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EANO guidelines for the diagnosis and treatment of ependymal tumors

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Abstract

Ependymal tumors are rare CNS tumors and may occur at any age, but their proportion among primary brain tumors is highest in children and young adults. Thus, the level of evidence of diagnostic and therapeutic interventions is higher in the pediatric compared with the adult patient population.

The diagnosis and disease staging is performed by craniospinal MRI. Tumor classification is achieved by histological and molecular diagnostic assessment of tissue specimens according to the World Health Organization (WHO) classification 2016. Surgery is the crucial initial treatment in both children and adults. In pediatric patients with intracranial ependymomas of WHO grades II or III, surgery is followed by local radiotherapy regardless of residual tumor volume. In adults, radiotherapy is employed in patients with anaplastic ependymoma WHO grade III, and in case of incomplete resection of WHO grade II ependymoma. Chemotherapy alone is reserved for young children <12 months and for adults with recurrent disease when further surgery and irradiation are no longer feasible. A gross total resection is the mainstay of treatment in spinal ependymomas, and radiotherapy is reserved for incompletely resected tumors. Nine subgroups of ependymal tumors across different anatomical compartments (supratentorial, posterior fossa, spinal) and patient ages have been identified with distinct genetic and epigenetic alterations, and with distinct outcomes. These findings may lead to more precise diagnostic and prognostic assessments, molecular subgroup-adapted therapies, and eventually new recommendations pending validation in prospective studies.

Key words

adults | children | ependymoma | molecular pathology | treatments

Ependymal tumors are rare central nervous system tumors.[1] According to the Central Brain Tumor Registry of the United States, the annual incidence of ependymal tumors is estimated at 0.43 patients per 100 000 population.[2] These tumors account for 1.8% of all primary CNS tumors and for 6.8% of all gliomas.[2] In children (0–19 y of

Importance of the study

This article reports the evidence-based guidelines on management of ependymal tumors in children and adults developed by a multidisciplinary task force of the European Association of Neuro-Oncology, composed of medical experts from different European countries representing the involved disciplines (neurology, neurosurgery, neuropathology, radiation oncology, and pediatric oncology). These guidelines should aid all professionals involved in the management of patients with ependymal tumors in the daily clinical practice and could serve as a source of knowledge for institutions and insurance companies involved in cancer care in Europe.

age), ependymal tumors are proportionally more common and account for 5.2% of all primary CNS tumors.[2] Overall, these tumors affect males more frequently than females (1.3:1).

Ependymal tumors are of neuroectodermal origin and subdivided according to the World Health Organization (WHO) classification of CNS tumors into distinct entities and histological variants.[3] The WHO classification also comprises a histological grading into 3 distinct grades of malignancy: WHO grades I, II, and III.

In addition to age and tumor grade, the prognosis is associated with tumor location (supratentorial, infratentorial, and spinal) and site-specific molecular genetics.[4–7] Population-based epidemiological data reported a 5-year overall survival (OS) rate of 83.4% and a 10-year OS rate of 79.1% in patients with ependymal tumors.[2]

A recent molecular classification has distinguished 9 subgroups of ependymal tumors that appear to reflect more precisely than histology alone the biological, clinical, and histopathological heterogeneity across the major anatomical compartments, age groups, and tumor grades.[6] Each of the 9 molecular subgroups is characterized by distinct DNA methylation profiles and associated genetic alterations.

Prospective studies on management of ependymoma patients have been performed in the pediatric population only, while smaller retrospective series are available for adult patients.[8] In this guideline, we have separated the review of evidence concerning diagnosis and treatment recommendations for children and adults, recognizing that this is somewhat artefactual and may be replaced by molecular profiling-based stratification for treatment in the future.

Methods

The European Association of Neuro-Oncology (EANO) ependymoma task force assessed the available English literature up to December 31, 2016, sorted the scientific evidence into classes I–IV, and rated recommendations at levels A–C according to the European Federation of the Neurological Societies Guidelines.[9] When sufficient evidence for recommendations was not available, the task force offered advice as a Good Practice Point. Specific recommendations for the therapeutic management of ependymomas in adults and children are reported in Tables 1–6.

Table 1 Key recommendations for the treatment of newly diagnosed intracranial WHO grades II and III ependymomas in adults

	Class of Evidence	Level of Recommendation
Resection is recommended to obtain a histological diagnosis and should be a gross total resection whenever feasible. As the morbidity can be significant, detailed informed preoperative counseling by a surgeon experienced in performing such surgery is important.	II	B
Postoperative MRI should be performed to evaluate the extent of resection.	n.a.	Good Practice Point
A second-look surgery should be considered when the result of the first resection has not been satisfactory.	III	C
Because a risk of CSF dissemination exists for all patients with newly diagnosed ependymoma, disease staging, including both craniospinal MRI and CSF cytology, is mandatory following surgery (not earlier than 2–3 wk).	n.a.	Good Practice Point
Postoperative conformal radiotherapy with doses up to 60 Gy is recommended for patients with WHO grade III (anaplastic) ependymomas regardless of the extent of resection.	II	B
Postoperative conformal radiotherapy with doses of 54–59.4 Gy is recommended for patients with WHO grade II ependymomas following incomplete resection.	III	C
Craniospinal irradiation (CSI) of 36 Gy is recommended in case of CSF or spinal dissemination with a boost up to 45–54 Gy on focal lesions.	IV	Good Practice Point
Because of the risk of asymptomatic and/or late relapses, patients should be followed long term with contrast-enhanced MRI.	n.a.	Good Practice Point

Table 2 Key recommendations for the treatment of newly diagnosed intracranial WHO grades II and III ependymomas in children

	Class of Evidence	Level of Recommendation
Resection is recommended to obtain a histological diagnosis and should be a gross total resection whenever feasible. As the morbidity can be significant, detailed informed preoperative counseling by a surgeon experienced in performing such surgery is important.	II	B
Postoperative MRI should be performed to evaluate the extent of resection.	n.a.	Good Practice Point
A second-look surgery should be considered when residual tumor is demonstrated on postoperative MRI and gross total resection is a realistic goal.	II	B
Because a risk of CSF dissemination exists for all patients with newly diagnosed ependymoma, a disease staging, including both craniospinal MRI and CSF cytology, is mandatory following surgery (not earlier than 2–3 wk)	n.a.	Good Practice Point
Postoperative conformal radiotherapy with doses up to 59.4 Gy is recommended in children older than 18 months.	II	B
Postoperative conformal radiotherapy with doses of 54 Gy is recommended in children between 12 months and 18 months or in older children with poor neurological status.	II	B
Chemotherapy alone is an option in children less than 18 months old, while it is recommended in children aged less than 12 months.	III	C
Craniospinal irradiation (CSI) is recommended in case of CSF or spinal dissemination with a boost on focal lesions with doses adapted to patient age.	IV	Good Practice Point
Because of the risk of asymptomatic and/or late relapses, patients should be followed long term with an enhanced MRI.	n.a.	Good Practice Point
Serial monitoring of cognitive and endocrine functions with specific batteries following radiotherapy is recommended whenever feasible.	n.a.	Good Practice Point

Clinical and Neuroimaging Diagnosis

The clinical presentation of ependymomas (see Supplementary material) depends primarily on patient age, tumor location, and tumor size.[10–14]

MRI with contrast enhancement is the modality of choice for diagnosing ependymal tumors.[15,16] CT can better depict calcifications, which are most commonly observed in subependymomas. Infratentorial ependymomas arise from the floor of the fourth ventricle, while supratentorial ependymomas can be located in the brain rather than in the ventricles. Intracranial ependymomas commonly appear as well-circumscribed mass lesions and have a heterogeneous appearance on T1-, T2-, and postcontrast MRI, displaying varying degrees of contrast enhancement.

