EANO–EURACAN clinical practice guideline for diagnosis, treatment, and follow-up of post-pubertal and adult patients with medulloblastoma

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The European Association of Neuro-Oncology (EANO) and EUropean RAre CANcer (EURACAN) guideline provides recommendations for the diagnosis, treatment, and follow-up of post-pubertal and adult patients with medulloblastoma. The guideline is based on the 2016 WHO classification of tumours of the CNS and on scientific developments published since 1980. It aims to provide direction for diagnostic and management decisions, and for limiting unnecessary treatments and cost. In view of the scarcity of data in adults with medulloblastoma, we base our recommendations on adult data when possible, but also include recommendations derived from paediatric data if justified. Our recommendations are a resource for professionals involved in the management of post-pubertal and adult patients with medulloblastoma, for patients and caregivers, and for health-care providers in Europe. The implementation of this guideline requires multidisciplinary structures of care, and defined processes of diagnosis and treatment.

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Introduction

Medulloblastoma is an embryonal tumour of the cerebellum and represents the second most common malignant neoplasm of the CNS in children. Medulloblastoma is rare in post-pubertal patients and adults, constituting less than 1% of CNS tumours in this age group (females with a bone age of at least 15 years and males with a bone age of at least 17 years, or adults), with an incidence of 0·6–1 case per million per year.[1] For readability purposes, this population will be called adult in this Review. The biology of medulloblastoma varies across different age groups leading to distinct prognostic patterns that can influence treatment decisions.

Medulloblastoma is potentially curable and current treatments lead to 5-year overall survival rates in adults of up to 70% when using multimodal chemoradiotherapy approaches following surgical resection.[2–7] To achieve these results, interdisciplinary management is crucial. Medulloblastoma has a good prognosis, however late outcomes also need to be addressed. Available data are scarce regarding the management of medulloblastoma in adult patients and thus, an evidence-based guideline is not feasible. We therefore provide a multidisciplinary clinical practice consensus guideline that follows the revision of the fourth edition of the WHO *Classification of Tumours of the Central Nervous System*.[8] All authors were asked to categorise their statements according to published guidelines into levels of evidence and grades of recommendation. Here, classes of evidence for diagnostic measures and therapeutic interventions are categorised into four classes (I–IV, with class I being the highest level of evidence) and recommendations into three levels (levels A, B, and C, with level A being the highest level of recommendation).[9]

This Review provides the best possible approach to guide diagnostic and therapeutic procedures for adults with medulloblastoma, and covers prevention, diagnosis, screening, therapy, and follow-up, including adverse effects of treatment and supportive care. It does not address palliative care. This is the first EANO–EURACAN guideline on medulloblastoma in adult patients.

Development and molecular genetics

Medulloblastoma represents a biologically and clinically heterogeneous group of embryonal tumours of the cerebellum. Four molecular subgroups are recognised (wingless-type [WNT], sonic hedgehog [SHH], group 3, and group 4), each associated with different molecular and clinical characteristics, and prognosis. The subgroups form an essential foundation for adaptating treatments on the basis of disease risk, determining whether to use targeted therapies, and defining avenues for ongoing research.[8]

WNT-subgroup medulloblastoma (WNT-MB) is thought to arise from lower rhombic lip progenitors and accounts for approximately 10% of all medulloblastoma. These tumours occur in both childhood (>4 years) and post-pubertal or adult patients. Adults with WNT-MB might not share the same favourable outcomes of patients with WNT-MB aged younger than 16 years old.[2,10,11]

Cerebellar granule neuron progenitors (GNP) are the probable cell of origin for SHH medulloblastoma (SHH-MB), which frequently occurs in the cerebellar hemispheres. In infants (<3 years of age) and adults (>16 years of age; approximately 60% of adult patients), SHH-activated *TP53*^{WT} medulloblastoma represents the most common subgroup.[2,4] Adult SHH-MB tends to have

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a higher burden of mutations than does childhood SHH-MB, with more than 80% of adult SHH-MB patients harbouring alterations in either *PTCH1* or *SMO*, who are excellent candidates for molecularly targeted therapy.[12–14] Immunotherapy has not been evaluated in medulloblastoma so far, but the overall mutational burden is known to be low, as is the degree of immune cell infiltration.

Most of the non-WNT and non-SHH-MB are in group 4.[2,15] These tumours are thought to arise from neural progenitor cells located in the cerebellar midline. Group 3 tumours are rare in adulthood.[2,10]

Key genetic events and prognostic factors, such as high-level *MYC* amplifications (poor prognosis) and concerted whole-chromosome genetic aberration patterns (favourable prognosis) have been identified for the childhood disease. Prognostic factors have also been identified in adult medulloblastoma (eg, *CDK6* amplification);[4] however, their relevance and any association with the defined medulloblastoma entities or molecular subgroups remain to be confirmed.[11,14,16–18] In the past few years, novel molecular subtypes within non-SHH and non-WNT were identified that could provide an essential platform for further investigations.[16,19]

Panel: **Diagnosis and therapy options from the high-level evidence[9]**

Level I A

- Medulloblastoma must be classified according to the WHO classification of 2016[9]
- Staging and response assessment must include cerebrospinal fluid cytology to detect leptomeningeal dissemination[1]
- Adults with medulloblastoma should be treated with radiotherapy of the craniospinal axis[10]

Level II A

- Craniospinal MRI should be used as standard diagnostic imaging[1]
- A gross total resection should be done;[7] however, in cases where it is either not safe, not feasible, or both, maximal safe resection, sparing eloquent areas, and leaving residual tumour behind should be done[8]
- Adults with medulloblastoma should be treated with systemic therapy, irrespective of their risk category[3,11–14]

Level II B

- T-stage evaluation should be done as it is likely to have prognostic value in adults[2,3]

Level III A

- All patients should be offered psychological and social support[15]

Level III B

- M-stage evaluation can be done, although its prognostic value in adults is unclear[4–6]

Diagnostics

Early diagnosis and screening

Medulloblastoma is a rare sporadic disease in adults and can evolve rapidly, which renders early detection and screening challenging. Patients with medulloblastoma are usually diagnosed after they have presented with clinical symptoms. Brain MRI should be used to detect medulloblastoma (level II A; panel).[20] Investigations in specialised neuro-oncological centres might be advantageous in allowing more rapid and coordinated diagnosis and treatment initiation.

