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Informationsportal zu Krebserkrankungen bei Kindern und Jugendlichen

## **Medulloblastoma – Brief Information**

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# Medulloblastoma – Brief Information

## 1. General information on the disease

Medulloblastoma is a highly malignant, *solid tumour* that develops due to a malignant transformation of *cells* of the *cerebellum*, a part of the brain. Since it directly originates from the *central nervous system* (CNS), it is also called a *primary CNS tumour*, thereby differentiating it from malignant tumours of other organs that have spread (metastasised) to the CNS.

Medulloblastoma are "embryonal tumours", which means, they originate from extremely immature (undifferentiated) cells of the central nervous system, which divide at a high rate. Therefore, these tumours grow very fast.

Generally, a medulloblastoma spreads – by uncontrolled proliferation – from the cerebellum into the adjacent tissue, for example into the *brainstem*, but also into the cavities of the brain (*cerebral ventricles*) – to be precise, into the fourth ventricle, which is located within the back part of the brain (*posterior cranial fossa*).

The tumour cells also spread via the *cerebrospinal fluid* (CSF), thereby forming metastases [see *metastasis*] in other parts of the central nervous system, such as the spinal canal (*spinal cord*). A total of one third of the patients with medulloblastoma already present with solid metastases at initial diagnosis, which are visible by *imaging* diagnostics. About a quarter of the patients present with tumour cells in the cerebrovascular fluid (CSF), which can be identified under the *microscope*. Metastasis outside the CNS, for instance to bones, *bone marrow*, lung, or *lymph nodes*, is very rare for medulloblastoma.

Depending on the microscopic (histological) features as well as on *molecular* characteristics of the tumour, medulloblastoma are differentiated and, thus, classified into different subgroups. Their incidences and outcomes vary accordingly (see *chapter "Treatment planning"*).

## 2. Incidence

Approximately 3 % of all malignancies in children and adolescents are medulloblastoma. They account for about 12 % of all CNS tumours occurring in childhood and adolescence. According to the German Childhood Cancer Registry (Mainz), about 65 children and adolescents under 18 years of age are newly diagnosed with medulloblastoma in Germany per year. This corresponds to an incidence rate of 5 per 1,000,000 children/adolescents.

Medulloblastoma are most frequent within the first nine years of life. The patients' average age at diagnosis is approximately seven years. Boys are affected more often than girls (gender ratio: about 1.8 : 1).

### 3. Causes

Medulloblastoma is caused by a malignant transformation of *nerve tissue* cells. The reasons for tumour development have not been completely found out yet. It is known so far, that children and adolescents with certain inherited diseases (such as *Gorlin-Goltz syndrome*, *Li-Fraumeni syndrome*, or *Fanconi anaemia*) have a higher risk of developing a medulloblastoma than their healthy peers. Since these genetic conditions are associated with an elevated risk for tumour development, they are also known as *cancer predisposition syndromes*.

In addition, it has been shown that medulloblastoma are frequently associated with certain *genetic* and/or *chromosomal* aberrations within cells. The resulting impairments of cell development and cell communication may be contributing factors promoting the transformation of a healthy into a cancer cell. Also, *radiotherapy* of the brain, for example as received by patients with certain forms of *leukaemia* or with eye cancer (*retinoblastoma*), may lead to an increased risk of developing a CNS tumour later in life.

### 4. Symptoms

Due to the uncontrolled and aggressive growth pattern of medulloblastoma, *symptoms* typically develop and deteriorate fast. Similar to those of other tumours of the *central nervous system* (CNS), the presenting symptoms of medulloblastoma primarily depend on the patient's age, the site and size of the tumour as well as its pattern of spread within the CNS. The following general (nonspecific) and local (specific) symptoms can occur:

#### 4.1. General (nonspecific) symptoms

Unspecific general symptoms occur independently of the tumour's location. They may be similar to and therefore mimic other, non-CNS diseases. General symptoms of a child or adolescent with a CNS tumour may include headaches and/or back pain, dizziness, loss of appetite, nausea and vomiting (particularly after getting up in the morning), weight loss, increasing fatigue, inability to concentrate, school problems, mood swings, and character changes as well as developmental delay, to name a few.

Major reason for these symptoms is the slowly but continuously increasing intracranial pressure (ICP). An elevated intracranial pressure may be caused by the growing, thus more and more space-occupying tumour within the bony skull. It may as well be due to the tumour blocking the regular flow of the *cerebrospinal fluid* – as is frequent in medulloblastoma patients –, thereby forming *hydrocephalus*. In babies or small children with soft spots (open *fontanelles*), elevated intracranial pressure and hydrocephalus typically present with a bulging fontanelle or a larger than expected head circumference (*macrocephalus*), respectively.

#### 4.2. Local (specific) symptoms

Local symptoms may indicate the tumour location and, thus, which functional regions of the CNS might be affected. Thus, tumours like medulloblastoma, which arise in the *cerebellum* and frequently spread into the into the fourth ventricle and the *brainstem*, can cause dizziness and gait



disturbances, increasing imbalance including insecurity when jumping or walking stairs as well as sensory and coordination problems.