Advanced imaging modalities may assist in diagnosis or management in some clinical scenarios; however, the available data from the literature are too scarce and do not allow for definitive recommendations for daily clinical practice. Diffusion-weighted imaging may be useful for differentiating pilocytic astrocytomas, medulloblastomas, and ependymomas in the posterior fossa.[17] MR spectroscopy reveals elevated choline and reduced N-acetylaspartate levels.[8] Perfusion MRI may display elevated cerebral blood volume values and have some prognostic value.[18] Spinal cord ependymomas display more distinct borders than diffuse astrocytomas.[14] Cyst formation and T2 hypointensity of the cyst wall due to blood products ("hemosiderin cap") are suggestive of ependymoma. An associated syringomyelia is common.

Myxopapillary ependymoma (MPE) is typically located in the conus medullaris, cauda equina, and filum terminale region.

Neuropathological Diagnostics of Ependymal Tumors

Ependymal tumors are classified according to the WHO classification of CNS tumors 2016.[3] Histological assessment is primarily based on hematoxylin/eosin-stained sections and some ancillary techniques, including silver impregnation for reticulin fibers, Alcian blue for demonstration of mucoid changes, and periodic acid–Schiff staining for glycogen. Immunohistochemically, ependymal tumors react positive for glial fibrillary acidic protein and protein S100 but usually lack nuclear positivity for OLIG2. Dot-like perinuclear and ring-like cytoplasmic immunoreactivity for epithelial membrane antigen is a characteristic feature.[19] Nuclear immunoreactivity for v-rel avian reticuloendotheliosis viral oncogene homolog A (RELA) and expression of L1 cell adhesion molecule may help to identify RELA fusion-positive ependymomas.[20,21] However, molecular testing for C11orf95-RELA fusion by fluorescent in situ hybridization or reverse-transcription PCR analysis is required for a firm diagnosis.[3] Loss of nuclear expression of trimethylated histone 3 lysine 27 (H3-K27me3) distinguishes a prognostically unfavorable group of posterior fossa ependymomas (PF-EPNs) in children,[22] largely corresponding to PF-EPN group A (see "New Molecular Subgroups" section below).[6,23] Proliferative activity is commonly assessed by Ki-67 immunostaining; however, definite cutoffs for grading have not been defined.

The 2016 WHO classification of CNS tumors includes 5 distinct entities of ependymal tumors.[3] Myxopapillary ependymoma WHO grade I is histologically characterized by cuboidal or elongated tumor cells forming fibrillary

Table 3 Key recommendations for the treatment of recurrent intracranial ependymomas in adults and children

	Class of Evidence	Level of Recommendation
Re-operation and/or re-irradiation should be proposed whenever possible. However, if only incomplete resection was achievable due to functional restrictions at first surgery, the same limitations will be faced at re-operation; hence, in these cases the indication for another incomplete resection should be made cautiously.	III	C
In patients with recurrent ependymomas who are no longer eligible for local treatments, chemotherapy might be warranted, particularly in patients with a good performance status.	III	C
In adults, either platinum compounds or temozolomide (based on a more favorable toxicity profile) should be considered. Options for participation in a clinical trial should be explored.	IV	Good Practice Point
In children, the choice of chemotherapeutic drugs depends on previous exposures. Options for participation in a clinical trial should be explored.	n.a.	Good Practice Point

processes toward fibrovascular cores typically showing perivascular mucoid degeneration. Mitotic activity is low. Subependymoma WHO grade I is characterized by clusters of bland to mildly pleomorphic, mitotically inactive cells embedded in an abundant fibrillary matrix with frequent microcystic changes and dystrophic calcifications. Ependymoma WHO grade II usually shows a solid, well-circumscribed growth and is composed of uniform cells forming perivascular pseudorosettes and, in some tumors, true ependymal rosettes. Mitotic activity is low while non-palisading necroses may be present in a fraction of cases. Three variants of ependymoma, each characterized by distinct histological features, are recognized in the WHO classification, namely papillary ependymoma, clear cell ependymoma, and tanycytic ependymoma. Ependymoma, RELA fusion-positive is a novel supratentorial ependymoma entity that is defined by the presence of a C11orf95-RELA fusion.[6,20] It may correspond to WHO grade II or III, but patient outcome is worse compared with other types of supratentorial ependymomas.[6] Anaplastic ependymoma WHO grade III carries histological features of anaplasia, in particular high mitotic activity and microvascular proliferation. Pseudopalisading necrosis may also be observed. However, accurate histological distinction of WHO grades II and III ependymomas is challenging and its role in predicting survival has been disputed.[24] Hence, WHO grading is inadequate to reliably predict the outcome in individual patients, and molecular subgrouping or single molecular markers may offer new perspectives for improved prognostic stratification.[4,6,25–27]

Treatment of Newly Diagnosed Intracranial Ependymal Tumors in Adults

Adult intracranial ependymomas are rare tumors, and WHO grade II tumors are more frequent than WHO grade III (anaplastic) counterparts.[10]

Surgery is considered the first and crucial step of standard treatment. In the majority of studies, extent of resection has emerged as one of the most significant predictors of outcome.[28–33] In a retrospective series of WHO grade II ependymomas in adults,[31] the 5- and 10-year OS rates were 86.1% and 81%, respectively. Preoperative KPS, extent of resection, and tumor location were independent prognostic factors for OS. In particular, gross total resection (GTR), defined as no residual disease on postcontrast T1- and T2-weighted images on a 3-month postoperative MRI, and infratentorial location were associated with a longer OS. GTR and tumor location were also independent factors predicting progression-free survival (PFS). Conversely, incomplete resection has an increased risk of tumor recurrence and CSF dissemination. However, in posterior fossa tumors, encasement of the cranial nerves and brainstem vasculature might limit resectability.[34] In case of persistent hydrocephalus despite tumor resection, shunting or endoscopic ventriculostomy needs to be performed.

Concepts regarding target volume for radiation therapy have evolved. In the past, patients with ependymoma often received craniospinal irradiation. However, numerous studies demonstrated the efficacy of local fields in the treatment of ependymoma, achieving good local control with low risk of spinal dissemination.[35] In adults, there is agreement that postoperative radiotherapy should be included in the standard of care for patients with anaplastic ependymoma (WHO grade III) and for patients with ependymomas (WHO grade II) after an incomplete resection.[29,36] Conversely, the role of postoperative radiotherapy in patients with ependymoma WHO grade II undergoing GTR remains controversial.[37] In 2 large retrospective studies including patients with intracranial WHO grade II ependymomas,[31,38] no significant association of radiotherapy with PFS or OS was found. However, in the French study,[31] the subgroup of patients with incompletely resected tumors receiving postoperative radiotherapy had longer PFS and OS than those who did not.

Intracranial subependymoma is a rare WHO grade I tumor. Long-term survival can be expected after surgical removal, although poorly defined borders have been reported to be associated with a shorter PFS.[39] Postoperative radiotherapy has been employed in few patients after subtotal or partial resection.

Recommendations regarding treatment of intracranial ependymomas in adults are summarized in Table 1.