Medulloblastoma is associated with rare hereditary cancer predisposition syndromes. Waszak and colleagues[21] defined and characterised six clinically relevant medulloblastoma predisposition genes in paediatric cohorts on the basis of rare variant burden analysis (*APC, BRCA2, PALB2, PTCH1, SUFU,* and *TP53*). Half of the patients with damaging germline mutations were not recognised on the basis of familial history of cancer. The authors recommend genetic counselling and genetic testing as a standard-of-care procedure in patients with APC^{mut} WNT-MB and SHH-MB with germline mutations. Patients with germline *TP53, PTCH1,* and *SUFU* mutations have been reported to be predisposed to SHH-MB. So far, some consensus regarding screening for medulloblastoma has been achieved for relatives of patients with Li-Fraumeni (ie, germline *TP53* mutations) syndrome. Long-term compliance with a surveillance protocol for early tumour detection, including an annual brain MRI, in individuals with pathogenic germline *TP53* variants has been shown to be feasible, and early tumour detection was associated with improved long-term survival.[22] Gorlin syndrome (nevoid basal cell carcinoma syndrome), with germline mutations in the SHH pathway, including *PTCH1* and *SUFU,* is responsible for an autosomal dominant, tumour-prone condition. About 5% of family members develop SHH-MB, usually in the first 3 years of life. Brain MRI in the first years of life in *SUFU* mutation carriers has therefore been recommended.[23] Patients with Turcot's syndrome, who have a germline mutation in the *APC* gene, are predisposed to WNT-MB. Whole-exome sequencing of germline DNA is likely to reveal other putative causes of medulloblastoma in cancer syndromes.[24] Recommendations for early medulloblastoma surveillance for rare germline carriers, however, remains an area of great challenge.

Although serum markers or liquid biopsies for early detection of medulloblastoma seem technically feasible, these procedures are still under preclinical evaluation.[25] In addition to disseminating through the cerebrospinal fluid (CSF), medulloblastoma can metastasise through circulating tumour cells in the blood, providing a potential tool for early diagnosis.[26]

History and clinical examination

Patients often present with a combination of increased intracranial pressure, hydrocephalus, or cerebellar

symptoms because of the tumour's typical location in the posterior fossa. Clinical features include truncal ataxia and gait disturbances (68%), headache (>90%), nausea and vomiting (specifically with fasting emesis in the morning; 59%), neck stiffness, a decreasing general condition, and lethargy, with symptoms varying according to age at diagnosis. Adults will more often present with ataxia of the extremities,[4,27] as they have a high incidence of SHH-mutated tumours that are located in the hemispheres of the cerebellum.[28,29] Neurocognitive deficits might also occur, mostly consisting of impaired attention, visual perception, and verbal fluency.[30] Medulloblastoma has a propensity to disseminate within the subarachnoid space, and much less frequently to extraneural locations, such as the lymph nodes, bone marrow, skeleton, lungs, and liver, which might cause symptoms. Therefore, a thorough clinical and neurological examination is warranted at each consultation. However, in most cases, such disseminations are asymptomatic and usually found only in surveillance studies, except for metastasis to the bones, which often causes localised pain.

Diagnostic imaging

MRI of the brain is the method of choice to assess and follow-up medulloblastoma. Hyperintensity on CT of the brain could help to differentiate medulloblastoma from pilocytic astrocytoma (figure 1). Recommendations for MRI imaging have been formulated within the Response Assessment in Pediatric Neuro-Oncology (RANO) committee.[20] Cerebral MRI at diagnosis and follow-up should include axial or three-dimensional (3D) T1-weighted, T2-weighted, fluid-attenuated inversion recovery, diffusion-weighted images (DWI), and postcontrast T1-weighted sequences (level III A). Sequential slice thickness should not exceed 4 mm without gap, requiring modern phased-array coils to keep the acquisition time within reasonable limits. The RANO working group has recommended that non-contrast-enhancing tumour components should be an additional key feature of response.[20] Medulloblastoma often has a high signal on DWI due to restricted diffusion with low apparent diffusion coefficient values.[31] Most medulloblastoma enhances heterogeneously (85–100%) and shows little oedema.[32] Additional cysts or necrosis (50–90% of tumours), calcifications (10–40%), and bleeding (5–15%) add to their heterogeneity.

SHH-MB often has a lateral localisation within the cerebellar hemispheres, more oedema than other types of medulloblastoma, and a strong diffusion restriction.[33] WNT-MB is frequently localised around the foramen of Luschka,[34] and tends to bleed. Group 4 tumours are characterised by minimal or absent contrast uptake.[33] Due to the group 4 medulloblastomas' propensity to disseminate along the neuroaxis including the most caudal parts, medulloblastoma can produce drop metastases and adherent meningeosis, and therefore requires accurate spinal MRI staging. Postoperative scans can show surgical artefacts or bleeding. Thus, spinal MRI should be done preoperatively or 2–3 weeks postoperatively in all patients and during follow-up in the case of local relapse, systemic metastasis, and if clinical symptoms appear that can be attributed to the spinal cord, but not routinely (level II B).[35] Spinal imaging should include postcontrast T1-weighted images in sagittal and axial planes or 3D sequences; axial images should be taken to discriminate perimedullary veins from pathological contrast uptake (level III B).[20] To guarantee high-resolution imaging, the spinal canal of adults should be examined in at least two separate parts. The absence of intracranial progression is highly predictive of an absence of subarachnoid dissemination on spinal MRI.[36] A complete radiological staging with cranial and spinal MRI is therefore not considered standard in the follow-up of adult patients with medulloblastoma.

Subarachnoid tumour nodules often do not enhance on postcontrast T1-weighted images. DWI is a very sensitive tool to detect these non-enhancing nodules and helps to differentiate tumour recurrence from therapy-induced changes.[37] In addition, subarachnoid non-enhancing metastases are clearly detectable on high-resolution T2-weighted images, of which 3D myelography techniques best depict spinal metastases. Relevant discrepancies between local radiology reports and central neuroradiology review support the importance of special expertise in this field.[20,38] A central review or reference consultation should therefore be done before treatment.

Perioperative investigation

In addition to MRI imaging, staging, and response assessment should include CSF cytology to detect leptomeningeal dissemination (level II A),[20] which should be done before or 14 days after surgery. Whether postoperative lumbar CSF draws are more sensitive than CSF draws during ventriculocystostomy for diagnosing leptomeningeal disease is unclear.[20,39] Given the high cure rates, patients should be counselled for preservation of fertility (level III A). Presurgical and postsurgical neurological, neurocognitive, endocrine, auditory, ocular, peripheral nerve, and renal function should be regularly documented (level III A), and all patients should be offered psychological and social support.[40]

Ancillary studies

Patients with corresponding clinical symptoms and those with tumour recurrence should receive a CT of the chest and abdomen, or alternatively a fluorodeoxyglucose PET scan (level III B). PET should not be used as part of routine tests at diagnosis or follow-up.[41,42] Electroencephalography should not be used in the diagnosis or follow-up of patients without seizures (level III A). For all patients, medulloblastoma tissue, CSF, and blood samples should be cryopreserved for future molecular marker studies.