Also, visual deficits (such as strabism, double vision, and uncontrolled eye movements) due to impaired cranial nerves can occur. In case medulloblastoma has spread to other areas of the central nervous system, other symptoms may occur, such as back pain or muscle weakness when the *spinal cord* is affected.

**Good to know:** Not all patients presenting with one or more of the symptoms mentioned above do have a medulloblastoma or another type of brain tumour. Many of these symptoms may also occur with other, harmless diseases that are not associated with a brain tumour at all. However, if certain symptoms persist or get worse (for example repetitive headaches or rapid increase of head circumference in a young child), a doctor should be seen to find the underlying reason. In case it is a medulloblastoma or some other brain tumour, treatment should be started as soon as possible.

## 5. Diagnosis

If the paediatrician thinks that the young patient's history (*anamnesis*) and *physical examination* are suspicious of a tumour of the central nervous system (CNS), the child should immediately be referred to a hospital with a childhood cancer program (paediatric oncology unit), where further diagnostics can be initiated and performed by childhood cancer professionals. Very close collaboration between various specialists (such as *paediatric oncologists*, paediatric neurosurgeons, paediatric *radiologists*, to name a few) is required, both to find out, whether the patient really suffers from a malignant *CNS tumour* and, if so, to determine the tumour type and the extension of the disease. Knowing these details is absolutely essential for optimal treatment and *prognosis*.

### 5.1. Tests to secure diagnosis

The initial diagnostic procedures for a young patient presenting with a suspected CNS tumour at a childhood cancer centre include another assessment of the patient's history, a thorough physical/*neurological exam* and *imaging* diagnostics, such as *magnetic resonance imaging* (MRI) with and without *contrast agent* or (less often) *computed tomography* (CT). These tests help find out exactly whether the patient has a tumour of the central nervous system. Also, localisation and extent of the tumor, its demarcation regarding adjacent tissue as well as a potential *hydrocephalus* can be diagnosed by these imaging techniques very well.

In order to validate the final diagnosis, *histological* and *molecular* analysis of surgically obtained tumour tissue is required. Usually, this is done using the tissue obtained during surgical tumour removal.

The extent of histological and, especially, *molecular genetic* workup has been substantially increased over the past years. Today's option of using modern lab techniques makes it possible to identify molecular tissue characteristics that do not only help finalize the diagnosis, but can also provide information on what to expect regarding the course of the disease (such as growth



behaviour). Hence, molecular diagnostics already play an important role in treatment planning and will most certainly become even more relevant in the future.

## 5.2. Tests to assess spread of disease

Once the diagnosis of a medulloblastoma has been confirmed, additional tests are required to assess the extent of the disease within the central nervous system (CNS). Apart from *MRI* scans of the complete CNS (brain and spine) for macroscopic metastases [see *metastasis*], these tests also include microscopic checking of the *cerebrospinal fluid* (CSF) for tumour cells in the spinal cord (which are not visible by MRI scan). Cerebrospinal fluid is mostly obtained from the spine in the lower back (*lumbar puncture*), since the risk of the puncture needle damaging the spinal cord is lowest at the lower back level.

## 5.3. Tests before treatment begins

In preparation for the intensive treatment of the brain tumour, further investigations are performed. The scope of these examinations depends on the planned therapy and any concomitant diseases present. Diagnostic testing may include check of heart function by *electrocardiography* (ECG) and/ or *echocardiography*, a check of hearing (by an *audiogram* as well as by *otoacoustic emissions* (OAE) and/ or *BERA hearing test*), an *electroencephalography* (EEG) or electrophysiological examinations (e.g. *sensory evoked potentials*, SEPs), to name a few.

Furthermore, additional blood tests are needed to assess the patient's general health condition and to check whether the function of certain organs (such as liver and kidneys) is affected by the disease and whether there are any metabolic disorders to be considered prior or during therapy. The condition and function of the hormonal glands will be checked in order to detect and manage potential tumour- and/ or treatment-associated endocrinological impairments as early as possible. For the same reason, neuropsychological testing [see *neuropsychology*] might be done prior to cancer treatment. Any changes occurring during the course of treatment can be assessed and managed better based on the results of those initial tests, which thus help to keep the risk of certain treatment-related side effects as low as possible.

Also, the patient's *blood group* needs to be determined in case a *blood transfusion* is required during treatment. In sexually mature females (which means after they have experienced their first menstrual bleeding), a pregnancy test is recommended prior to treatment as well.

**Good to know:** Not every patient needs the complete check-up. On the other hand, tests might be added that haven't been mentioned here, depending on the individual situation of the patient. Your caregivers will inform you and your child, which diagnostic procedures are individually required in your case and why.

