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## EANO guidelines for the diagnosis and treatment of ependymal tumors

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## **EANO guidelines for the diagnosis and treatment of ependymal tumors**

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### **Importance of the study**

This manuscript reports the evidence-based guidelines on management of ependymal tumors in children and adults developed by a multidisciplinary Task Force of the EANO, 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 also serve as a source of knowledge for institutions and insurance companies involved in cancer care in Europe.

**Keywords:** Ependymoma, **Molecular Pathology, Treatments, Children, Adults.**

### **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 cranio-spinal magnetic resonance. Tumor classification is achieved by histological and molecular diagnostic assessment of tissue specimens according to the 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.

## Introduction

Ependymal tumors are rare central nervous system tumors.<sup>1</sup> According to the Central Brain Tumor Registry of the United States of America (CBTRUS), the annual incidence of ependymal tumors is estimated at 0.43 patients per 100,000 population.<sup>2</sup> **These tumors account for 1.8 % of all primary central nervous system (CNS) tumors and for 6.8 % of all gliomas<sup>2</sup>.** In children (0-19 years of age) ependymal tumors are proportionally more common and account for 5.2 % of all primary CNS tumors.<sup>2</sup> 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.<sup>3</sup> The WHO classification also comprises a histological grading into three distinct grades of malignancy, i.e. WHO grade I, II or III.

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

A recent molecular classification has distinguished nine 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.<sup>6</sup> Each of the nine 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.<sup>8</sup> 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 until 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.<sup>9</sup> 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.

### **Clinical and neuroimaging diagnosis**

**The clinical presentation of ependymomas (Supplementary Material) depends primarily on patient age, tumor location and tumor size.<sup>10-14</sup>**

Magnetic resonance imaging (MRI) with contrast enhancement is the modality of choice for diagnosing ependymal tumors.<sup>15,16</sup> Computed tomography (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 post-contrast 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 (DWI) may be useful for differentiating pilocytic astrocytomas, medulloblastomas, and ependymomas in the posterior fossa.<sup>17</sup> MR spectroscopy (MRS) reveals elevated choline and reduced N-acetylaspartate (NAA) levels.<sup>8</sup> Perfusion MRI may display elevated cerebral blood volume (CBV) values **and have some prognostic value.**<sup>18</sup> **Spinal cord ependymomas display more distinct borders than diffuse astrocytomas.**<sup>14</sup> 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 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.<sup>3</sup> 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 PAS staining for glycogen. Immunohistochemically, ependymal tumors react positive for glial fibrillary acidic protein (GFAP) and protein S100 but usually lack nuclear positivity for OLIG2. Dot-like perinuclear and ring-like cytoplasmic

immunoreactivity for epithelial membrane antigen (EMA) is a characteristic feature.<sup>19</sup> Nuclear immunoreactivity for RELA and expression of L1CAM may help to identify RELA fusion-positive ependymomas.<sup>20,21</sup> However, molecular testing for C11orf95-RELA fusion by fluorescent in situ hybridization (FISH) or reverse-transcription PCR analysis is required for a firm diagnosis.<sup>3</sup> Loss of nuclear expression of trimethylated histon 3 lysine 27 (H3-K27me3) distinguishes a prognostically unfavorable group of posterior fossa ependymomas in children,<sup>22</sup> largely corresponding to the posterior fossa ependymoma type A (see below).<sup>6,23</sup> Proliferative activity is commonly assessed by Ki-67 immunostaining; however, definite cut-offs for grading have not been defined.