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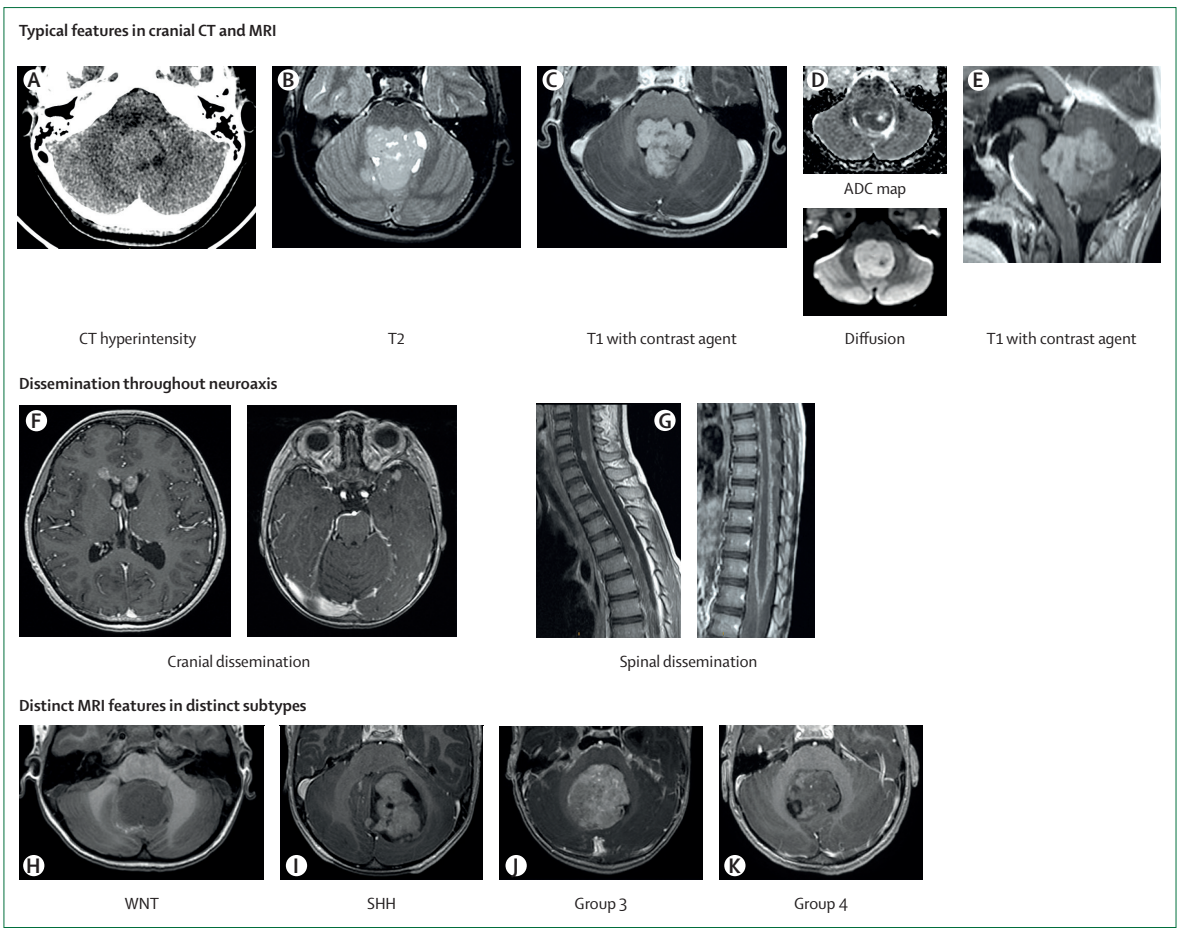

Figure 1: **CT and MRI features of medulloblastoma**
(A) Hyperintensity in CT, in contrast to hypointense low-grade astrocytomas. (B) Isointense to slightly hyperintense appearance on T2-weighted magnetic resonance images. (C) Typically, only parts of the tumour enhance heterogeneously. (D) Diffusion-weighted imaging and apparent diffusion coefficient maps with high cell density. (E) Most medulloblastomas arise from the roof of the fourth ventricle. The spreading of the aqueduct is a typical sign of intraventricular growth. (F) Medulloblastoma typically spreads along the cerebrospinal fluid (CSF) pathways. CSF seeding is common at first presentation and in tumour recurrence. (G) Contrast-enhanced imaging of the whole neuroaxis. Pattern that may give diagnostic hints in direction of subtype: haemorrhage in WNT (H); hemispheric cerebellar location in SHH (I); prominent enhancement and leptomeningeal spread in group 3 (J); mild or no enhancement in group 4 (K).

Preoperative management

Since medulloblastoma frequently presents as an emergency with signs and symptoms of increased intracranial pressure, rapid preoperative imaging with CT, MRI, or both is needed to detect and characterise the lesion. The surgical treatment algorithm depends on the severity of obstructive hydrocephalus. If possible, surgery with definite tumour removal should be used to relieve the obstruction-causing hydrocephalus (level III A).[43] After tumour removal, in most cases no further CSF diversion procedure is needed. In case immediate definitive surgery is not possible, an emergency external ventricular drain through Kocher's point, or through a Frazier burr hole should be placed temporarily (level II A). An alternative procedure is an endoscopic third ventriculostomy.

Vasogenic tumour oedema should be reduced by administration of corticosteroids before surgery (level III A), typically with 8 mg dexamethasone per day, in a single dose in the morning.[44] Primary antiepileptic prophylaxis is not indicated in patients without seizures. Patients with medulloblastoma who have had the rare event of an epileptic seizure should receive anticonvulsant drugs from the timepoint of their first epileptic seizure (level III A). Preoperative management should follow multidisciplinary discussion in a brain tumour board.

Biopsy and resection

Most patients present with hydrocephalus or symptoms from mass effect caused by the tumour. A gross total resection (GTR) with a residual volume of less than 1·5 cm² should be done in all patients to alleviate symptoms and to facilitate rapid diagnosis (level II A).[3] Tumour resection should be done with intraoperative neuromonitoring and should take place in high-volume centres. If a total resection is anatomically feasible, a second-look operation should be considered in case the

initial operation did not result in a GTR.[3] In cases of brain stem involvement, leaving a residue is typically safe.[45] A postoperative MRI should be done within 48 h (level III A).[46]

In patients with group 4 tumours, a progression free-survival benefit of GTR is proven. In cases where GTR is either not safe or not feasible, a maximal safe resection sparing eloquent areas and leaving residual tumour behind should be done (level II A).[47] Postsurgical cerebellar mutism has been rarely described in adult patients with medulloblastoma.[48] However, self-reported speech difficulties might be higher than previously thought.[49] For midline tumours, we therefore recommend the telovelar approach with minimal retraction.