Table 4 Key recommendations regarding nonsurgical treatment of WHO grades II and III ependymomas in children

	CT Indication	CT Regimen	CT Timing	RT Indication	RT Timing	GTV (defined with MRI)	CTV	Total Dose, Gy	Dose/fraction, Gy	Technique
Localized tumor, age >18 mo	Debatable	VEC ± cisplatin	Maintenance	Systematically	Postoperatively	Tumor bed and 3D identifiable residual disease	5–10 mm around GTV	59.4	1.8	3DCRT or IMRT or proton
Localized tumor, age >18 mo with visible residual tumor after surgery	Recommended	VEC ± cisplatin ± high-dose methotrexate	Postoperatively	Stereotactic additional boost recommended within a prospective clinical trial with residue after chemotherapy	Postoperatively and post-chemotherapy	Tumor bed and 3D identifiable residual disease		59.4+8	4	3DCRT or IMRT or proton
Localized tumor, age 12–18 mo	Recommended	Baby UK	Maintenance	To be discussed	Postoperatively	Tumor bed and 3D identifiable residual disease		54	1.6–1.8	
Localized tumor, age <12 mo	Recommended	Baby UK	Postoperatively	NORT	NORT	–	–	–	–	
Metastatic tumor	Debatable	VEC ± cisplatin	Before RT	Salvage treatment	Postoperatively or postchemotherapy	Tumors and 3D identifiable residual disease	CSI + boost 5–10 mm around GTV	24 or 36 depending on age + boost up to 59	1.8	
Local relapse	None outside clinical trial	–	–	Recommended	Postoperatively	3D identifiable disease	GTV+2 mm	59 or in a prospective trial 25 Gy/5 fractions or 24 Gy/3 fractions	1.8 or hypofractionation (5–8)	3DCRT or IMRT or proton or hypofractionated stereotactic irradiation

CT, chemotherapy; RT, radiotherapy; VEC, vincristine/etoposide/ cyclophosphamide regimen; GTV, growth tumor volume; CTV, clinical target volume; 3DCRT, 3D conformal radiotherapy; IMRT, intensity modulated radiotherapy;

Treatment of Newly Diagnosed Intracranial Ependymal Tumors in Children

More than half of all pediatric ependymomas occur in children younger than 3 years,[40] and about two thirds of tumors are located in the posterior fossa.[32]

Surgery and radiotherapy are the mainstay of treatment for ependymomas in children.[41] Extent of resection is the most important prognostic factor, but the site of the lesions (eg, posterior fossa tumors involving the ponto-cerebellar region) can limit surgery due to involvement of the lower cranial nerves and brainstem[42]; thus, an incomplete resection is frequent in these patients. OS is around 70% at 5 years in case of GTR, but it is much lower with incomplete resection.[43–45] A second-look surgery is increasingly undertaken when the first resection has been incomplete.[46–48]

The benefit of postoperative radiotherapy has been shown in terms of local control and survival rates in children with intracranial ependymomas.[45] An Italian study[44] reported on attempted GTR followed by postoperative radiotherapy and showed a 7-year estimate of local control, event-free survival (EFS), and OS of 83.7%, 69%, and 81%, respectively. Data from St Jude Children's Research Hospital[45] showed improved local control, EFS, and OS with 59.4 Gy in 1.8 Gy fractions with 3D conformal radiotherapy without any apparent increase of late neurocognitive deficits. Therefore, postoperative radiotherapy with 59.4 Gy (1.8 Gy/fraction) has been advocated[45] for children older than 3 years, while for children as young as 18 months or children with altered neurological status, the doses can be lowered to 54 Gy.[49] This can be true even for children between 12 and 18 months. A recent retrospective study on 206 patients reported that the main pattern of relapse was within the radiation fields even at 59.4 Gy.[50] As local control remains the primary goal of treatment, the possibility to compensate for an incomplete surgery by applying a hypofractionated stereotactic boost in addition to conventional radiotherapy has been proposed.[51] In an Italian prospective clinical trial, patients with residual disease after first surgery who received a boost of 8 Gy in addition to radiation and chemotherapy had a 5-year PFS rate higher than 58%.[52] A prospective study has shown that hyperfractionated radiotherapy is safe but provides no outcome benefit compared with standard fractionated regimens.[53]

The toxicity of radiotherapy in younger children is of concern, and intensity-modulated radiation therapy has been employed to limit late sequelae.[44] Merchant and colleagues[54] developed a model combining dose-volume data with clinical factors to predict intelligence quotient (IQ) outcomes and concluded that the radiation dose remains the most clinically significant determinant of IQ outcomes and that even low doses, such as <20 Gy, delivered to the supratentorial brain, have an impact on the IQ. Proton therapy could be an alternative to conventional photon radiotherapy.[55] In this regard, the Massachusetts General Hospital group reported the outcome of 70 children with localized ependymomas treated with proton therapy.[56] At a median follow-up of 46 months, local control and survival were excellent and the complication rate particularly low. Proton therapy may be useful for PF-EPN,[57] as it can spare the dose exposure to supratentorial compartments of the brain and auditory structures. Supratentorial ependymomas, which are often large tumors and occur in children over 10 years of age, also could represent a good indication for proton therapy in order to reduce neurocognitive impairment, and in this regard the preliminary data are encouraging.[58]

However, recent studies[59–61] have suggested that brainstem toxicity, including radiation necrosis, with proton treatment can occur. Thus, it has been recommended to limit the dose to the brainstem. Another study reported more imaging changes in brainstem with protons than with photons.[62] The benefit and risks of proton therapy need to be confirmed with modern proton treatments and in prospective studies.[63] A prospective study (NCT01288235) with proton therapy is ongoing in the US.

The role of chemotherapy in children remains unproven despite intensive investigation.[64] As there is reluctance to deliver radiation to very young children, postoperative chemotherapy has been frequently proposed, while in older children chemotherapy is delivered as an adjunct to radiotherapy. Postoperative chemotherapy, using various combinations of etoposide, vincristine, cyclophosphamide, platinum derivatives, and high-dose methotrexate, showed a 40% to 50% response rate.[44,65–67] The role of intensified schedules of chemotherapy was suggested in baby protocols,[66] especially for supratentorial tumors.[68] In contrast, the use of immediate postoperative high-dose conformal radiotherapy in children under the age of 3 years led to 7-year PFS rates of 77%,[45] albeit long-term follow-up for toxicity on development is pending. Thus far, radiotherapy deferral strategies that use chemotherapy have been abandoned in most institutions for children aged more than 12 months.

Two randomized trials are currently comparing post-irradiation chemotherapy with observation.

Recommendations regarding treatment of intracranial ependymomas in children are summarized in Tables 2, 3, and 4. A summary of prospective studies on radiotherapy in pediatric patients with ependymoma can be found in the Supplementary material.

Treatment of Recurrent Intracranial Ependymal Tumors in Adults and Children

Standard salvage options for recurrent ependymomas have not been identified. However, re-operation as well as re-irradiation are increasingly employed.

Re-operation has been shown to be associated with improved prognosis.[69] Among children who underwent re-operation, there was a 5-year EFS of 19% in case of GTR, of 14% in case of incomplete resection, and of 8% without repeat surgery.[70] Re-irradiation is performed in adults as well as in children, using either a full course of fractionated irradiation[69,71] or hypofractionated stereotactic irradiation[72–76] or proton therapy,[77] and can achieve durable responses.