The 2016 WHO classification of CNS tumors includes five distinct entities of ependymal tumors.<sup>3</sup> Myxopapillary ependymoma WHO grade I is histologically characterized by cuboidal or elongated tumor cells forming fibrillary processes towards 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 tancytic ependymoma. Ependymoma, RELA fusion-positive is a novel supratentorial ependymoma entity that is defined by the presence of a C11orf95-RELA fusion.<sup>6,20</sup> It may correspond to WHO grade II or III but patient outcome is worse compared to other types of supratentorial ependymomas.<sup>6</sup> 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 grade II and III ependymomas is challenging and its role in predicting survival has been disputed.<sup>24</sup> 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.<sup>4,6,25,26,27</sup>

### **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.<sup>10</sup>

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.<sup>28-33</sup> In a retrospective series of WHO grade II ependymomas in adults<sup>31</sup> the 5- and 10- year OS rates were 86.1 and 81%, respectively. Preoperative Karnofsky Performance Score (KPS), extent of resection and tumor location were independent prognostic factors for overall survival. In particular, gross total resection (GTR), defined as no residual disease on post-contrast T1 and T2-weight images on a 3-month post-operative 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.<sup>34</sup> In case of persistent hydrocephalus despite tumor resection, shunting or endoscopic ventriculostomy need 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.<sup>35</sup> In adults, there is agreement that post-operative 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.<sup>29,36</sup> Conversely, the role of postoperative radiotherapy in patients with ependymoma WHO grade II undergoing GTR remains controversial.<sup>37</sup> In two large retrospective studies, including patients with intracranial WHO grade II ependymomas,<sup>31,38</sup> no significant association of radiotherapy with PFS or OS was found. However, in the French study<sup>31</sup> 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.<sup>39</sup> 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.

### **Treatment of newly diagnosed intracranial ependymal tumors in children**

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

Surgery and radiotherapy are the mainstay of treatment for ependymomas in children<sup>41</sup>. Extent of resection is the most important prognostic factor, but the site of the lesions (e.g. posterior fossa tumors involving the ponto-cerebellar region) can limit surgery due to involvement of the lower cranial nerves and brainstem<sup>42</sup>: 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.<sup>43-45</sup> A second-look surgery is increasingly undertaken when the first resection has been incomplete.<sup>46-48</sup> The benefit of post-operative radiotherapy has been shown in terms of local control and survival rates in children with intracranial ependymomas<sup>45</sup> An Italian Study<sup>44</sup> reported on attempted GTR followed by post-operative radiotherapy, and showed a 7-year estimate of local control, event-free survival and OS of 83.7%, 69% and 81%, respectively. Data from the St Jude's Children Hospital<sup>45</sup> showed improved local control, EFS and OS with 59.4 Gy in 1.8 Gy fractions with 3DRT without any apparent increase of late neurocognitive deficits. Therefore, postoperative radiotherapy with 59.4 Gy (1.8 Gy/fraction) has been advocated<sup>45</sup> 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<sup>49</sup>: 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.<sup>50</sup> As local control remains the primary goal of treatment, the possibility to compensate for an incomplete surgery by applying an hypofractionated stereotactic boost in addition to conventional radiotherapy has been proposed.<sup>51</sup> 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%<sup>52</sup>. A prospective study has shown that hyperfractionated radiotherapy is safe but provides no outcome benefit compared with standard fractionated regimens<sup>53</sup>.

The toxicity of radiotherapy in younger children is of concern, and IMRT has been employed to limit late sequelae.<sup>44</sup> Merchant and colleagues<sup>54</sup> developed a model combining dose-volume data with clinical factors to predict IQ outcomes and concluded that the radiation dose remains the most clinically significant determinant of IQ outcomes and 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.<sup>55</sup> In this regard, the Massachusetts General Hospital group reported the outcome of 70 children with localized ependymomas treated with proton therapy:<sup>56</sup> 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 posterior fossa ependymoma,<sup>57</sup> 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 protons therapy in order to reduce the neurocognitive impairment, and in this regard the preliminary data are encouraging.<sup>58</sup>

**However, recent studies<sup>59-61</sup> 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.<sup>62</sup> The benefit and risks of proton therapy need to be confirmed with modern proton treatments and in prospective studies.<sup>63</sup> A prospective study (NCT01288235) with protons therapy is ongoing in US.**