Histological classification and molecular diagnosis

According to the concept of an integrated diagnosis in the revised WHO classification of tumours of the CNS (2016),[8] medulloblastoma entities must be defined by both histological and molecular or genetic features (level I A).The exact annotation of tumours to distinct medulloblastoma entities allows a precise assignment of patients for risk-adapted stratification. All medulloblastoma entities correspond to WHO grade IV. For a histopathological diagnosis, the tumours are assigned to one of four entities: classic, desmoplastic or nodular (DNMB), extensive nodular, or large cell/anaplastic on the basis of morphological criteria (figure 2).[8] The genetically defined component comprises four entities: WNT-activated, SHH-activated and *TP53*^{WT}, SHH-activated and *TP53*^{mut}, or non-WNT and non-SHH.[8]

Under the non-WNT or non-SHH designation, group 3 and group 4 were included as provisional variants (figure 2). Validated, robust methods are available for this classification and for a differential diagnosis. A combination of immunohistochemical markers including β-catenin, Yap1, filamin, p75-NGFR, Gab1, Otx2, and p53, with targeted sequencing and copy number assessment (eg, fluorescence in-situ hybridisation) allows precise assignment to a specific medulloblastoma entity and securely excludes histological mimics such as small cell carcinomas, melanocytic tumours, or glial tumours.[50,51] Complementary methods for classification at the mRNA (NanoString, RNA-Seq)[52,53] or DNA level (copy number variations, epigenetic classification by methylation array, or minimum methylation classifier assay)[16,54–57] are useful ancillary tools that are validated in clinical diagnostics, and might enable the distinction of differential diagnosis, provisional variants (eg, group 3 or 4), and novel subtypes.[18] Such molecular subclassification has become a routine procedure in the diagnosis of paediatric medulloblastomas and should also be regarded as part of the standard procedure for adult medulloblastoma.[54–56]

In adults, SHH-activated *TP53*^{WT} medulloblastoma represents the most frequent type.[2] SHH activation is caused by the quasi-diagnostic mutations of *PTCH1* or *SMO* in most adult cases. Most SHH-MB in adults carries somatic *TERT* promoter mutations.[13] In few SHH-activated and WNT-activated tumours, *IDH1* mutations are present.[19] As both *TERT* and *IDH1* mutations are genetic hallmark events in subgroups of gliomas, their presence alone, without consideration of the molecular, histological, and immunohistochemical context, does not allow differentiation between malignant cerebellar glioma and medulloblastoma. Histologically, most SHH-MB shows DNMB patterns in haematoxylin and eosin staining and reticulin staining. Even when this pattern occurs only in restricted areas, it qualifies the tumour for the diagnosis of DNMB. A smaller fraction of SHH-MB shows classic histology. *TP53*^{mut} is rare in adult SHH-MB but could occur de novo in recurrent tumours. According to the WHO classification,[8] *TP53* should be sequenced in all SHH-MB. Approximately 15% of adult medulloblastomas show WNT activation, mostly caused by activating somatic mutations in the *CTNNB1* gene. The presence of a *CTNNB1* mutation should therefore be confirmed by sequencing for the definite diagnosis of most WNT tumours.

However, alternative inactivating mutations in *APC* are rare and might indicate germline mutations (familial polyposis coli). Almost all WNT-MB shows classic histology, with a monosomy of chromosome 6 occurring in only a fraction of adult WNT-MB. Non-WNT or non-SHH-MB represents approximately 25% of adult medulloblastoma.[2,15] Transcriptomic and epigenetic classification has revealed that adult non-WNT and non-SHH-MB represents mostly group 4 variants.[2,15,58] Most non-WNT and non-SHH-MB shows classic morphology. Cytogenetically, isochromosome 17q is present in most cases. In addition, some cases show amplifications such as *CDK6*, while amplifications of *MYC* or *MYCN* are rare in adults.

General recommendations for therapy

We recommend treating patients with this rare disease in specialised neuro-oncological centres. Experienced high-volume centres could provide a more rapid, coordinated, and up-to-date treatment path. Inclusion into paediatric trials might be considered for younger adults up to the age of 21 years. In general, treatment within clinical trials should be prioritised in comparison to individual treatment.

Prognostic factors

Clinicobiological prognostic factors derive from analyses of large paediatric trials and have not been uniformly confirmed in retrospective series in adults. The Chang staging system describes the extent of tumour infiltration (T1–T4) and subdivides metastatic stages into M0 (no evidence of metastases), M1 (microscopic tumour cells in CSF), M2 (gross nodular seeding in the cerebellum, cerebral subarachnoid space, or third, or fourth ventricles), M3 (gross nodular seeding in the spinal subarachnoid space), and M4 (extraneuraxial metastases).[59] The T-stage is not prognostic in paediatric