## 5.4. Recommendations if a cancer predisposition syndrome is suspected

Certain *molecular genetic* and *histological* characteristics of medulloblastoma (such as SHH activation, desmoplastic/nodular extensively nodular type, see *following chapter*) may prompt the



treatment team to recommend human genetic counselling to the child's family. The reason is that those features are frequently associated with a *cancer predisposition syndrome* (such as *Gorlin-Goltz syndrome*, *Li-Fraumeni syndrome*, and, more rarely, *Fanconi anaemia* or *familial adenomatous polyposis*). These are hereditary diseases caused by *germline mutations* and associated with a predisposition to developing tumours such as medulloblastoma.

If a patient is diagnosed with a germline mutation, one possible reason may be that the disease has been inherited by one parent. In this case, the patient's siblings, too, are at a higher risk to develop a medulloblastoma (or another tumour). In order to rule out this risk or to diagnose it as early as possible, certain blood tests will be recommended to both parents first. If those come back positive for a germline mutation in one of the parents, the patient's siblings should also be tested. After providing information and obtaining written consent, the tests are carried out by laboratories specialising in human genetics.

If a cancer predisposition syndrome is known in the family and a germline mutation is found in a so far healthy family member, it is recommended that the affected child(ren) is (are) closely monitored from birth by regular physical/*neurological* examinations, *magnetic resonance imaging* and *ultrasound* (of the head, abdomen and chest).

**Note:** The presence of a cancer predisposition syndrome in a child with medulloblastoma also influences therapy planning and treatment (see *chapter "Therapy"*).

#### *Psychosocial Care*

A child's cancer is a stressful situation for the whole family. The psychosocial team of the clinic or later the aftercare facility provides advice and support to patients and their relatives from diagnosis to completion of treatment as well as during aftercare. Don't hesitate to take advantage of this offer. It is an integral part of the treatment concept of all paediatric oncology centres in many countries. Here you will find comprehensive information on this.

## 6. Treatment planning

Once the diagnosis and extent of a medulloblastoma has been confirmed, treatment planning starts. In order to provide the patient with the best possible individual and risk-adapted therapy, the treatment team considers specific factors that are known to have an impact on the *prognosis* (so-called *prognostic factors*).

One important prognostic factor is the type (subtype) of medulloblastoma. Further prognostic factors are the size, localization, and spread of the tumour (*metastasis*). In addition, response to chemotherapy and the patient's age at the time point of diagnosis play an important role. Age at diagnosis, for example, determines whether the patient may receive radiotherapy or not.

Also, cancer predisposition syndromes (such as *Li-Fraumeni syndrome*, *Gorlin-Goltz syndrome*, or *Fanconi anaemia*) and the patient's overall physical condition are of importance. All these factors are included in treatment planning in order to achieve the best outcome possible for each patient.

## 6.1. Classification of Medulloblastoma

According to the World Health Organization (*WHO*), medulloblastoma is defined as a high-grade malignant tumour (CNS WHO grade 4). However, there are various subtypes of medulloblastoma: They look different under the microscope, meaning *histologically*, and also present with different *molecular* characteristics. Since these differences are sometimes associated with different prognostic outcomes, too, considering them is crucial for optimal treatment planning.

As per current classification of the World Health Organization for Tumours of the Central Nervous System (CNS *WHO classification 2021*), the following histological subtypes of medulloblastoma have been defined:

- classic Medulloblastoma (CMB)
- desmoplastic/nodular Medulloblastoma (D/NMB or DMB)
- anaplastic / large cell Medulloblastoma (LCAMB)
- Medulloblastoma with extensive nodularity (MBEN)

However, the appearance of the tumours under the microscope is insufficient to predict their growth behaviour. Therefore, since 2016 classification has been based on *molecular genetic* (biological) tumour characteristics in addition to the histological features.

The WHO classification 2021 differentiates the following four genetic (molecular) medulloblastoma subgroups (with their naming largely based on the signal pathways involved, SHH and WNT):

- Medulloblastoma WNT-activated
- Medulloblastoma SHH-activated and *TP53* wildtype
- Medulloblastoma SHH-activated and *TP53* mutated
- Medulloblastoma without WNT or SHH activation (these can be further subdivided into group 3 and group 4 medulloblastomas, or into a total of eight subtypes)

**Important to know:** Histological and/or molecular medulloblastoma subgroups with either favourable or unfavourable prognosis exist. For example, a WNT-activated medulloblastoma is associated with a favourable outcome, whereas the risk of recurrent disease is high in patients with a SHH-activated medulloblastoma and *TP53* mutation or in patients with a medulloblastoma without WNT/SHH activation and *MYCC amplification* (the latter of which is a genetically unfavourable alteration).

Every patient will be stratified – based on all prognostic factors (histological and molecular subtype, metastasis, residual tumour, age at diagnosis) – into a specific treatment group (such as low-risk, standard risk or high-risk group), each of which considers the individual risk of relapse. The higher the risk of relapse, the more intense is usually the treatment.



## 7. Treatment

Treatment of children and adolescents with medulloblastoma should take place in a children's hospital with a paediatric oncology program. Only in such a childhood cancer centre, highly experienced and qualified staff (doctors, nurses and many more) is guaranteed, since they are specialized and focus on the diagnostics and treatment of children and teenagers with cancer according to the most advanced treatment concepts. The doctors in these centres collaborate closely with each other. Together, they treat their patients according to treatment plans (protocols) that are continuously optimised. The goal of the treatment is to achieve higher cure rates while avoiding side effects as much as possible.