The role of chemotherapy in children remains unproven despite intensive investigation.<sup>64</sup> As there is reluctance to deliver radiation to very young children, post-operative 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.<sup>44,65-67</sup> The role of intensified schedules of chemotherapy was suggested in baby protocols,<sup>66</sup> especially for supratentorial tumors.<sup>68</sup> In contrast, the use of immediate post-operative high-dose conformal radiotherapy in children under the age of 3 years led to 7-year progression-free survival rates of 77%,<sup>45</sup> 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 to 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.<sup>69</sup> 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.<sup>70</sup> Re-irradiation is performed in adults as well as in children, using either a full course of fractionated irradiation<sup>69,71</sup> or hypo-fractionated stereotactic irradiation<sup>72-76</sup> or proton therapy,<sup>77</sup> 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.<sup>78,79</sup>

Similar to other gliomas, temozolomide has been used for the treatment of adult patients with ependymoma. Some case reports suggested that temozolomide alone or in combination is active against recurrent WHO grade II or III ependymoma.<sup>80-84</sup> A retrospective study on 18 patients with recurrent WHO grade II and III intracranial ependymomas failing re-operation or re-irradiation or both suggested an activity of temozolomide in the standard schedule both in terms of response (22% CR + PR) and outcome (PFS 9.69 months and OS 30.55 months).<sup>85</sup> Responses were observed in chemotherapy-naïve patients only, and in most cases were delayed in appearance. Conversely, in another retrospective study<sup>86</sup> on patients with WHO grade II intracranial ependymomas refractory to first line chemotherapy with platinum compounds, temozolomide 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<sup>86</sup> were heavily pretreated, while the majority of patients of the other cohort<sup>85</sup> 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.<sup>87</sup> Lapatinib targets the epidermal growth factor receptor (ErbB1) and the related family member HER-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 temozolomide against ependymoma might be due to the lack of O6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation in ependymoma cells;<sup>88,89</sup> however, even when present, MGMT promoter methylation may not correlate with response to temozolomide.<sup>85</sup>

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.<sup>90</sup> Another retrospective series reported higher response rates in patients with progressive or recurrent ependymoma treated with cisplatin compared to non platinum regimens, but no difference in terms of PFS and OS was observed.<sup>91</sup> Other drugs and regimens were only used in single patients, such as tamoxifen and isotretinoin.<sup>92</sup> 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.<sup>93</sup>

Phase II studies in children with relapsing ependymomas have reported a low response rate with either standard<sup>94</sup> or high dose chemotherapy.<sup>95</sup> Metronomic therapies have produced some long term-stabilizations.<sup>96</sup> Responses have been reported with oral etoposide<sup>97</sup> or temozolomide.<sup>98</sup> Bevacizumab, in association with either irinotecan<sup>99</sup> or lapatinib,<sup>100</sup> has proven disappointing. Targeted agents, such as erlotinib<sup>97</sup> or sunitinib<sup>101</sup>, 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.<sup>10</sup> They include WHO grade I subependymoma and myxopapillary ependymoma, and WHO grade 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.<sup>102</sup> Advances in microsurgical techniques have allowed en bloc GTR over piecemeal subtotal resection 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.<sup>103,104</sup> When GTR is not feasible because of infiltration of spinal cord or nerves roots, postoperative local radiotherapy is commonly employed. A recent review of the literature on 348 patients with WHO grade II and III spinal cord ependymomas, who underwent surgery with known extent of resection (GTR or STR), with or without postoperative radiotherapy, has been performed.<sup>105</sup> After multivariate analysis, extent of resection and tumor grade were independent prognostic factors for OS and PFS, and radiotherapy prolonged PFS in patients receiving subtotal resection: median PFS was 48 months in patients treated with STR alone and 96 months for patients 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.<sup>105,106</sup>