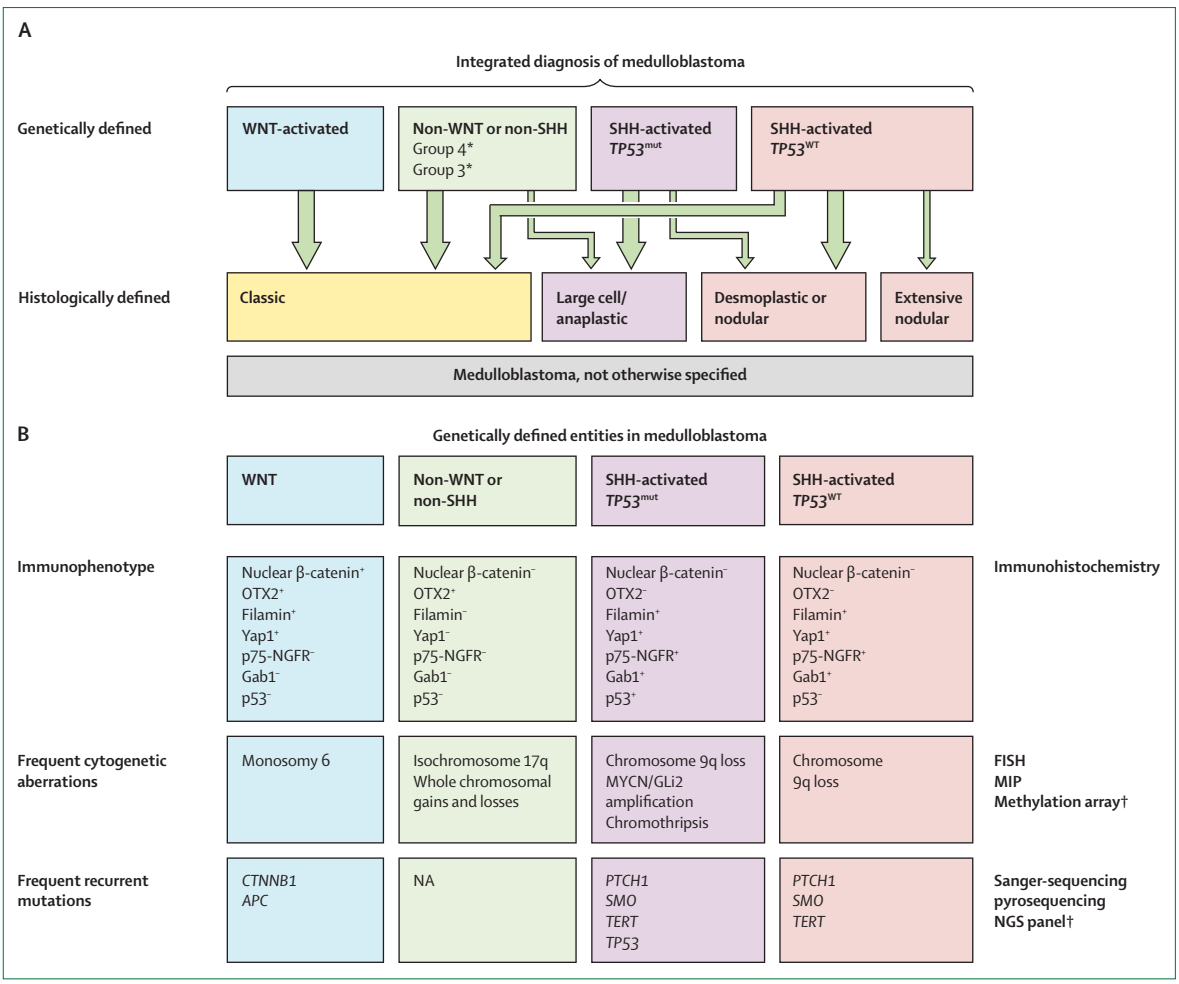

Figure 2: **Neuropathological classification of medulloblastoma**
(A) Integrated diagnoses[8] with the most frequent entities in adults. Width of the green arrows indicates the most prominent associations between histologically and genetically defined entities. (B) Genetically defined, most frequent entities in adults. FISH=fluorescence in-situ hybridisation. MIP=molecular inversion probe assay. NGS=next-generation sequencing. NA=not available. *Groups 3 and 4 are provisional variants. †Currently in validation for application in clinical diagnostics.

studies,[60,61] however, data from adults show a role of T-stage in prognosis,[7,62] and staging should therefore be done in adults (level II B). Advanced methods, such as radiomics, could facilitate the staging of medulloblastoma; however, these methods are far away from clinical application. M-stage at diagnosis is prognostic in children,[38,60,63] but its role in adults is less clear: some series report worse outcomes for patients with metastatic disease, while others do not.[6,64,65] M-staging might eventually be used to allocate patients to prognostic groups (level III C). Residual tumour after surgery is an independent prognostic factor in some paediatric studies,[3,60,63] but not in others[66–68] or in adults.[7]

Of note, within the same subgroups, outcomes in adults differ from infants and children.[2] Large cell/anaplastic histology is considered as a high-risk feature in adults.[15,69,70] SHH-MB has more favourable progression-free survival and overall survival than group 4 tumours.[2,10,15] WNT-MB do not appear to share the same favourable outcomes of patients younger than 16 years.[2,10,11] *MYCN* amplifications and *TP53* mutations in the SHH subtype[10,16,71] confer a worse prognosis in children compared with their wild type counterparts. *TP53* mutations in adults more likely constitute somatic mutations than in children, since they are rarely associated with clinical definitions of genetic syndromes such as Li-Fraumeni syndrome. Therefore, they might not confer the same prognostic significance in adults as in children.[17] In children, the poor prognosis associated with *MYCN* amplification does not extend to group 4 tumours; however, any similar relationship in adults remains to be determined.[11]

Taken together, large cell/anaplastic histology, and non-WNT or non-SHH (group 4) medulloblastoma appear to be associated with a worse outcome in adults compared with children. Residual tumour, metastatic disease, and SHH-MB with *TP53* mutations might be associated with worse outcomes than not having these characteristics. The available information should be used with caution

because it is mostly derived from retrospective cohorts of patients without homogenous treatment. In addition, the data for adults are either conflicting or based on very small numbers, and prospective confirmation for adult patients will be necessary in future trials.

Surgical therapy

Midline medulloblastoma can be approached in two ways, either by the midline transvermian or the preferred telovelar approach. Resection of the inferior vermis might be required for intraventricular tumours. If the resection extends superiorly, one should attempt to obtain enough access to the fourth ventricle to avoid extensive cerebellar retraction (level III B).[44] Up to a half of adult medulloblastoma occurs in the cerebellar hemisphere and requires a paramedian approach.[72] The telovelar approach is advantageous for the resection of tumours that extend to the lateral cisterns. The patient is positioned prone or in park-bench position. A sitting position has the advantage of a clear operative field, but is accompanied by a relevant risk of developing air embolism and pneumatocephalus.[73] A postoperative MRI is recommended within 48 h to quantify the extent of resection, define the amount of residual tumour, and acquire a baseline imaging for further follow-up studies. A second look surgery should be considered if residual tumour of more than 1·5 cm² is noted on the postoperative scan.

Radiotherapy

In paediatric cohorts, the quality of radiotherapy with adequate dosing schedules strongly relates to the outcome.[74] Hence, a high level of quality assurance is recommended (level III A). Radiotherapy data from paediatric trials are extrapolated, in most cases, to adults. Craniospinal irradiation is mandatory (level I A),[75] and due to the large target volume, it is a technically complex approach. In the standard setting, radiotherapy is delivered postoperatively. The backbone is craniospinal irradiation with a total dose of 36 Gy in daily fractions of 1·8 Gy, or a dose of 35·2 Gy in daily fractions of 1·6 Gy, each five times weekly. In addition, a local dose escalation to the posterior fossa, generally with a total dose up to 54–55·8 Gy, is done.[75]

There is an ongoing discussion about the appropriate dose to the tumour bed or posterior fossa. In the posterior fossa, a dose of higher than 50 Gy is associated with a better outcome than lower doses (level III A).[62] In a paediatric trial (COG ACNS0331), a reduced boost volume only to the tumour bed was equally effective to a standard dose;[76] however, this modification has not been investigated in adults so far. A craniospinal irradiation dose reduction to 23·4 Gy in combination with chemotherapy has been used in paediatric trials,[77] and might be used in adults (level III B). A dose decrease for radiotherapy in addition to chemotherapy for intermediate-risk adult medulloblastomas will be prospectively explored in upcoming trials (eg, NCT01857453).