The role of chemotherapy for treatment of recurrent ependymoma in adults remains unclear and is considered only when local treatment options (surgery and radiotherapy) have been exhausted.[78,79]

Similar to other gliomas, temozolomide (TMZ) has been used for the treatment of adult patients with ependymoma. Some case reports suggested that TMZ alone or in combination is active against recurrent WHO grade II or III ependymoma.[80–84] A retrospective study of 18 patients with recurrent WHO grades II and III intracranial ependymomas failing re-operation or re-irradiation or both suggested an activity of TMZ in the standard schedule both in terms of response (22% complete + partial) and outcome (PFS 9.69 mo and OS 30.55 mo).[85] Responses were observed in chemotherapy-naïve patients only and in most cases were delayed in appearance. Conversely, in another retrospective study[86] of patients with WHO grade II intracranial ependymomas refractory to first-line chemotherapy with platinum compounds, TMZ in the standard schedule had a more limited activity with a response rate of 4%, a PFS of 2 months, and OS of 3 months. An explanation of this difference could be that all patients of this cohort[86] were heavily pretreated, while the majority of patients of the other cohort[85] were chemo naïve, thus receiving TMZ in an earlier phase of the disease. Temozolomide has also been used in combination with lapatinib in a single-arm phase II study in patients with recurrent intracranial and spinal ependymoma.[87] Lapatinib targets the epidermal growth factor receptor (ErbB1) and the related family member human epidermal growth factor receptor 2/neu (ErbB2), which are expressed on the surface of ependymoma cells. Fifty patients were enrolled in this trial and the treatment was overall well tolerated. Median PFS was 45 weeks for patients with WHO grade II, and 25.3 weeks for patients with WHO grade III anaplastic ependymomas. Responses to treatment correlated with higher ErbB2 mRNA expression in the tumor tissue. The rather modest activity of TMZ against ependymoma might be due to the lack of O^6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation in ependymoma cells[88,89]; however, even when present, MGMT promoter methylation may not correlate with response to TMZ.[85]

A few studies on the administration of platinum-based regimens, using either cisplatin or carboplatin, have been published. A retrospective study, including pediatric as well as adult patients, indicated a superiority of platinum-based over nitrosourea-based regimens.[90] Another retrospective series reported higher response rates in patients with progressive or recurrent ependymoma treated with cisplatin compared with nonplatinum regimens, but no difference in terms of PFS and OS was observed.[91] Other drugs and regimens, such as tamoxifen and isotretinoin, were used in only single patients.[92] The anti-angiogenic agent bevacizumab has been administered in a small cohort of 8 patients with recurrent WHO grade II or III adult intracranial ependymoma with a median PFS of 6.4 months and OS of 9.4 months.[93]

Phase II studies in children with relapsing ependymomas have reported a low response rate with either standard[94] or high-dose chemotherapy.[95] Metronomic therapies have produced some long-term stabilizations.[96] Responses have been reported with oral etoposide[97] or TMZ.[98] Bevacizumab, in association with either irinotecan[99] or lapatinib,[100] has proven disappointing. Targeted agents, such as erlotinib[97] and sunitinib,[101] failed to show activity in unselected patient cohorts.

Recommendations regarding treatment of recurrent ependymomas are summarized in Table 3.

Treatment of Ependymal Tumors of the Spinal Cord

Ependymal tumors of the spinal cord are more common in adults than in children.[10] They include WHO grade I subependymoma and MPE, and WHO grades II and III (anaplastic) ependymoma. Spinal cord ependymomas have a better prognosis than spinal cord astrocytomas, but factors affecting prognosis have not been defined except for GTR.[102] Advances in microsurgical techniques have allowed en bloc GTR over piecemeal subtotal resection (STR) as standard of care for spinal cord ependymomas. In the majority of cases a GTR can be performed with good functional results. Since good functional outcome is related to small tumor size and good neurological status at the time of surgery, resection is considered at an early stage of the disease.[103,104] When GTR is not feasible because of infiltration of spinal cord or nerve roots, postoperative local radiotherapy is commonly employed. A recent review of the literature has been performed for 348 patients with WHO grades II and III spinal cord ependymomas who underwent surgery with known extent of resection (GTR or STR), with or without postoperative radiotherapy.[105] After multivariate analysis, extent of resection and tumor grade were independent prognostic factors for OS and PFS, and radiotherapy prolonged PFS in patients receiving STR: median PFS was 48 months in patients treated with STR alone and 96 months for patients treated with STR followed by radiotherapy. The optimal dose is still a matter of debate, with studies suggesting either better or equivalent results with doses >50 Gy.[105,106]

Regarding conventional chemotherapy, a small study of 10 patients with recurrent intramedullary ependymoma has reported that continuous oral etoposide is well tolerated and may be active.[107] Bevacizumab can provide clinical benefit in some patients, although the changes on MRI do not meet the current criteria for radiological tumor response.[108]

Recommendations regarding treatment of spinal cord ependymomas are summarized in Table 5.

Large retrospective series on MPE have been performed, including a large multi-institutional series of 183 patients[109] that showed a 10-year OS of 92.4% and a 5- and 10-year PFS of 69.5% and 61.2%. MPE recurrence was local in 84% of patients, and leptomeningeal spread was observed in 9.3% of patients. Extent of resection was a major independent factor predicting local control, while younger age (<36 y) was a negative prognostic factor. However, the irregular shape, contact with surrounding nerve roots, and production of a myxoid matrix, particularly in the filum terminale, can make GTR particularly challenging with risks

Table 5 Key recommendations for the treatment of WHO grades II and III spinal cord ependymomas

	Class of Evidence	Level of Recommendation
Gross total resection is the goal of spinal ependymoma surgery.	II	B
Postoperative MRI should be performed to evaluate the extent of resection.	n.a.	Good Practice Point
Because a risk of CSF dissemination exists for all patients with newly diagnosed ependymoma, disease staging, including both craniospinal MRI and CSF cytology, is recommended following surgery (not earlier than 2–3 wk).	n.a.	Good Practice Point
In case of WHO grade III (anaplastic) ependymomas, postoperative radiotherapy with doses of 45–54 Gy is recommended regardless of the extent of resection.	III	C
In case of WHO grade II ependymomas following gross total resection, a watch-and-wait strategy is recommended.	III	C
In case of incomplete resection of a WHO grade II ependymoma, postoperative local radiotherapy is recommended with doses of 45–54 Gy.	II	B
Because of the risk of asymptomatic and/or late relapses, patients should be followed long term with an enhanced MRI.	n.a.	Good Practice Point

Table 6 Key recommendations for the treatment of MPEs WHO grade I

	Class of Evidence	Level of Recommendation
Gross total resection is recommended whenever feasible.	II	B
Postoperative MRI should be performed to evaluate the extent of resection.	n.a.	Good Practice Point
Because a risk of CSF dissemination exists for all newly diagnosed patients, disease staging, including both craniospinal MRI and CSF cytology, is recommended following surgery (not earlier than 2–3 wk).	n.a.	Good Practice Point
Postoperative radiotherapy with doses ≥50 Gy is recommended in case of incomplete resection.	II	B
In case of relapse, consideration should be given to re-operation, re-irradiation, and chemotherapy.	III	C
Because of the risk of asymptomatic and/or late relapses, patients should be followed long term with an enhanced MRI.	n.a.	Good Practice Point

of postoperative neurological disability. A strong correlation between capsular violation at surgery and recurrence has been found.[110] An OS at 10 years exceeding 90% has been recently confirmed in an analysis by the Surveillance, Epidemiology, and End Results (SEER) program of 773 patients.[111] Presacral MPE shows a worse outcome compared with MPE of the filum terminale/cauda equina region.

Compared with patients treated with surgery alone, postoperative radiotherapy, especially with high doses (≥50 Gy), has been shown to increase the local control and PFS (10-y PFS from ˂40% to 70%) with good tolerance and without substantial late toxicity.[112,113] A small series on adult patients with spinal MPE has shown that patients treated by GTR followed by adjuvant radiotherapy had better local control than patients treated with GTR alone.[114] However, prospective confirmatory data are needed.