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

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

Large retrospective series on myxopapillary ependymomas (MPE) have been performed, including a large multinstitutional series of 183 patients,<sup>109</sup> that showed a 10-year OS of 92.4% and a 5- and 10-year PFS rates of 69.5% and 61.2%. MPE recurrence was local in 84% patients, and leptomeningeal spread was observed in 9.3% patients. Extent of resection was a major independent factor predicting local control, while younger age (<36 yrs) 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 of postoperative neurological disability. A strong correlation between capsular violation at surgery and recurrence has been found.<sup>110</sup> An OS at 10 years exceeding 90% has been recently confirmed in a SEER analysis on 773 patients.<sup>111</sup> Presacral MPE shows a worse outcome compared to MPE of the filum terminale/cauda equina region.

Compared to patients treated with surgery alone, post-operative radiotherapy, especially with high doses ( $\geq 50$  Gy), has been shown to increase the local control and PFS (10-year PFS from <40% to 70%) with good tolerance and without substantial late toxicity.<sup>112,113</sup> A small series on adult patients with spinal MPE has shown that patients treated by GTR followed by adjuvant radiotherapy had a better local control than patients treated with GTR alone<sup>114</sup>: 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,<sup>115</sup> the OS at 5 and 10 years in the SEER database is estimated at 97% and 95%, respectively.<sup>116</sup> A recent series from Johns Hopkins Hospital<sup>117</sup> indicated a significant reduction in local failure for patients receiving radiotherapy following STR or GTR. A smaller series<sup>118</sup> also confirmed the good local control with surgery and radiotherapy compared to GTR alone.

Recommendations on treatment of myxopapillary ependymomas are summarized in Table 6.

### **New molecular subgroups: implications for management**

**The aforementioned international molecular classification recognizes** nine molecular subgroups of ependymal tumors, three in each anatomical compartment of CNS, i.e. spine (SP), posterior fossa (PF), and supratentorial region (ST).<sup>6</sup> One of the subgroups within each compartment **corresponds to** WHO grade I subependymomas (SE), (SP-SE, PF-SE and ST-SE), occurs **exclusively** in adults, and shows **favourable** prognosis, **while the** two other molecular

subgroups within the spine predominantly **correspond to the histological diagnoses of** myxopapillary ependymoma (SP-MPE) and WHO grade II-III ependymoma (SP-EPN).<sup>6</sup>

Two molecular types of ependymomas have been identified in the posterior fossa, termed PF-EPN-A and PF-EPN-B (posterior fossa ependymoma group A and 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.<sup>23</sup> Conversely, PF-EPN-B tumors occur largely in adolescent and young adults and are associated with a more favorable prognosis. Data from a recent retrospective study on four independent non-overlapping cohorts of posterior fossa ependymomas<sup>119</sup> found that patients with either PF-EPN-A or PF-EPN-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<sup>120</sup> agreed that for PF-EPN-A tumors in patients older than 12 months of age 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 supratentorial ependymomas are characterized by fusions between C110RF95 and the RELA gene (ST-EPN-RELA),<sup>6,20</sup> 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 supratentorial ependymomas harbors recurrent fusion with the oncogene YAP1 (St-EPN-YAP1), is enriched in the pediatric population, and shows a favorable prognosis.<sup>6,20</sup> 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.<sup>26,121,122</sup>

In conclusion, **all these** molecularly subtypes with distinct prognosis **will hopefully benefit from distinct personalized therapies.**

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## **Response to reviewers' comments:**

Reviewer #1: we thank the reviewer for the suggestions

- 1) INTRODUCTION. Ependymoma frequency in children seems not so low from available papers. This sentence need a quotation.

We have inserted the reference and replaced the CBTRUS report of 2015 with that of 2016

- 2) INTRODUCTION. "Ependymal tumors are of neuroectodermal origin and classified according to the World Health Organization (WHO) classification of CNS tumors into distinct entities and histological variants": please avoid repetition (classification and classified in the same sentence<sup>9</sup>)

We have removed the repetition

- 3) INTRODUCTION. In the following sentence be consistent by using infratentorial instead of posterior fossa.