In centres that use hyperfractionated radiotherapy on a daily basis, and in patients with a self-containing performance status but macroscopic metastatic disease and a bad prognosis, a hyperfractionated radiotherapy (1·0 Gy twice per day to 40 Gy craniospinal irradiation dose; 60 Gy posterior fossa-boost; 68 Gy tumour bed-boost; 50–60 Gy metastatic deposits-boost) could be an alternative to standard fractionation, together with chemotherapy, yielding a 4-year overall survival of 91% (level II B).[7,64]

If photon radiotherapy is used, helical tomotherapy or volumetric intensity modulated arc therapy should be used because of better dose conformity and uniformity (level III B).[78] Moreover, field patching can be avoided, which eliminates a substantial source of potential setup errors if helical intensity-modulated radiotherapy (also known as tomotherapy) is used. If available, proton therapy can be considered as an alternative to helical intensity-modulated radiotherapy or volumetric intensity modulated arc therapy for reduction of long-term side-effects (level III B).[79,80] Similar survival outcomes were reached in children treated with protons and children treated with photon irradiation.[81] In accordance with paediatric study protocols, we would recommend initiation of radiotherapy within 28–42 days after surgery.

Systemic therapy

Medulloblastoma is a chemosensitive tumour. Adult patients with medulloblastoma should be treated with systemic therapy, in addition to resection and radiotherapy, irrespective of their risk category (level II A). Treatment recommendations are based on paediatric trials, on retrospective analysis of adult cohorts within paediatric trials, and on single-arm, prospective trials in adults.

The Packer chemotherapy regimen (eight doses of vincristine 1·5 mg/m² [maximum of 2 mg] during radiotherapy, followed by a maximum of eight cycles of lomustine 75 mg/m² on day 1, cisplatin 70 mg/m² on day 1 and vincristine 1·5 mg/m² [maximum of 2 mg] on days 1, 8, and 15 of 6-week cycles) was developed with and without radiotherapy dose reduction.[75,82] This regimen has set the basis for a series of paediatric trials,[6,67,83] and has also been used in adults. In a retrospectively evaluated trial cohort (HIT-2000), 49 adults with non-metastatic disease who received combined chemoradiotherapy had a 4-year event-free survival of 74% and overall survival of 94%.[6] Tolerance to the Packer chemotherapy regimen appears to be worse in adolescents and adults than in children.[30,84] In general, an age-related lower tolerance to intensive chemotherapy for adult patients compared with children must be expected for all regimens. Since we do not have any study results yet where cisplatin, lomustine, or vincristine have been replaced by drugs with fewer acute and late toxicities, only strict de-escalation rules can be advised. Substitution of cisplatin by carboplatin to prevent

non-haematological side-effects is considered at some sites but has not been investigated as a primary therapy in adults. Alternative regimens, such as the Taylor regimen (preradiation chemotherapy comprising vincristine, etoposide and carboplatin alternating with cyclophosphamide in children aged 3–16 years), have not been prospectively evaluated in adults.[68]

In adults, only single-arm, prospective trials with different chemotherapy regimens exist, mainly based on cisplatin combinations. In a prospective phase 2 trial by Brandes and colleagues,[7] 26 patients at high risk (T3b–T4, M1–M3 disease, or postoperative residual tumour) received two cycles of upfront chemotherapy, mainly consisting of cisplatin, followed by radiotherapy and adjuvant chemotherapy. After a median follow-up of 7·6 years, 5-year progression-free survival was 69% (95% CI 54–89) and 5-year overall survival was 73% (58–92). Ten patients at low risk received radiotherapy alone, and their 5-year progression-free survival was 80% (95% CI 59–100) and 5-year overall survival was 80% (58–100). A further retrospective analysis of this trial with a median follow-up of 10 years showed that patients at low risk who had received cisplatin-based chemotherapy after radiotherapy obtained a 5-year and 10-year overall survival of 100%, compared with 100% and 78·6%, respectively, in patients treated with radiotherapy alone (p=0·079).[7,85]

The prospective phase 2 trial (NOA-07) for non-risk stratified patients aged older than 21 years used the Packer regimen and evaluated toxicity and therapy-related terminations of postoperative chemoradiotherapy. The regimen was feasible for most patients for up to six cycles, but leucopenia, polyneuropathy, and ototoxicity were major toxicities. Feasibility was age dependent with more adverse events and substantially more severe adverse events in patients older than 45 years compared with patients younger than 45 years. The authors recommend discontinuing vincristine on the first signs of polyneuropathy.[30] 3-year event-free survival was 66·6%, 3-year progression-free survival was 66·6%, and overall survival was 70·0%.

Meta-analyses also suggest a greater benefit with combined radiotherapy and chemotherapy in comparison to radiotherapy alone. Kocakaya and colleagues[5] scrutinised 227 publications with 907 adult patients treated from 1969 to 2013. Patients receiving chemotherapy at any point during treatment (71%) survived longer (median overall survival of 108 months, 95% CI 68·6–148·4) than those treated with radiotherapy alone (29%, 57 months, 39·6–74·4).[5] A retrospective analysis of the National Cancer Database registry of 751 patients aged 18 years or older treated between 2004 and 2012 also supports the superiority of postoperative radiotherapy and chemotherapy over radiotherapy alone.[86]

There are no randomised data on the best chemotherapy partners for radiotherapy in adults. Vincristine is commonly used, however, treatment is often terminated early because of polyneuropathy. No data are available to support high-dose chemotherapy with autologous stem cell transplantation to further improve outcome in adults with medulloblastoma.

Other therapeutic approaches

With the recognition of medulloblastoma subtyping, personalised targeted therapies could be available in the future. SMO inhibitors were investigated in several trials[87,88] and should be integrated in prospective clinical studies in adults. Large registries have been initiated that characterise tumour samples with high-throughput methods on several molecular levels (NCT02238899, NCT02417324). These initiatives show that screening patients on the molecular level is feasible within an acceptable timeframe and with a potentially actionable readout. A systematic investigation of targeted agents that are based on such screenings has not been done yet. Dose-reduced conventional radiotherapy and methods such as tomotherapy and protons are potential alternatives to the current standard that are being explored within prospective clinical trials. One such trial is testing a decreased radiotherapy dose in combination with chemotherapy for adult patients with intermediate-risk medulloblastoma (NCT01857453).

Monitoring and follow-up

In addition to clinical examination, MRI should be used to evaluate disease status, treatment response, and follow-up (level IV A[9]). Surveillance MRI allows early detection of local tumour recurrence. At recurrence, the diagnosis of medulloblastoma is challenging, especially in cases with dissemination along the subarachnoid space since such dissemination is often asymptomatic. No specific recommendations for clinical and MRI follow-up in adults have been published so far. Every 3 months, MRI scanning during treatment is common practice and recommended for all subgroups (figure 3). After the active treatment phase, a 3–6 monthly follow-up schedule with cranial MRI until the end of year 5 after diagnosis, followed by annual follow-ups for up to 10 years might be practical.[36,41,89] In case of suspected progressive disease, a short-term (4–6 weeks) confirmatory MRI should be done (level IV A). Monitoring and follow-up should include at least clinical examination and endocrinological functions, evaluation of vision, hearing, kidney function, skin integrity, polyneuropathy and fertility, and consider psychosocial aspects at each visit.