MPE is very rare in children. Although patients frequently present with disseminated tumor and/or develop recurrent or progressive disease following treatments,[115] the OS at 5 and 10 years in the SEER database is estimated at 97% and 95%, respectively.[116] A recent series from Johns Hopkins Hospital[117] indicated a significant reduction in local failure for patients receiving radiotherapy following STR or GTR. A smaller series[118] also confirmed good local control with surgery and radiotherapy compared with GTR alone.

Recommendations on treatment of MPEs are summarized in Table 6.

New Molecular Subgroups: Implications for Management

The aforementioned international molecular classification recognizes 9 molecular subgroups of ependymal tumors, 3 in each anatomical compartment of CNS: spine (SP), posterior fossa (PF), and supratentorial region (ST).[6] One of the subgroups within each compartment corresponds to WHO grade I subependymomas (SEs: SP-SE, PF-SE, and

ST-SE), occurs exclusively in adults, and shows favorable prognosis, while the 2 other molecular subgroups within the spine predominantly correspond to the histological diagnoses of MPE (SP-MPE) and WHO grades II–III ependymoma (SP-EPN).[6]

Two molecular types of ependymomas have been identified in the posterior fossa, termed PF-EPN-A and PF-EPN-B (group A and group B). PF-EPN-A tumors occur predominantly in infants and young children, are often in a lateral location and difficult to resect completely, and are associated with a high recurrence rate.[23] Conversely, PF-EPN-B tumors occur largely in adolescents and young adults and are associated with a more favorable prognosis. Data from a recent retrospective study on 4 independent nonoverlapping cohorts of PF-EPNs[119] found that patients with either group A or group B tumors appeared to benefit from GTR, with the survival rates being particularly poor for subtotally resected PF-EPN-A, even in association with radiation therapy. Moreover, a large subset of patients with PF-EPN-B who received a GTR did not recur even without adjuvant radiotherapy. Based on these data, participants in a multidisciplinary international consensus conference[120] agreed that for PF-EPN-A tumors in patients older than 12 months, maximal safe resection and focal radiotherapy should be defined as standard of care; furthermore, due to the challenging localization of tumors, patients would benefit from being treated in specialized centers by experienced neurosurgeons. Conversely, for patients with PF-EPN-B tumors undergoing GTR, a randomized clinical trial comparing observation versus standard focal radiotherapy could be launched.

A number of ST-EPNs are characterized by fusions between C11orf95 and the RELA gene (ST-EPN-RELA)[6,20] and occur in both children and adults. Retrospective studies have suggested that these tumors are associated with a poor prognosis, extent of resection not being significantly associated with outcome. Thus, in this patient population, postoperative radiotherapy seems to be recommended. Another molecular subgroup of ST-EPNs harbors recurrent fusion with the oncogene YAP1, is enriched in the pediatric population, and shows a favorable prognosis.[6,20] Gain of chromosome arm 1q occurs in a subset of PF-EPN-A, PF-EPN-B, and ST-EPN-RELA tumors and has been shown to be an independent negative prognostic factor.[26,121,122]

In conclusion, all these molecular subtypes with distinct prognosis will hopefully benefit from distinct personalized therapies. Table 4

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

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References

1. Dorfer C, Tonn J, Rutka JT. Ependymoma: a heterogeneous tumor of uncertain origin and limited therapeutic options. *Handb Clin Neurol*. 2016;134:417–431.
2. Ostrom QT, Gittleman H, Xu J, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2009–2013. *Neuro Oncol*. 2016;18(Suppl 5):iv1–iv76.
3. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131(6):803–820.
4. Wani K, Armstrong TS, Vera-Bolanos E, et al; Collaborative Ependymoma Research Network. A prognostic gene expression signature in infratentorial ependymoma. *Acta Neuropathol*. 2012;123(5):727–738.
5. Raghunathan A, Wani K, Armstrong TS, et al; Collaborative Ependymoma Research Network. Histological predictors of outcome in ependymoma are dependent on anatomic site within the central nervous system. *Brain Pathol*. 2013;23(5):584–594.
6. Pajtler KW, Witt H, Sill M, et al. Molecular classification of ependymal tumors across all CNS compartments, histopathological grades, and age groups. *Cancer Cell*. 2015;27(5):728–743.
7. Vera-Bolanos E, Aldape K, Yuan Y, et al; CERN Foundation. Clinical course and progression-free survival of adult intracranial and spinal ependymoma patients. *Neuro Oncol*. 2015;17(3):440–447.
8. Wu J, Armstrong TS, Gilbert MR. Biology and management of ependymomas. *Neuro Oncol*. 2016;18(7):902–913.
9. Brainin M, Barnes M, Baron JC, et al; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces—revised recommendations 2004. *Eur J Neurol*. 2004;11(9):577–581.
10. Rudà R, Gilbert M, Soffietti R. Ependymomas of the adult: molecular biology and treatment. *Curr Opin Neurol*. 2008;21(6):754–761.
11. Acquaye AA, Vera E, Gilbert MR, Armstrong TS. Clinical presentation and outcomes for adult ependymoma patients. *Cancer*. 2017;123(3):494–501.
12. Armstrong TS, Vera-Bolanos E, Bekele BN, Aldape K, Gilbert MR. Adult ependymal tumors: prognosis and the M. D. Anderson Cancer Center experience. *Neuro Oncol*. 2010;12(8):862–870.
13. Extremera VC, Alvarez-Coca J, Rodríguez GA, Pérez JM, de Villanueva JL, Díaz CP. Torticollis is a usual symptom in posterior fossa tumors. *Eur J Pediatr*. 2008;167(2):249–250.
14. Engelhard HH, Villano JL, Porter KR, et al. Clinical presentation, histology, and treatment in 430 patients with primary tumors of the spinal cord, spinal meninges, or cauda equina. *J Neurosurg Spine*. 2010;13(1):67–77.
15. Yuh EL, Barkovich AJ, Gupta N. Imaging of ependymomas: MRI and CT. *Childs Nerv Syst*. 2009;25(10):1203–1213.
16. Nowak J, Seidel C, Pietsch T, et al. Systematic comparison of MRI findings in pediatric ependymoblastoma with ependymoma and CNS primitive neuroectodermal tumor not otherwise specified. *Neuro Oncol*. 2015;17(8):1157–1165.
17. Jaremko JL, Jans LB, Coleman LT, Ditchfield MR. Value and limitations of diffusion-weighted imaging in grading and diagnosis of pediatric posterior fossa tumors. *AJNR Am J Neuroradiol*. 2010;31(9):1613–1616.