Current treatment concepts involve neurosurgical tumour removal, chemotherapy and, depending on the patient's age, radiotherapy of the brain and spinal cord. For some patients, high-dose chemotherapy followed by stem cell transplantation may be an option, too.

### 7.1. Surgery

Immediate *surgery* for tumour removal is crucial for patients with medulloblastoma, because most of them are in critical clinical condition due to the tumour and subsequent impairment of *cerebrospinal fluid* flow (which can cause *hydrocephalus*). Goal of surgery is gross (microsurgical) total tumour resection. This means that at the end of the surgical procedure, no tumour tissue can be identified through the surgical microscope.

Due to these neurosurgical techniques [*neurosurgery*], total tumour resection can be achieved for more than 50 % of patients with medulloblastoma today. If – at the beginning of treatment – the tumour cannot be completely removed without risking a substantial damage of the healthy brain tissue, a second attempt of complete resection may be evaluated at a later time point, for example after radio- and/or chemotherapy.

In most medulloblastoma patients, tumour removal also results in normalising the flow of cerebrospinal fluid (CSF). Patients initially presenting with hydrocephalus may need a transient hydrocephalus drainage **prior to** tumour removal. Sometimes, even a permanent *drainage* system may be necessary during the course of treatment or later, even when the tumour has been completely removed.

### 7.2. Additional, non-surgical treatment

Since medulloblastomas tend to infiltrate adjacent tissue and, furthermore, often spread into other parts of the central nervous system via the cerebrovascular fluid (CSF), only treating the tumour locally is not sufficient. Therefore, surgery is followed by additional non-surgical treatment, comprising *chemotherapy* and, partly, *radiotherapy*.

#### Chemotherapy

Chemotherapy uses drugs (so-called cytostatic agents or *cytostatics*) that can kill fast-dividing cells, such as cancer cells, or inhibit their growth, respectively. In order to eliminate as many of the cancer



cells as possible, a combination of several cytostatics is usually applied. Frequently-used agents are, for example, cisplatin, vincristine, cyclophosphamide, etoposide, carboplatin, lomustine, and methotrexate.

### Radiation therapy

Radiotherapy is done using energy-rich, *electromagnetic* radiation, given through the skin to the tumour region. Radiation causes *DNA* damage in tumour cells, thereby leading to cell death. Modern radiation techniques, such as *intensity-modulated radiotherapy* (IMRT), help minimise radiation damages in healthy tissue. Aside from this conventional radiotherapy (with *photons*), *proton therapy* (using *proton radiation*) has become an option for many patients as well. This type of radiotherapy allows to reduce the effects of radiation in healthy tissue even better and is, therefore, gaining an increasing importance in the treatment of children and teenagers with solid tumours.

Radiotherapy is usually an option for children between 3–5 years of age (the age-cutoff depends on the medulloblastoma subtype), sometimes also for younger children. Children with *germline mutations* in certain genes (*PTCH*, *SUFU*) and *Gorlin-Goltz syndrome* are excluded from this treatment option, since they have a higher risk to later develop *basal-cell carcinoma* in the radiation field. Considering the risk for developing a secondary malignancy in children with *Li-Fraumeni syndrome* and a *TP53* germline mutation, benefits and risks of radiotherapy need to be assessed individually.

Decision upon which therapy is to be applied (treatment methods, kind and intensity of chemo-/radiotherapy) is based on the patient's age, the histological and molecular subtype of the tumour, certain genetic risk factors as well as on the extent of both metastases and surgical tumour removal (see chapter "Therapy planning").

The following paragraphs provide an overview of various treatment options. Please note, that – due to the complexity of treatment options (according to the large spectrum of molecular subtypes and other relevant risk factors) – we do not claim completeness. Your child's caregiver team will provide you with the details applying to the best treatment options for your child. In general, high-risk patients receive a more intense therapy than patients with low- or standard-risk medulloblastoma.

#### 7.2.1. Treatment of low- and standard-risk medulloblastoma in patients older that 3–5 years

Children and adolescents with non-metastasised medulloblastoma, who – based on the tumour biology – have been stratified into the low- or standard-risk group, respectively, and who are older than 3 to 5 years at diagnosis (the age limit is adjusted to the medulloblastoma subtype), usually receive *radiotherapy* of the complete central nervous system (craniospinal radiotherapy), followed by an additional radiation boost to the tumour site (local radiation). Radiotherapy is followed by a so-called maintenance *chemotherapy*, which includes a combination of cytostatic agents.