We have replaced “posterior fossa” with “infratentorial”

- 4) The part dedicated to clinical symptoms could be shorten and put in a table.

We have moved the description of clinical symptoms as a table in the Supplementary Material

- 5) TREATMENT FOR CHILDREN. The second page of children treatment contains a sentence concerning the safety of proton therapy that needs to be less enthusiastic.

We have modified the sentence accordingly, and inserted new references on the effects of proton therapy

- 6) NEW MOLECULAR SUBGROUPS. Mitigate also the sentence about a PF-EPN-B tumor study substituting "should" with "could".

We have replaced “should” with “could”

- 7) NEW MOLECULAR SUBGROUPS. Be precise about RELA study and prognosis by specifying that these report are retrospective studies.

We have specified that data regarding RELA subtype come from retrospective studies

- 8) REFERENCES. Kilday paper needs a number.

Done

- 9) Table 4 needs amendment. Since one of the Authors in the SIOP responsible for ependymoma protocol, ask him to properly edit this table. SOME ASPECTS:

All commas in the numbers must be substituted with fullstops. It is not true that the GTV is contrast enhancing lesions because many ependymomas do not have enhancement. This must be corrected in all the table. Not all ependymomas have contrast enhancement. Boost must be erogated to 3D identifiable residual disease.

Table 4 has been modified.

10) In table 5 there are some mistake in spaces.

Done

11) The supplementary table about radiotherapy in children is quite confusing. I propose to put only prospective trials since retrospective are a very big number. Add also Neuro Oncol. 2016 Oct;18(10):1451-60, already quoted in references and the last to be published and Int J Radiat Oncol Biol Phys. 2009 Aug 1;74(5):1536-42 We have reported prospective studies only , and added the reference (Couter et al, 2009) that has been suggested

Reviewer #3: we thank the reviewer for the kind comments. No changes requested.

Reviewer #4: this is a well written review and a herculean effort involving physician from the multidisciplinary teams across different European countries to develop evidence-based clinical practice guidelines for diagnosis and treatment of children with ependymal tumors. No new data are presented. There is little discussion of recent molecular alterations that have been identified.

We thank the reviewer for the comments. We agree that we did not present new data as the aim of the Guidelines was to review the evidence from the literature and draw recommendations. This is the reason also for the limited discussion of recent molecular alterations.

### **Supplementary Material: Neurological symptoms and signs at presentation in ependymal tumors**

- Symptoms of raised intracranial pressure, such as headache, vomiting, and altered mental status, due an obstruction of the flow of cerebrospinal fluid (CSF), thus causing hydrocephalus.
- Ataxia due to cerebellar compression, edema and, sometimes, infiltration
- Vertigo and nausea from compression and infiltration of the lateral recess and inferior half of the 4th-ventricular floor.
- Cranial neuropathies due to brainstem involvement
- Focal neurological deficit and/or seizures in supratentorial tumors
- Torticollis and cervicgia due to a tumor extension through the foramen of Magendie and into the cervical spinal canal in infratentorial tumors of children
- Central spinal cord syndrome with pain and/or sensory disturbances (often a “suspended sensory level”), in spinal ependymomas.