18. Tensaouti F, Ducassou A, Chaltiel L, et al; radiotherapy committee of the French Society for Childhood Cancer (SFCE). Prognostic and predictive values of diffusion and perfusion MRI in paediatric intracranial ependymomas in a large national study. *Br J Radiol*. 2016;89(1066):20160537.
19. Hasselblatt M, Paulus W. Sensitivity and specificity of epithelial membrane antigen staining patterns in ependymomas. *Acta Neuropathol*. 2003;106(4):385–388.
20. Parker M, Mohankumar KM, Punchihewa C, et al. C11orf95-RELA fusions drive oncogenic NF-κB signalling in ependymoma. *Nature*. 2014;506(7489):451–455.
21. Pietsch T, Wohlers I, Goschzik T, et al. Supratentorial ependymomas of childhood carry C11orf95-RELA fusions leading to pathological activation of the NF-κB signaling pathway. *Acta Neuropathol*. 2014;127(4):609–611.
22. Bayliss J, Mukherjee P, Lu C, et al. Lowered H3K27me3 and DNA hypomethylation define poorly prognostic pediatric posterior fossa ependymomas. *Sci Transl Med*. 2016;8(366):366ra161.
23. Witt H, Mack SC, Ryzhova M, et al. Delineation of two clinically and molecularly distinct subgroups of posterior fossa ependymoma. *Cancer Cell*. 2011;20(2):143–157.
24. Ellison DW, Kocak M, Figarella-Branger D, et al. Histopathological grading of pediatric ependymoma: reproducibility and clinical relevance in European trial cohorts. *J Negat Results Biomed*. 2011;10:7.
25. Korshunov A, Witt H, Hielscher T, et al. Molecular staging of intracranial ependymoma in children and adults. *J Clin Oncol*. 2010;28(19):3182–3190.
26. Godfraind C, Kaczmarska JM, Kocak M, et al. Distinct disease-risk groups in pediatric supratentorial and posterior fossa ependymomas. *Acta Neuropathol*. 2012;124(2):247–257.
27. Gramatzki D, Witt H, Hentschel B, et al. Clinical and molecular subgroups of ependymoma in adulthood: an analysis of the German Glioma Network. *J Clin Oncol*. 2017(suppl; abstr 2038):35.
28. Reni M, Brandes AA, Vavassori V, et al. A multicenter study of the prognosis and treatment of adult brain ependymal tumors. *Cancer*. 2004;100(6):1221–1229.
29. Rogers L, Pueschel J, Spetzler R, et al. Is gross-total resection sufficient treatment for posterior fossa ependymomas? *J Neurosurg*. 2005;102(4):629–636.
30. Metellus P, Barrie M, Figarella-Branger D, et al. Multicentric French study on adult intracranial ependymomas: prognostic factors analysis and therapeutic considerations from a cohort of 152 patients. *Brain*. 2007;130(Pt 5):1338–1349.
31. Metellus P, Guyotat J, Chinot O, et al. Adult intracranial WHO grade II ependymomas: long-term outcome and prognostic factor analysis in a series of 114 patients. *Neuro Oncol*. 2010;12(9):976–984.
32. McGuire CS, Sainani KL, Fisher PG. Incidence patterns for ependymoma: a Surveillance, Epidemiology, and End Results study. *J Neurosurg*. 2009;110(4):725–729.
33. Hollon T, Nguyen V, Smith BW, Lewis S, Junck L, Orringer DA. Supratentorial hemispheric ependymomas: an analysis of 109 adults for survival and prognostic factors. *J Neurosurg*. 2016;125(2):410–418.
34. Spagnoli D, Tomei G, Ceccarelli G, et al. Combined treatment of fourth ventricle ependymomas: report of 26 cases. *Surg Neurol*. 2000;54(1):19–26; discussion 26.
35. Oya N, Shibamoto Y, Nagata Y, Negoro Y, Hiraoka M. Postoperative radiotherapy for intracranial ependymoma: analysis of prognostic factors and patterns of failure. *J Neurooncol*. 2002;56(1):87–94.
36. Mansur DB, Perry A, Rajaram V, et al. Postoperative radiation therapy for grade II and III intracranial ependymoma. *Int J Radiat Oncol Biol Phys*. 2005;61(2):387–391.
37. Ghia AJ, Mahajan A, Allen PK, et al. Supratentorial gross-totally resected non-anaplastic ependymoma: population based patterns of care and outcomes analysis. *J Neurooncol*. 2013;115(3):513–520.
38. Nuño M, Yu JJ, Varshneya K, et al. Treatment and survival of supratentorial and posterior fossa ependymomas in adults. *J Clin Neurosci*. 2016;28:24–30.
39. Bi Z, Ren X, Zhang J, Jia W. Clinical, radiological, and pathological features in 43 cases of intracranial subependymoma. *J Neurosurg*. 2015;122(1):49–60.
40. Amirian ES, Armstrong TS, Aldape KD, Gilbert MR, Scheurer ME. Predictors of survival among pediatric and adult ependymoma cases: a study using Surveillance, Epidemiology, and End Results data from 1973 to 2007. *Neuroepidemiology*. 2012;39(2):116–124.
41. Pejavar S, Polley MY, Rosenberg-Wohl S, et al. Pediatric intracranial ependymoma: the roles of surgery, radiation and chemotherapy. *J Neurooncol*. 2012;106(2):367–375.
42. Kulkarni AV, Piscione J, Shams I, Bouffet E. Long-term quality of life in children treated for posterior fossa brain tumors. *J Neurosurg Pediatr*. 2013;12(3):235–240.
43. Timmermann B, Kortmann RD, Kühl J, et al. Combined postoperative irradiation and chemotherapy for anaplastic ependymomas in childhood: results of the German prospective trials HIT 88/89 and HIT 91. *Int J Radiat Oncol Biol Phys*. 2000;46(2):287–295.
44. Massimino M, Gandola L, Giangaspero F, et al; AIEOP Pediatric Neuro-Oncology Group. Hyperfractionated radiotherapy and chemotherapy for childhood ependymoma: final results of the first prospective AIEOP (Associazione Italiana di Ematologia-Oncologia Pediatrica) study. *Int J Radiat Oncol Biol Phys*. 2004;58(5):1336–1345.
45. Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. *Lancet Oncol*. 2009;10(3):258–266.
46. Good CD, Wade AM, Hayward RD, et al. Surveillance neuroimaging in childhood intracranial ependymoma: how effective, how often, and for how long? *J Neurosurg*. 2001;94(1):27–32.
47. Massimino M, Solero CL, Garrè ML, et al. Second-look surgery for ependymoma: the Italian experience. *J Neurosurg Pediatr*. 2011;8(3):246–250.
48. Millward CP, Mallucci C, Jaspan T, et al. Assessing 'second-look' tumour resectability in childhood posterior fossa ependymoma-a centralised review panel and staging tool for future studies. *Childs Nerv Syst*. 2016;32(11):2189–2196.
49. Koshy M, Rich S, Merchant TE, Mahmood U, Regine WF, Kwok Y. Postoperative radiation improves survival in children younger than 3 years with intracranial ependymoma. *J Neurooncol*. 2011;105(3):583–590.
50. Tensaouti F, Ducassou A, Chaltiel L, et al. Patterns of failure after radiotherapy for pediatric patients with intracranial ependymoma. *Radiother Oncol*. 2017;122(3):362–367.
51. Aggarwal R, Yeung D, Kumar P, Muhlbauer M, Kun LE. Efficacy and feasibility of stereotactic radiosurgery in the primary management of unfavorable pediatric ependymoma. *Radiother Oncol*. 1997;43(3):269–273.
52. Massimino M, Miceli R, Giangaspero F, et al. Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma. *Neuro Oncol*. 2016;18(10):1451–1460.
53. Conter C, Carrie C, Bernier V, et al. Intracranial ependymomas in children: society of pediatric oncology experience with postoperative hyperfractionated local radiotherapy. *Int J Radiat Oncol Biol Phys*. 2009;74(5):1536–1542.
54. Merchant TE, Kiehna EN, Li C, Xiong X, Mulhern RK. Radiation dosimetry predicts IQ after conformal radiation therapy in pediatric patients with localized ependymoma. *Int J Radiat Oncol Biol Phys*. 2005;63(5):1546–1554.