#### 7.2.2. Treatment of high-risk medulloblastoma in patients older that 3–5 years

Patients over 3 to 5 years with metastasised disease and/or who have been stratified to the high-risk group based on the biology of their tumour (such as patients with an SHH-activated, *TP53*-

mutated medulloblastoma or with a group 3 medulloblastoma harbouring a MYCC-*amplification*, respectively) will usually receive an intensified treatment. An intensified regimen includes at least a *radiotherapy* with higher doses as usual. For some patients, even a so-called induction chemotherapy may be given prior to radiotherapy. Either or, radiotherapy (of central nervous systems and tumour site) is always followed by maintenance *chemotherapy*.

**Note on the current SIOP HR medulloblastoma study for patients 3 years of age and older:**

As part of the SIOP HR medulloblastoma *therapy optimising trial*, it is currently being examined whether hyperfractionated accelerated radiotherapy (HART) or *high-dose chemotherapy* plus standard radiotherapy leads to better survival rates than current standard radiotherapy. In hyperfractionated radiotherapy, higher total radiation doses are administered in a larger number of sessions, twice daily and with a slightly lower radiation dose per session. High-dose chemotherapy is accompanied by a subsequent *autologous stem cell transplantation*.

In addition, two types of maintenance chemotherapy are compared, also with regard to treatment outcomes and thus survival rates. The allocation of patients to the respective treatment arms (standard arm, study arms) is randomized [see *randomisation*].

### 7.2.3. Treatment of children younger than 3–5 years

Brain development is ongoing in children younger than 3 to 5 years of age. Therefore, in order to prevent or at least minimise the risk of severe late effects, current treatments do not routinely include radiotherapy for this age group or consider it as a delayed treatment option. Instead, surgical tumour removal is followed by *chemotherapy* with multiple agents. Chemotherapy can differ in intensity, depending on the tumour type and individual risk status (standard-/high-risk medulloblastoma).

Subsequent therapy, as well, is based on the tumour type, existing metastasis and patient's age at diagnosis. Standard-risk patients with good response to treatment (that means complete or partial tumour elimination) usually continue with chemotherapy. In case of no or insufficient tumour shrinkage, children older than 18 months of age may receive radiotherapy of the tumour region. In younger children, time until they are 18 months old is bridged by another round of chemotherapy. Also, a second surgery to remove residual tumour is regularly being considered.

Some patients may also benefit from *high-dose chemotherapy* followed by *autologous stem cell transplantation* to increase their chances of survival. Current treatment regimens particularly consider this option for children with metastasised medulloblastoma who are younger than four years, as well as for certain patients with recurrent disease (*recurrence*, relapse).

### 7.2.4. Treatment in case of relapse

The treatment regimens for patients with relapse are generally considering the patient's overall condition, the intensity of prior treatment, and the initial response to chemotherapy. In general, the



treatment of recurrent disease includes all options of local treatment (*surgery, radiotherapy*) as well as *chemotherapy*.

## 8. Therapy optimising trials and registries

The majority of the children and adolescents with medulloblastoma or a relapse of this disease receive therapy according to the treatment plans of *therapy optimising trials* or registries. Therapy optimising trials are standardised and controlled clinical trials that aim at steadily developing and improving treatment concepts for sick patients based on the current scientific knowledge.

Patients who cannot participate in any study, for example because none is available or open for them at that time, or since they do not meet the required inclusion criteria, respectively, are often included in a so-called **registry**. One goal of a registry is to collect treatment data for research questions. Furthermore, the registry center supports the doctors at site with (non-committal) treatment recommendations based on the most recent data on best treatment options, in order to provide the patient with optimal therapy even without the framework of a clinical study.

Currently, the following therapy optimising trials and registries are available for patients with medulloblastoma in Germany:

- **SIOP HR-Medulloblastoma:** Since November 2023, the international therapy optimising trial SIOP HR-Medulloblastoma (a phase III study) has been available for patients with high-risk medulloblastoma (*also see chapter "Therapy – Non-surgical treatment"*). The trial admits children, adolescents and young adults who are at least 3, but still under 21 years of age at the timepoint of diagnosis or surgery, respectively. Numerous treatment centres in Germany as well as in other European countries are participating in this study. The national (German) headquarters of the trial are located at the Children's Cancer Centre at the University of Hamburg, Germany. The head of the trial is Prof. Dr. med. Stefan Rutkowski.
- **I-HIT-MED Registry:** Medulloblastoma patients under 22 years of age, who, for different reasons, cannot or do not want to participate in any currently available or open trial, can be enrolled in the international HIT-MED Registry, regardless of the treatment given. These patients will receive treatment as per individually designed treatment plans. The goal of the registry is not to assess the feasibility of an ongoing trial, safety or efficacy of a certain treatment. It rather aims at collecting individual patient data for future analysis. The headquarters of the registry are located in the Children's Cancer Centre at the University of Hamburg, Germany. Head of the registry is Prof. Dr. med. Stefan Rutkowski.
- **Trial SIOP-PNET 5 MB for patients with medulloblastoma:** From April 2014 to April 2022, patients with medulloblastoma (age over 3–5 years at diagnosis, depending on the medulloblastoma subtype) had the possibility to participate in the European-wide study SIOP-PNET 5 MB. The trial headquarters are located at the Children's Cancer Centre at the University of Hamburg, Germany (head of the trial: Prof. Dr. med. Stefan Rutkowski). **Note:** The study has been closed to new patients since 6 April 2022 and is currently being evaluated.