**Supplementary material : Summary of radiotherapy studies in pediatric patients with ependymoma**

Author, year	Type of study	Treatment			Number of patients	Efficacy	
		RT		Chemotherapy		Overall survival	Progression-free survival
		Photon	Proton				
Timermann et al, 2000	Prospective trial	54Gy at primary site in 13 pts, 1Gy/fr; 35.2Gy CSI (1.5Gy/fr)+20Gy boost (2.0Gy/fr) in 40 pts		+	53 pts	3-y: 75.6% (all)	3-y: 59.7% (all) 3-y: 83.3% (CR) 3-y: 38.5% (R+)
Massimino et al, 2004	Prospective trial	HFRT 70.4Gy, 1.1Gy/fr twice daily		+ in case of residual tumour (17 pts)	63 pts	5-y: 75% (all) 5-y: 82% (CR) 5-y: 61% (R+)	5-y: 56% (all) 5-y: 65% (CR) 5-y: 35% (R+)
Merchant et al, 2009	Prospective trial	59.4 Gy(131 pts), 1.8Gy/fr/d; 54Gy (22pts) kids<18 months with complete resection		+ for 35 pts	153 pts	7-y: 81% 5-y: 93% (CR) 5-y: 52.4% (R+)	7-y EFS: 69.1% 7-y LC: 87.3% 5-y EFS: 81.5% (CR) 5-y EFS: 41% (R+)
Conter et al, 2009	Prospective trial	60 Gy after complete resection (CR) and 66 Gy after partial resection, delivered in two daily fractions of 1 Gy, according to the early postoperative imaging findings.		no	24 pts	5-y: 74.8%	5-y: 54.2%
Massimino et al, 2016	Prospective trial	59.4 Gy(131 pts), 1.8Gy/fr/d; with and additional boost of 2X4Gy if residue.		+ for all pts	160 pts	5-y : 65.4 % 5-y :58.1% (residue and boost)	5-y : 81.1 % 5-y : 68.7 % (residue and boost)

Table 1. Key recommendations for the treatment of newly diagnosed intracranial WHO grade II and III ependymomas in adults.	Class of Evidence	Level of Recommendation
Resection is recommended to obtain an 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 weeks).	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 grade II and III ependymomas in children.	Class of Evidence	Level of Recommendation
Resection is recommended to obtain an 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 weeks)	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

**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

**Table 4. Key recommendations regarding non-surgical treatment of WHO grade 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 months	Debatable	VEC +/_ Cisplatin	Maintenance	systematically	Post-operatively	tumour bed and 3D identifiable residual disease	5-10 mm around GTV	59.4	1.8	3DCRT or IMRT or proton
Localized tumor, age >18 months with visible residual tumor after surgery	Recommended	VEC +/_ Cisplatin +/- HD Methotrexate	Post-operatively	Stereotactic additional boost recommended within a prospective clinical trial with residue after chemotherapy	Post-operatively and post-chemotherapy	tumour bed and 3D identifiable residual disease		59.4+8	4	3DCRT or IMRT or proton
Localized tumor, age 12-18 months	Recommended	Baby UK	Maintenance	To be discussed	Post-operatively	tumour bed and 3D identifiable residual disease		54	1.6 – 1.8	
Localized tumor, age <12 months	Recommended	Baby UK	Post-operatively	NO	NO	-	-	-	-	
Metastatic tumor	Debatable	VEC +/_ Cisplatin	Before RT	Salvage treatment	Post-operatively or post-chemotherapy	tumours 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	Post-operatively	3D identifiable disease	GTV+2 mm	59 or in a prospective trial 25Gy/5 fractions or 24 Gy/ 3 fractions	1.8 or hypofractionation (5 – 8)	3DCRT or IMRT or proton or hypofractionated stereotactic irradiation

CT : Chemotherapy. VEC : Vincristine/Etoposide/ cyclophosphamide regimen. GTV: Growth tumor volume; CTV : clinical target volume.

Table 5. Key recommendations for the treatment of WHO grade II and III spinal cord ependymomas	Class of Evidence	Level of Recommendation
Gross total resection is the goal of spinal ependymoma surgery.	II	B
Post-operative 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 weeks).	n.a.	Good Practice Point
In case of WHO grade III (anaplastic) ependymomas, postoperative radiotherapy with doses of 45-54Gy 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 myxopapillary ependymomas (MPE) 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 weeks).	n.a.	Good Practice Point
Post-operative radiotherapy with doses $\geq 50$ Gy is recommended in case of incomplete resection.	II	B
In case of relapse, re-operation, re-irradiation and chemotherapy should be considered.	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