Most recurrences are focal or multifocal within the brain. Systemic metastases occur, including extraneural dissemination to the bone marrow, skeleton, lung, and liver,[36,41,89] with a moderate prevalence of about 5% in WNT-dependent medulloblastoma and a high prevalence of about 30% in group 4 medulloblastoma. Adult SHH-MB more frequently relapses locally in the tumour bed than does analogous paediatric medulloblastoma and

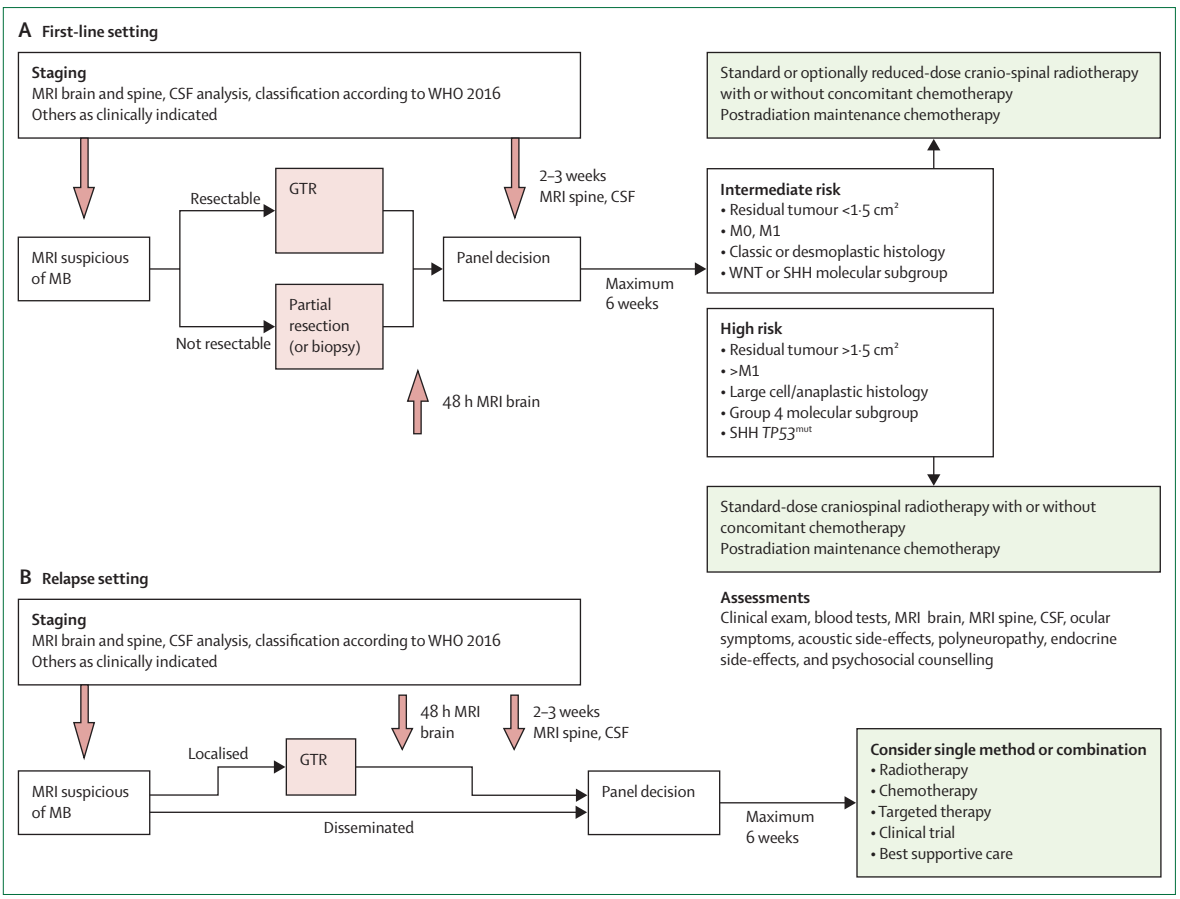

Figure 3: **Diagnostic and therapeutic pathway in adult medulloblastoma**
Only recommendations with a high level of evidence after complete staging have been included. (A) Diagnostic and therapeutic pathway in the first-line setting. (B) Diagnostic and therapeutic pathway in the relapse setting. GTR=gross total resection. MB=medulloblastoma. CSF=cerebrospinal fluid. M0=no evidence of metastases. M1=microscopic tumour cells in CSF.

has a high propensity for late extraneural relapse.[90,91] We recommend bone marrow sampling only in the case of bone pain or impaired haematological parameters. The interval to recurrence varies greatly, with most recurrences reported within 6 years of diagnosis, with median intervals ranging from 24 months to 50 months,[41,92] although isolated recurrences have been reported in adults as late as 18 years after diagnosis. Survival in post-pubertal patients and adults depends more on the medulloblastoma subgroup than on the age of the patient.[93]

Diagnosis and therapy in relapse

For adult patients with medulloblastoma, no definite recommendations have been published. Follow-up should follow the recommendations for first-line treatment (level III A), and staging should be extended on the basis of clinical signs and symptoms, if appropriate. Patients should be treated within controlled clinical trials whenever possible.

Second surgery should be done if a total resection appears possible and in cases of disseminated tumour if symptoms can be relieved (level III A; eg, if the spinal cord is compressed by solid intraspinal metastases). In selected paediatric cases who initially received reduced dose craniospinal irradiation, salvage treatment with a second craniospinal irradiation appears feasible.[94] Whether these data can be translated to adults has not yet been investigated. In cases of focal relapse, focal radiotherapy can be used also in adults (level III B).[95]

The role of chemotherapy in relapse has not been systematically investigated in adults. Recommendations for the treatment of children with medulloblastoma can be used as a basis for decision making, considering the age-specific biology. Intravenous chemotherapy with carboplatin and etoposide was explored in the HIT-REZ-2005 study (NCT00749723); an oral alternative consists of a combination chemotherapy with etoposide and trofosfamide. Other regimens, such as metronomic and targeted anti-angiogenesis therapy (NCT01356290),[96] topotecan and temozolomide (NCT00918320)[97] or temozolomide and irinotecan,[98] some of them supplemented with bevacizumab[96,99] can be considered on an individual basis. If molecular data are available, sonidegib

or vismodegib, with or without cytostatic therapy, can be considered in recurrent or refractory adult patients with SHH medulloblastoma on the basis of their biology, despite the scarce available data that show individual objective responses in small cohorts.[87,88] There are no data supporting high-dose chemotherapy with stem cell rescue in recurrent disease.

