to cranial gliomas, there is yet no firm consensus being established regarding the impact of the extent of resection on postoperative outcomes.[62] However, there seems to be little doubt that resection can improve local control, delay tumor progression, and improve survival.[24,63,64] For pediatric patients a national cohort study that GTR or partial resection significantly improved survival in children with intramedullary astrocytomas compared to those receiving biopsy only or no surgery.[4] Nevertheless, such tumors may still identify with a somewhat less favorable prognosis compared to adult patients.[65] In large series of adults and mixed pediatric/adult populations, the extent of resection was associated with OS however with more pronounced effects in lower grade gliomas.[13,31,43,63,66,67] It has to be noted that GTR was achieved in different studies in 13–38 % of astrocytomas grades 2–4.[13,22,67] Although more aggressive resection may lead to a higher rate of neurological deterioration in the postoperative period,[62]

short- and long-term functional outcome was shown to be rather related to age, infiltration, histopathological subtype, tumor size, and preoperative neurological status.[22,68] Since the latter 2 of these parameters may get worse over time when a wait-and-scan policy is being followed, any documented growth or neurological symptom/deterioration should trigger consideration of early surgical intervention.

Surgical Complications, Adverse Effects, and Quality of Life

Neurological deterioration, potentially involving tetra or paraplegia, is a seriously dreaded complication of surgery. Timing of the surgical intervention and meticulous surgical technique in combination with optimal preoperative imaging and intraoperative neuromonitoring strategies are crucial for the best possible results. As the results get worse the larger the tumor and the more pronounced the initial deficit is, surgery should be initiated before significant clinical symptomatology or substantial tumor growth occurs. Elderly patients, severe comorbidity, and substantial presurgical deficits might limit the chances of a successful postoperative rehabilitation. Early recovery has been shown to be prognostic of function outcome.[69] In turn, it remains to be noted that tumor progression will eventually result in the same condition. This should be discussed in advance with both patients as well as proxy caregivers. Given the dismal prognosis of high-grade tumors especially in these cases, a well-balanced decision about the risk of surgery and potential benefit appears mandatory.

Both laminectomy and laminoplasty bear the risk of postoperative spinal deformity, particularly in children.[70] Whether laminoplasty reduces the risk of impaired wound healing is still a matter of debate, but seemingly it reduces the risk of future spinal deformity, especially in the cervical region.[13,71–73] A very good postoperative physiotherapy program is important to diminish the risk of kyphotic deformity.

Concerning radiotherapy, potential benefits must be balanced against the limited capacity of the spinal cord to tolerate radiation.[48] Again, also here likewise to surgery, pretreatment functional status determines the tolerance against impairment due to therapy. In children, RT can affect growth and bone metabolism influencing the development of the spine and also lead to radionecrosis and vasculopathy.[49] Like in cranial neurooncology, maintaining the quality of life is key in the treatment concept for intramedullary astrocytomas aside from oncological efficacy. Severe disability and deterioration from the neurologic status leading to reduced quality of life and should be avoided whenever possible.

Emerging Therapies and Future Directions

Novel Targeted Therapies and Personalized Medicine

While a large body of evidence exists about the molecular profile of cranial astrocytomas, only recently increasing interest emerged to identify the genomic landscape of intramedullary astrocytomas.[74] Aside of prognostication the

Table 1. Interventional Clinical Trials for Targeted Therapies in Astrocytic Gliomas CNS WHO Grades 1–4. Overview of Studied or Approved Targeted Therapies and Therapies Currently Under Investigation in Phase 3 Trials for Cranial Astrocytic Gliomas CNS WHO Grades 1–4. Molecular Targets, Study Design, Study Population, Treatment and Outcome Measurements are Indicated. ClinicalTrials.gov was Searched for Interventional Phase 3 Clinical Trials on Targeted Therapies for Patients with Intracranial Astrocytic Gliomas CNS WHO grades 1–4. Database Closure was on December 1, 2023