## 9. Prognosis

The chances of cure (prognosis) for children and adolescents with medulloblastoma have improved considerably over the last decades. Today's modern diagnostic procedures and the use of intensive, standardised combination therapies currently result in 5-year survival rates of about 75 % and 10-year survival rates of almost 70 %.

Individual *prognosis* is influenced by the medulloblastoma subtype, existence of *metastasis*, age at diagnosis and response to therapy. Patients with a favourable risk profile can achieve survival rates higher than 80%, particularly patients with a SHH-activated medulloblastoma without *TP53* mutation or a WNT-activated medulloblastoma. Patients with unfavourable risk profile (such as with anaplastic or large-cell medulloblastoma or with *MYCN amplification*) have a lower chance of cure. Metastases can (though not necessarily always) be associated with a more unfavourable outcome, since prognostic co-factors such as tumour type and treatment response have an impact, too.

Until the end of the Eighties, prognosis of young children (younger than 4 years) was significantly poorer than in older children and adolescents. It improved substantially after the introduction of treatment protocols with intensified chemotherapy. Patients with recurrent disease (*recurrence*) usually have a rather unfavourable prognosis. In individual settings, chances of long-term survival can be achieved by *high-dose chemotherapy* followed by *autologous stem cell transplantation*.

**Note:** The survival rates mentioned in the text above are statistical values. Therefore, they only provide information on the total cohort of patients with childhood medulloblastoma. They do not predict individual outcomes.

In the context of cancer, the term "cure" should rather be referred to as "free of cancer", for even if current treatment regimens may help remove the tumour, the the tumour's growth may have caused irreparable damage to the brain or the treatment may be associated with late-effects. Early detection and appropriate management of these long-term secondary effects typically require intensive *rehabilitation* and thorough long-term follow-up care, although a patient may have been "cured" from the cancer.

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# Glossary

amplification	here: gene amplification; this refers to the multiplication of individual genes or parts of the genome. Amplification of oncogenes (such as MYCN) is associated with the development and/or spread of certain types of cancer;
anamnesis	medical interview, a patient's history, development of signs of illness; the type, onset and course of the (current) symptoms as well as any risk factors (e.g. hereditary diseases) are evaluated during a medical interview.
audiogram	hearing test; graphical representation of the subjective hearing ability of sounds; the audiogram records a persons hearing sensitivity in different frequency ranges. The examination is carried out with the help of the patient. By audiogram, the severity, type and cause of a hearing disorder can be determined. A separate audiogram is created for each ear, usually by the ear-nose-throat-(ENT) specialist. An audiogram that deviates from the norm suggests a disease of the ear. The audiogram is one of many methods used to examine hearing (audiometry).
autologous stem cell transplantation	(re)transfer of blood stem cells, e.g. after a chemotherapy or radiotherapy; the patient receives his own cells that were previously taken from their own bone marrow or blood. Autologous stem cell transplantation may be an option, for example, for certain patients with lymphoma, neuroblastoma, soft tissue sarcoma, or a brain tumour.
basal-cell carcinoma	a malignant skin tumour that grows from the skin into neighbouring tissue, where it can destroy bone and cartilage, but does not form metastases; the most common malignant skin tumour in Central Europe. The tumour develops in the basal cells of the epidermis and can occur anywhere on the body. However, the areas most commonly affected are those exposed to the sun on the head and neck. The main causes are long-term, intense exposure to sunlight (UV radiation) and genetic factors. Fair-skinned people are particularly at risk.
BERA hearing test	ENT examination to determine hearing damage; it essentially measures the electrical activity of the auditory nerve and the auditory pathways to the brain stem and does not require the patients assistance (objective hearing test). In the BERA test, certain auditory stimuli (sounds) are emitted via headphones: with the help of an electroencephalogram (EEG), the reaction (in the



		<p>form of brain waves, so-called acoustically evoked potentials) is measured. This is the brainstem's response to the acoustic stimulus. The measurement of these brain waves makes it possible to detect hearing disorders or abnormalities in the cranial nerve or brainstem.</p>
blood group		<p>hereditary, usually stable, structural characteristics (blood group antigens) of blood components (e.g. ABO blood groups) located on the cell walls of blood and other tissue cells;</p>
blood transfusion		<p>transfer of blood (whole blood) or blood components (e.g. red blood cells or platelets) from a donor to a recipient</p>
bone marrow		<p>site of blood formation; spongy tissue with a strong blood supply that fills the cavities inside many bones (e.g., vertebrae, pelvic and thigh bones, ribs, sternum, shoulder blade, and collarbone); in the bone marrow, all forms of blood cells develop from blood progenitor cells (blood stem cells).</p>
brainstem		<p>the section of the brain that forms the transition between the brain and the spinal cord; it controls vital functions, such as breathing, heart rate and blood pressure, and is responsible for important reflexes such as the blinking, swallowing or coughing reflex, lacrimation and saliva production. This is also where the roots of the cranial nerves are located.</p>
cancer syndrome	predisposition	<p>genetic disorders that can include malformations and intellectual disability in addition to an increased risk of tumors; according to current knowledge, about 10% of childhood and adolescent cancers develop due to a known hereditary change or cancer predisposition syndrome. Cancer predisposition syndromes include Louis Bar syndrome (= ataxia telangiectatica), Beckwith-Wiedemann syndrome, Down syndrome, Hippel-Lindau syndrome, Li-Fraumeni syndrome, MEN syndrome, neurofibromatosis and WAGR syndrome. The familial form of retinoblastoma is also part of it.</p>
cell		<p>the smallest functional unit in organisms with the ability to perform metabolism, involuntary muscle movement and reproduction and to respond to stimuli; each cell contains a nucleus and a cell body (cytoplasm) and is externally bounded by the cell membrane.</p>
central nervous system		<p>comprises the brain and spinal cord and is separated from the so-called peripheral nervous system; as a central organ of integration, coordination and regulation, it serves to process</p>