55. Leroy R, Benahmed N, Hulstaert F, Van Damme N, De Ruysscher D. Proton therapy in children: a systematic review of clinical effectiveness in 15 pediatric cancers. *Int J Radiat Oncol Biol Phys*. 2016;95(1):267–278.
56. Macdonald SM, Sethi R, Lavally B, et al. Proton radiotherapy for pediatric central nervous system ependymoma: clinical outcomes for 70 patients. *Neuro Oncol*. 2013;15(11):1552–1559.
57. Giantsoudi D, Adams J, MacDonald SM, et al. Proton treatment techniques for posterior fossa tumors: consequences for linear energy transfer and dose-volume parameters for the brainstem and organs at risk. *Int J Radiat Oncol Biol Phys*. 2017;97(2):401–410.
58. Pulsifer MB, Sethi RV, Kuhlthau KA, MacDonald SM, Tarbell NJ, Yock TI. Early cognitive outcomes following proton radiation in pediatric patients with brain and central nervous system tumors. *Int J Radiat Oncol Biol Phys*. 2015;93(2):400–407.
59. Indelicato DJ, Flampouri S, Rotondo RL, et al. Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy. *Acta Oncol*. 2014;53(10):1298–1304.
60. Kralik SF, Ho CY, Finke W, Buchsbaum JC, Haskins CP, Shih CS. Radiation necrosis in pediatric patients with brain tumors treated with proton radiotherapy. *AJNR Am J Neuroradiol*. 2015;36(8):1572–1578.
61. Indelicato DJ, Bradley JA, Sandler ES, et al. Clinical outcomes following proton therapy for children with central nervous system tumors referred overseas. *Pediatr Blood Cancer*. 2017; doi: 10.1002/pbc.26654.
62. Gunther JR, Sato M, Chintagumpala M, et al. Imaging changes in pediatric intracranial ependymoma patients treated with proton beam radiation therapy compared to intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2015;93(1):54–63.
63. MacDonald SM, Laack NN, Terezakis S. Humbling advances in technology: protons, brainstem necrosis, and the self-driving car. *Int J Radiat Oncol Biol Phys*. 2017;97(2):216–219.
64. Khatua S, Ramaswamy V, Bouffet E. Current therapy and the evolving molecular landscape of paediatric ependymoma. *Eur J Cancer*. 2017;70:34–41.
65. Grill J, Le Deley MC, Gambarelli D, et al; French Society of Pediatric Oncology. Postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age: a multicenter trial of the French Society of Pediatric Oncology. *J Clin Oncol*. 2001;19(5):1288–1296.
66. Grundy RG, Wilne SA, Weston CL, et al; Children's Cancer and Leukaemia Group (formerly UKCCSG) Brain Tumour Committee. Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study. *Lancet Oncol*. 2007;8(8):696–705.
67. Garvin JH Jr, Selch MT, Holmes E, et al; Children's Oncology Group. Phase II study of pre-irradiation chemotherapy for childhood intracranial ependymoma. Children's Cancer Group protocol 9942: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2012;59(7):1183–1189.
68. Venkatramani R, Ji L, Lasky J, et al. Outcome of infants and young children with newly diagnosed ependymoma treated on the "Head Start" III prospective clinical trial. *J Neurooncol*. 2013;113(2):285–291.
69. Merchant TE, Boop FA, Kun LE, Sanford RA. A retrospective study of surgery and reirradiation for recurrent ependymoma. *Int J Radiat Oncol Biol Phys*. 2008;71(1):87–97.
70. Zacharoulis S, Ashley S, Moreno L, Gentet JC, Massimino M, Frappaz D. Treatment and outcome of children with relapsed ependymoma: a multi-institutional retrospective analysis. *Childs Nerv Syst*. 2010;26(7):905–911.
71. Bouffet E, Hawkins CE, Ballourah W, et al. Survival benefit for pediatric patients with recurrent ependymoma treated with reirradiation. *Int J Radiat Oncol Biol Phys*. 2012;83(5):1541–1548.
72. Liu AK, Foreman NK, Gaspar LE, Trinidad E, Handler MH. Maximally safe resection followed by hypofractionated re-irradiation for locally recurrent ependymoma in children. *Pediatr Blood Cancer*. 2009;52(7):804–807.
73. Kano H, Yang HC, Kondziolka D, et al. Stereotactic radiosurgery for pediatric recurrent intracranial ependymomas. *J Neurosurg Pediatr*. 2010;6(5):417–423.
74. Hoffman LM, Plimpton SR, Foreman NK, et al. Fractionated stereotactic radiosurgery for recurrent ependymoma in children. *J Neurooncol*. 2014;116(1):107–111.
75. Lobón MJ, Bautista F, Riet F, et al. Re-irradiation of recurrent pediatric ependymoma: modalities and outcomes: a twenty-year survey. *Springerplus*. 2016;5(1):879.
76. Murphy ES, Chao ST, Angelov L, et al. Radiosurgery for pediatric brain tumors. *Pediatr Blood Cancer*. 2016;63(3):398–405.
77. Eaton BR, Chowdhry V, Weaver K, et al. Use of proton therapy for reirradiation in pediatric intracranial ependymoma. *Radiother Oncol*. 2015;116(2):301–308.
78. Gilbert MR, Ruda R, Soffietti R. Ependymomas in adults. *Curr Neurol Neurosci Rep*. 2010;10(3):240–247.
79. Iqbal MS, Lewis J. An overview of the management of adult ependymomas with emphasis on relapsed disease. *Clin Oncol (R Coll Radiol)*. 2013;25(12):726–733.
80. Rehman S, Brock C, Newlands ES. A case report of a recurrent intracranial ependymoma treated with temozolomide in remission 10 years after completing chemotherapy. *Am J Clin Oncol*. 2006;29(1):106–107.
81. Freyschlag CF, Tuettenberg J, Lohr F, Thomé C, Schmieder K, Seiz M. Response to temozolomide in supratentorial multifocal recurrence of malignant ependymoma. *Anticancer Res*. 2011;31(3):1023–1025.
82. Kim WH, Kim WH, Yoon SH, et al. Temozolomide for malignant primary spinal cord glioma: an experience of six cases and a literature review. *J Neurooncol*. 2011;101(2):247–254.
83. Khoo HM, Kishima H, Kinoshita M, et al. Radiation-induced anaplastic ependymoma with a remarkable clinical response to temozolomide: a case report. *Br J Neurosurg*. 2013;27(2):259–261.
84. Lombardi G, Pambuku A, Bellu L, et al. Cisplatin and temozolomide combination in the treatment of supratentorial anaplastic ependymoma. *Chemotherapy*. 2013;59(3):176–180.
85. Rudà R, Bosa C, Magistrello M, et al. Temozolomide as salvage treatment for recurrent intracranial ependymomas of the adult: a retrospective study. *Neuro Oncol*. 2016;18(2):261–268.
86. Chamberlain MC, Johnston SK. Temozolomide for recurrent intracranial supratentorial platinum-refractory ependymoma. *Cancer*. 2009;115(20):4775–4782.
87. Gilbert MR, Yuan Y, Wani K, et al. A Phase II Study of lapatinib and dose-dense temozolomide (TMZ) for adults with recurrent ependymoma: a CERN clinical trial [Abstract]. *Neuro Oncol*. 2014;16(5):AT-23.
88. Buccoliero AM, Castiglione F, Rossi Degl'Innocenti D, et al. O6-methylguanine-DNA-methyltransferase in recurring anaplastic ependymomas: PCR and immunohistochemistry. *J Chemother*. 2008;20(2):263–268.
89. Gramatzki D, Roth P, Felsberg J, et al. Chemotherapy for intracranial ependymoma in adults. *BMC Cancer*. 2016;16:287.
90. Gornet MK, Buckner JC, Marks RS, Scheithauer BW, Erickson BJ. Chemotherapy for advanced CNS ependymoma. *J Neurooncol*. 1999;45(1):61–67.
91. Brandes AA, Cavallo G, Reni M, et al. A multicenter retrospective study of chemotherapy for recurrent intracranial ependymal tumors in adults by the Gruppo Italiano Cooperativo di Neuro-Oncologia. *Cancer*. 2005;104(1):143–148.
92. Rojas-Marcos I, Calvet D, Janoray P, Delattre JY. Response of recurrent anaplastic ependymoma to a combination of tamoxifen and isotretinoin. *Neurology*. 2003;61(7):1019–1020.
93. Green RM, Cloughesy T, Stupp R, et al. Bevacizumab for recurrent ependymoma. *J Clin Oncol*. 2009;27(15_suppl):2060.