Target	Study Design	Study Population	Number of Patients	Treatment	Outcome	NCT
IDH						
Mellinghoff et al. (2023)[79]	Randomized, placebo-controlled phase 3 study	Adults with residual or recurrent grade 2 IDH-mutant glioma	331	Vorasidenib vs. Placebo	Median PFS: 27.7 vs. 11.1 months FDA approval pending	NCT04164901
BRAF V600E						
Bouffet et al. (2023)	Open-label, randomized phase 2 study	Patients with pediatric low-grade glioma with BRAF V600 mutations	110	Dabrafenib plus trametinib vs. Carboplatin + Vincristin	Median PFS: 20.1 vs. 7.4 months FDA approved, EMA approval pending	NCT02684058
VEGF						
Gilbert et al. (2014)[81]	Randmoized, placebo-controlled phase 3 study	Adults with newly diagnosed glioblastoma	637	Bevacizumab + RT +TMZ vs. Placebo + RT +TMZ	OS: negative PFS: 10.7 vs. 7.3 months FDA approved	NCT00884741
Chinot et al. (2014)[82]	Randmoized, placebo-controlled phase 3 study	Adults with newly diagnosed glioblastoma	921	Bevacizumab + RT +TMZ vs. Placebo + RT +TMZ	OS: negative PFS: 10.6 vs. 6.2 months FDA approved	NCT00943826
EGFR/EGFRvIII						
Westphal et. al. (2015)[83]	Open-label, randomized phase 3 study	Adults with newly diagnosed glioblastoma	149	Nimotuzumab + RT +TMZ vs. Placebo + RT +TMZ	Negative	NCT00753246
Lassman et al. (2023)[84]	Randomized, placebo-controlled phase 3 study	Adults with newly diagnosed glioblastoma with EGFR-amplification	639	Depatuxizumab Mafodotin + RT +TMZ vs. Placebo + RT +TMZ	Negative	NCT02573324
mTOR						
Franz et al. (2013)[85]	Randomized, placebo-controlled phase 3 study	Children and adults with SEGA and Tuberous Sclerosis Complex	117	Everolimus vs. Placebo	Confirmed radiographic response: 35% vs. 0%	NCT00789828
MGMT						
Blumenthal et al. (2014)[86]	Open-label, randomized phase 3 study	Adults with newly diagnosed glioblastoma or gliosarcoma	183	O^6-benzylguanine + RT + BCNU vs. RT + BCNU	negative	NCT00017147
αvβ3 and αvβ5 integrin						
Stupp et al. (2014)[87]	Open-label, randomized phase 3 study	Adults with newly diagnosed glioblastoma with methylated MGMT promoter	545	Cilengitide +TMZ vs. TMZ	Negative	NCT00689221
TGF-beta-2						
Study terminated	Open-label, randomized phase 3 study	Adults with anaplastic astrocytoma or glioblastoma	27	Trabedersen vs. TMZ, BCNU or CCNU chemotherapy	negative	NCT00761280
PARP						
Sarkaria et al. (2022)[88] (ASCO abstract)	Randomized, placebo-controlled phase 2/3 study	Adults with newly diagnosed, MGMT promoter hypermethylated glioblastoma	447	Veliparib +TMZ vs. Placebo +TMZ	Ongoing Preliminary results: negative	NCT02152982.

Table 1. Continued

Target	Study Design	Study Population	Number of Patients	Treatment	Outcome	NCT
20S Proteasome						
Roth et al. (2021)[89] (ASCO abstract)	Open-label, randomized phased 3 study	Adults with newly diagnosed glioblastoma	749	Marizomib + RT + TMZ vs. RT + TMZ	Ongoing Preliminary results: negative	NCT03345095
MAP/ERK Kinase I/II						
Not yet published	Open-label, randomized phase 3 study	Children with newly diagnosed NF-1-associated LGG	ND	Selumetinib vs. Carboplatin + Vincristin	Recruiting	NCT03871257
Not yet published	Open-label, randomized phase 3 study	Children with newly diagnosed non-NF-1-associated LGG	ND	Selumetinib vs. Carboplatin + Vincristin	Recruiting	NCT04166409

Abbreviations: BCNU—carmustine; BRAF V600E—V-raf murine sarcoma viral oncogene homolog B V600E mutation; CCNU—lomustine; EGFR(vIII)—epidermal growth factor receptor (variant 3); IDH—isocitrate dehydrogenase; MAP/ERK—mitogen-activated protein/extracellular signal-regulated kinase; MGMT—O-6-methylguanine-DNA methyltransferase; mTOR—mammalian target of rapamycin; NCT—national clinical trials number; PARP—poly-ADP ribose polymerase; RT—radiotherapy; TGF-beta-2—transforming growth factor-Beta 2; TMZ—temozolomide; VEGF—vascular endothelial growth factor.

detection of target genes or biomarkers might uncover novel opportunities for personalized "targeted" therapy. Multiple clinical trials have been conducted and are ongoing to investigate targeted therapies for cranial astrocytic gliomas (Table 1). So far, only a few clinical reports exist regarding spinal astrocytomas; however, in analogy to cranial astrocytomas, it is tempting to speculate about potential drugs which might be explored in this context. As an example, markers for which some substantiated information exists are:

- H3F3A missense-mutation: associated with a poor prognosis; potential candidate for CART-cell immunotherapy.[75]
- MGMT promoter methylation: makes tumor more susceptible to alkylating chemotherapy.[76]
- BRAF fusion with KIAA1549 or missense-mutation: Results in improved prognosis, a frequent occurrence in pilocytic astrocytomas, a potential candidate for BRAF-MEK inhibitors, for example vemurafenib/cobimetinib, dabrafenib/trametinib, and encorafenib/binimetinib.[77,78]
- IDH1 mutation: Citric acid cycle enzyme, low frequency in intramedullary astrocytomas, a potential candidate for IDH1 inhibitor ivosidenib or vorasidenib.[79]
- CDK4 amplification: promotes cell cycle progression; mutation drives proliferation, poor prognosis, and potential candidate for CDK4 inhibitor Palbociclib.[80]

Biomarkers and Imaging Modalities

Future developments in terms of more refined tools for diagnostics as well as surveillance for recurrent/progressive disease might include advanced imaging (both MRI as well as molecular imaging using PET technology) and liquid biopsy from blood or, more likely, cerebrospinal fluid (CSF).[90,91] Most likely machine learning algorithms and programs of "artificial intelligence" might help deconvolute these large datasets.

Collectively, intramedullary astrocytomas deserve more attention and should be studied more extensively in analogy to their intracranial counterparts. In order to derive meaningful results, consortia efforts are needed to build biobanks and datasets for this rather rare tumor entity.

Conflict of interest statement

None declared.

Authorship statement

Conceptualization: J-.C.T.; Writing—original draft: J-.C.T.; Writing—review and editing: J-.C.T.; N.T.; P.K.; Writing—revising: J-.C.T.; N.T.; P.K.

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