	external sensory impressions as well as stimuli produced by the organism itself.
cerebellum	part of the brain that is located in the posterior fossa of the skull, between the cerebrum and the brainstem; it is mostly responsible for the coordination of all body movements and also for maintaining balance.
cerebral ventricles	cerebral ventricles filled with cerebrospinal fluid; the four cerebral ventricles represent the continuation of the spinal canal merging into these four chambers in the brain.
cerebrospinal fluid	fluid produced by cells of the cerebral ventricles; it floats around the brain and spinal cord to protect them from injury and provide them with nutrients.
chemotherapy	here: use of drugs (chemotherapeutic agents, cytostatics) for the specific inhibition of tumor cells in the organism
chromosomal	referring to the chromosomes, carriers of the genetic material (see chromosomes)
CNS tumour	tumour of the central nervous system; a primary CNS tumour is a solid tumour that originates from brain or spinal cord tissue. Secondary CNS tumours are metastases of tumours located in other organs or tissues.
computed tomography	imaging, X-ray diagnostic procedure; it produces an image by computer-controlled evaluation of a large number of X-rays from different directions. This makes it possible to produce sliced images of body parts (tomograms, transverse or longitudinal sections of the human body)
contrast agent	substance that can be used to improve the visualization of structures and functions of the body in imaging techniques; contrast agents are mainly used in X-ray diagnostics (X-ray examination, computed tomography), magnetic resonance imaging (MRI) and ultrasound examinations.
cytostatics	drugs that inhibit cell growth; cytostatics can affect the metabolism of different types of cells, thereby destroying them and/or preventing them from multiplying. Cells that divide frequently are particularly affected.
DNA	abbreviation for deoxyribonucleic acid; it carries the genetic information and is found in all living beings. DNA contains the genes that provide the information for the production of ribonucleic acids (RNA) or proteins. It is a large molecule consisting of two



		nucleic acid chains twisted into a double helix. The individual chains consist of a sequence of four different building blocks (bases), the order (sequence) of which determines the genetic code.
drainage		here: drainage of pathological or increased natural body fluids to the outside, for example drainage of cerebrospinal fluid from the cerebral ventricles or of pathological fluid accumulation from the pleura (pleural drainage);
echocardiography		ultrasound examination of the heart to check its performance (cardiac function); the position or structure of the heart valves and walls, the wall thickness of the heart muscle, the size of the heart and the ejected blood volume (pumping function of the heart) are examined and assessed, among other things.
electrocardiography		method of measuring the electrical activity of the heart
electroencephalography		method of recording the electrical activity of the brain; the electroencephalogram (also abbreviated EEG) is the graphical representation of this electrical brain activity. Its evaluation can provide evidence of brain dysfunctions.
electromagnetic		electromagnetic rays (also known as electromagnetic waves) consist of coupled electric and magnetic fields; examples of electromagnetic radiation are X-rays and gamma rays as well as radio waves, thermal radiation and light.
evoked potentials		examination method that can be used to test the conductivity and thus the functionality of nerve pathways; the principle is based on a controlled stimulation of a sensory organ or peripheral nerve (e.g. eyes, hearing, sense of touch) and the verification of the stimulus response (electrical potential) triggered by this in processing regions of the central nervous system.
familial adenomatous polyposis		hereditary cancer syndrome (cancer predisposition syndrome), in which numerous glandular polyps develop in the colon and rectum; with their increase in size, the risk of degeneration also increases (transition into so-called adenocarcinomas).
Fanconi anaemia		hereditary haematopoietic disorder; it is mainly characterized by a progressive dysfunction of the bone marrow, which leads to a reduced formation of blood cells (bone marrow insufficiency), as well as by chronic anaemia and a high risk of cancer (especially for acute myeloid leukaemia). Other concomitant symptoms include skeletal malformations (e.g. short stature, malformations of the thumbs and arms). Fanconi anemia is one of