Side-effects and long-term patient care

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Early side-effects, such as delayed nausea or vomiting, hearing decline, or kidney toxicity secondary to platinum-based chemotherapy are disabling and can impact quality of life. They should be closely monitored during treatment as they can partly be prevented.[30,100] Early haematological toxicity is related to most chemotherapies used, but also to skull and spinal radiotherapy. Polyneuropathy frequently occurs early in treatment, not only due to cumulative doses of vinca alkaloids, but also with platinum derivates.[101] Any dose of cisplatin confers a risk of hearing loss. Cumulative doses above 300 mg/m² are related to both hypertension and profound hearing loss, if combined with radiotherapy to the mastoid region.[102] Hearing deficits might increase after treatment and have been reported in more than 40% of adult patients treated with radiotherapy alone or in combination with platinum-based chemotherapy.[103,104] In 2019, the International Guideline Harmonization Group[105] recently presented their recommendations to evaluate ototoxicity following platinum-based chemotherapy, and head or brain radiotherapy (≥30 Gy).

Delayed toxicity is a key issue in patients with medulloblastoma[106] and is probably underestimated. Adolescents and adults treated with radiotherapy and multiagent chemotherapy have a high prevalence of delayed haematological and neurotoxicity.[103] Long-term structural sequelae related to radiotherapy are leuko-encephalopathy, radiation-induced vasculopathy or stroke, secondary tumours such as meningiomas and glioblastomas, and the development of cataracts.[106,107] Neurocognitive impairment after craniospinal irradiation is more severe in children, but is also prevalent in patients irradiated as adults.[104] Neurocognition should be monitored by neurocognitive assessments (level II B; eg, in intervals of 1 year).

After treatment, a life-long clinical follow-up should be done to detect delayed toxicities at an early stage (level II B).[100] This follow-up should be carried out at a specialised institution and coordinated by one lead physician out of a multidisciplinary team. Visits should consist of a thorough clinical examination (including vision, hearing, skin, and assessment for polyneuropathy), cranial MRI (at least up to 10 years), laboratory testing (including haematological, kidney, and endocrine parameters), audiometry, and neurocognitive testing related to occupational reintegration and psychosocial counselling (level III B). Endocrine deficits with a focus on anterior pituitary gland insufficiency should be monitored by an endocrinologist (level II B).[108] Additional tests should be based on clinical symptoms.

Survivors of medulloblastoma are less likely to attain social independence, to earn a high education degree, or to marry, compared with the general population.[104,107] In addition, their risk of acquiring mental health problems might increase with age. A study of adult patients with medulloblastoma reported depression or anxiety requiring therapeutic intervention in 45% of patients.[104] Therefore, both anxiety and depression should be regularly monitored (level II B). Life-long follow-up can be documented in a standardised way (eg, with a passport for care).

Perspectives in diagnostics and therapy

A robust method to molecularly subgroup medulloblastoma is DNA methylation profiling.[19,55] As a complement to molecular subgrouping, gene panel sequencing or whole-exome sequencing has proven useful to identify potential targets for therapy (although not prospectively proven to be relevant) and to assess hereditary predisposition.[21] Future developments in molecular technologies and the integration of additional layers of information, such as radiomic imaging data, might help to further improve the classification and outcome evaluation of medulloblastoma.

The first clinical trials for children with medulloblastoma that will use the current histological or genetic classification schemes for patient subgrouping[8] are recruiting patients (eg, SJMB12 [NCT01878617] and PNET5 [NCT02066220]). The first genotype-based trial in adult patients (EORTC-1634-BTG) will start in mid 2020. Medulloblastoma is specifically amenable for such an approach, as molecular subtypes and their genetic drivers have been clearly defined,[8,19] and targeted treatments are available that need confirmation of their value.[87]

MRI techniques focusing on metabolism (magnetic resonance spectroscopy) and diffusion-tensor imaging are increasingly being used to visualise tumour biology and differentiate medulloblastoma subgroups.[109] In addition, advances in image feature analysis and machine-learning classification have allowed non-invasive prediction of genomic aberrations from magnetic resonance images in medulloblastoma.[110] Coupled with algorithmic strategies to model tumour growth in brain tumours, such analyses offer the potential to understand tumour dynamics during treatment. The armamentarium of diagnostic approaches could allow even easier classification and monitoring of side-effects of treatment in the future, and targeted therapies might be more readily available.

Conclusion

Medulloblastoma is an extremely rare tumour in post-pubertal patients and adults. In this Review, we provide the best possible approach to a rational diagnostic and therapeutic procedure for these patients. Most of the recommendations are based on adult data when possible,

Search strategy and selection criteria

This guideline was prepared by a panel of authors nominated by the Executive Board of the European Association for Neuro-Oncology (EANO) and the EUropean RAre Cancer (EURACAN) Brain Tumor Committee. The task force represents all disciplines involved in the diagnosis and care of post-pubertal and adult patients with medulloblastoma and reflects the multinational character of EANO and EURACAN. We retrieved references published in English on PubMed with the search terms "medulloblastoma AND/OR adolescent/post-pubertal /adult" in combination with "cerebrospinal fluid", "chemotherapy", "cognition", "CSF", "EEG", "electroencephalography", "endocrine", "event free survival", "FDG", "fertility", "FET", "follow-up", "genetics" "hearing loss", "imaging", "incidence", "histology", "kidney function", "methionine", "molecular pathology", "MRI", "neuropathy", "outcome", "overall survival", "pathology", "positron emission tomography", "prevention", "prognosis", "progression free survival", "psychosocial" "quality of life", "radiotherapy", "response", "risk factor", "screening", "side effects", "staging", "supportive therapy", "surgery"," symptoms", "targeted therapy", "toxicity", and "tyrosine", from Jan 1, 1980, to Jan 1, 2019. We also identified publications through searches of the authors' own files. We generated the definitive reference list on the basis of relevance to the broad scope of this guideline.

or, if justified, from paediatric data if no adult data were available.

Currently, medulloblastoma diagnosis is based on the WHO classification of 2016, which is continuously supplemented by new molecular findings and reliable diagnostic tools, such as DNA methylation and analysis-based classification, which are expected to enable a more thorough risk stratification. In adults, evidence from randomised studies concerning therapeutic options are lacking because of the rarity of the disease. Radiotherapeutic and systemic treatment is largely based on studies in children. Therefore, irrespective of the individual risk, after gross total resection most patients are treated with craniospinal irradiation followed by maintenance chemotherapy.

However, adults often have more pronounced toxicity than children. A thorough management of side-effects and coverage of psychosocial aspects is therefore a main focus in these patients. In consequence, recent clinical studies have been initiated with the aim of de-escalating treatment to reduce toxicity and adding targeted therapies to increase efficacy. The main therapeutic goal is to cure the disease while maintaining physical and psychosocial integrity of the affected patients.

Contributors

EF, SH, VD-R, EH, BW, SCC, TP, KWP, SMP, RG, WS, SEC, CS, DB, AAB, JB, FL-D, ASGS, and PH wrote the manuscript. DF, R-DK, NB, DF-B, FG, CH, MGM, and MG reviewed the consecutive drafts and provided input. MvdB, EF, PH, SH, AI, MP, and MW edited and approved the final version of the manuscript.

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