94. Bouffet E, Foreman N. Chemotherapy for intracranial ependymomas. *Childs Nerv Syst*. 1999;15(10):563–570.

95. Grill J, Kalifa C. High dose chemotherapy for childhood ependymona. *J Neurooncol*. 1998;40(1):97.

96. Robison NJ, Campigotto F, Chi SN, et al. A phase II trial of a multi-agent oral antiangiogenic (metronomic) regimen in children with recurrent or progressive cancer. *Pediatr Blood Cancer*. 2014;61(4):636–642.

97. Jakacki RI, Foley MA, Horan J, et al. Single-agent erlotinib versus oral etoposide in patients with recurrent or refractory pediatric ependymoma: a randomized open-label study. *J Neurooncol*. 2016;129(1):131–138.

98. Komori K, Yanagisawa R, Miyairi Y, et al. Temozolomide treatment for pediatric refractory anaplastic ependymoma with low MGMT protein expression. *Pediatr Blood Cancer*. 2016;63(1):152–155.

99. Gururangan S, Chi SN, Young Poussaint T, et al. Lack of efficacy of bevacizumab plus irinotecan in children with recurrent malignant glioma and diffuse brainstem glioma: a Pediatric Brain Tumor Consortium study. *J Clin Oncol*. 2010;28(18):3069–3075.

100. DeWire M, Fouladi M, Turner DC, et al. An open-label, two-stage, phase II study of bevacizumab and lapatinib in children with recurrent or refractory ependymoma: a Collaborative Ependymoma Research Network study (CERN). *J Neurooncol*. 2015;123(1):85–91.

101. Wetmore C, Daryani VM, Billups CA, et al. Phase II evaluation of sunitinib in the treatment of recurrent or refractory high-grade glioma or ependymoma in children: a Children's Oncology Group study ACNS1021. *Cancer Med*. 2016;5(7):1416–1424.

102. Tobin MK, Geraghty JR, Engelhard HH, Linninger AA, Mehta AI. Intramedullary spinal cord tumors: a review of current and future treatment strategies. *Neurosurg Focus*. 2015;39(2):E14.

103. Eroes CA, Zausinger S, Kreth FW, Goldbrunner R, Tonn JC. Intramedullary low grade astrocytoma and ependymoma. Surgical results and predicting factors for clinical outcome. *Acta Neurochir (Wien)*. 2010;152(4):611–618.

104. Lin Y, Smith ZA, Wong AP, Melkonian S, Harris DA, Lam S. Predictors of survival in patients with spinal ependymoma. *Neurol Res*. 2015;37(7):650–655.

105. Oh MC, Ivan ME, Sun MZ, et al. Adjuvant radiotherapy delays recurrence following subtotal resection of spinal cord ependymomas. *Neuro Oncol*. 2013;15(2):208–215.

106. Shaw EG, Evans RG, Scheithauer BW, Ilstrup DM, Earle JD. Radiotherapeutic management of adult intraspinal ependymomas. *Int J Radiat Oncol Biol Phys*. 1986;12(3):323–327.

107. Chamberlain MC. Etoposide for recurrent spinal cord ependymoma. *Neurology*. 2002;58(8):1310–1311.

108. Morris KA, Afridi SK, Evans DG, et al. The response of spinal cord ependymomas to bevacizumab in patients with neurofibromatosis Type 2. *J Neurosurg Spine*. 2017;26(4):474–482.

109. Weber DC, Wang Y, Miller R, et al. Long-term outcome of patients with spinal myxopapillary ependymoma: treatment results from the MD Anderson Cancer Center and institutions from the Rare Cancer Network. *Neuro Oncol*. 2015;17(4):588–595.

110. Abdulaziz M, Mallory GW, Bydon M, et al. Outcomes following myxopapillary ependymoma resection: the importance of capsule integrity. *Neurosurg Focus*. 2015;39(2):E8.

111. Bates JE, Choi G, Milano MT. Myxopapillary ependymoma: a SEER analysis of epidemiology and outcomes. *J Neurooncol*. 2016;129(2):251–258.

112. Schild SE, Nisi K, Scheithauer BW, et al. The results of radiotherapy for ependymomas: the Mayo Clinic experience. *Int J Radiat Oncol Biol Phys*. 1998;42(5):953–958.

113. Schild SE, Wong W, Nisi K. In regard to the radiotherapy of myxopapillary ependymomas. *Int J Radiat Oncol Biol Phys*. 2002;53(3):787.

114. Akyurek S, Chang EL, Yu TK, et al. Spinal myxopapillary ependymoma outcomes in patients treated with surgery and radiotherapy at M.D. Anderson Cancer Center. *J Neurooncol*. 2006;80(2):177–183.

115. Bandopadhayay P, Silvera VM, Ciarlini PD, et al. Myxopapillary ependymomas in children: imaging, treatment and outcomes. *J Neurooncol*. 2016;126(1):165–174.

116. Lucchesi KM, Grant R, Kahle KT, Marks AM, DiLuna ML. Primary spinal myxopapillary ependymoma in the pediatric population: a study from the Surveillance, Epidemiology, and End Results (SEER) database. *J Neurooncol*. 2016;130(1):133–140.

117. Agbahiwe HC, Wharam M, Batra S, Cohen K, Terezakis SA. Management of pediatric myxopapillary ependymoma: the role of adjuvant radiation. *Int J Radiat Oncol Biol Phys*. 2013;85(2):421–427.

118. Al-Halabi H, Montes JL, Atkinson J, Farmer JP, Freeman CR. Adjuvant radiotherapy in the treatment of pediatric myxopapillary ependymomas. *Pediatr Blood Cancer*. 2010;55(4):639–643.

119. Ramaswamy V, Hielscher T, Mack SC, et al. Therapeutic impact of cytoreductive surgery and irradiation of posterior fossa ependymoma in the molecular era: a retrospective multicohort analysis. *J Clin Oncol*. 2016;34(21):2468–2477.

120. Pajtler KW, Mack SC, Ramaswamy V, et al. The current consensus on the clinical management of intracranial ependymoma and its distinct molecular variants. *Acta Neuropathol*. 2017;133(1):5–12.

121. Mendrzyk F, Korshunov A, Benner A, et al. Identification of gains on 1q and epidermal growth factor receptor overexpression as independent prognostic markers in intracranial ependymoma. *Clin Cancer Res*. 2006;12(7 Pt 1):2070–2079.

122. Kilday JP, Mitra B, Domerg C, et al. Copy number gain of 1q25 predicts poor progression-free survival for pediatric intracranial ependymomas and enables patient risk stratification: a prospective European clinical trial cohort analysis on behalf of the Children's Cancer Leukaemia Group (CCLG), Societe Francaise d'Oncologie Pediatrique (SFOP), and International Society for Pediatric Oncology (SIOP). *Clin Cancer Res*. 2012;18(7):2001–2011.