	<p>the cancer predisposition syndromes. At the cellular level, there is an increased chromosomal fragility; this leads to chromosomal changes and, as a result, to disorders of cell cycle control.</p>
fontanelle	<p>soft spot on an infant's head, due to the bony plates not having connected yet; the final closure usually occurs before the age of two.</p>
genetic	<p>concerning the (level of) inheritance or genes; inherited</p>
germline mutation	<p>mutation that occurs in the female or male germ cells (eggs or sperm) and can thus be inherited by the offspring; in the case of a germline mutation, all body cells of the offspring are usually affected by the change. In contrast, "somatic" mutations arise in somatic cells outside the germline and are not inherited.</p>
Gorlin-Goltz syndrome	<p>a hereditary disease associated with a number of developmental disorders and a predisposition to various cancers, the most common being a form of skin cancer (basal cell carcinoma);</p>
high-dose chemotherapy	<p>the use of a particularly high dose of cell growth-inhibiting drugs (cytostatics); in the case of cancer, it aims to destroy all malignant cells. Since the haematopoietic system in the bone marrow is also destroyed, the patients own or foreign blood stem cells must then be transferred (autologous or allogeneic stem cell transplantation).</p>
histological	<p>concerning the tissues of the body; in a histological (fine tissue) examination, tissue samples are examined under the microscope after special preparation (preparation of tissue sections and use of certain staining techniques).</p>
hydrocephalus	<p>medical term for abnormal buildup of cerebrospinal fluid in the cavities (ventricles) in the brain; it is caused by a dilation of the brain's ventricles due to various causes.</p>
imaging	<p>diagnostic procedures generating images of the inside of the body, such as ultrasound and X-ray examination, computed tomography, magnetic resonance imaging, and scintigraphy</p>
intensity-modulated radiotherapy	<p>modern radiation technology, which provides maximum protection for the surrounding healthy tissue from radiation exposure by means of a highly precise distribution of the radiation dose at the tumour site; the intensity of the radiation dose can be precisely adjusted to the irradiation field only; this may also allow the use of a higher radiation dose.</p>



leukaemia	malignant disease of the blood forming (haematopoietic) system and the most common cancer in children and adolescents (about 33%); depending on the origin of the malignant cells, a distinction is made between lymphoblastic and myeloid leukaemias. Depending on the course of the disease (fast or slow), a distinction is made between acute and chronic leukaemias.
Li-Fraumeni syndrome	cancer predisposition syndrome characterized by the increased occurrence of various solid tumours within a family; in childhood and adolescence, tumours of the adrenal glands, as well as soft tissue sarcomas, leukaemias and CNS tumours are most commonly observed, in adulthood mainly bone tumours (osteosarcomas), breast cancer and lung tumours. In most cases, there is a change (mutation) of the so-called tumour suppressor gene TP-53 (protein p53).
lumbar puncture	puncture of the spinal canal in the lumbar spine, e.g. to remove cerebrospinal fluid (CSF) or for the purpose of administering medication (so-called intrathecal treatment); in the case of cancer, a sample and examination of cerebrospinal fluid can be used to detect malignant cells; in the case of increased intracranial pressure due to a CNS tumour, cerebrospinal fluid removal (CSF) is also used to relieve pressure.
lymph nodes	small lenticular to bean-shaped organs that are part of the body's immune system and are located in many parts of the body; they serve as filter stations for the tissue water (lymph) of a region of the body and contain cells of the immune system.
macrocephalus	large head, which can be caused by a hydrocephalus (hydrocephalus) in a child with unclosed fontanelles, but also by a large tumour or both
magnetic resonance imaging	diagnostic imaging method; very precise, radiation-free examination method for the visualization of structures inside the body; with the help of magnetic fields, cross-sectional images of the body are generated, which usually allow a very good assessment of the organs and many organ changes.
metastasis	1. tumour spread from the primary site of tumour to other parts of the body; characteristic feature of malignant tumours (cancer). 2. collective term for a disease process characterized by malignant cells spreading from their primary site to other areas of the body via the bloodstream and/or the lymphatic system.



microscope	an instrument that allows you to magnify objects or certain structures of objects that are not visible to the human eye
molecular	at the level of molecules
molecular genetic	referring to structure, formation, development, function and interactions of cells and cell building blocks (e.g. nucleic acids, proteins) at the molecular level; the focus is on the analysis of the genetic information stored in the nucleic acids (DNA and RNA) and its processing in the context of protein synthesis as well as gene regulation.
MRI	abbreviation for magnetic resonance imaging, a very precise, radiation-free examination method for imaging structures inside the body
MYCN amplification	duplication of the MYCN oncogene, a cancer-causing gene that can be detected in various types of tumours (for example, some neuroblastomas and medulloblastomas); amplification of oncogenes (such as MYCN) is associated with the development and/or spread of some tumours. Tumor cells with the MYCN oncogene are particularly resistant to chemotherapy and radiotherapy.
nerve tissue	tissue of the nervous system; it consists of nerve cells (neurons) and its own special connective tissue, the glial cells.
neurological	referring to the function of the nervous system / nerve tissue
neuropsychology	subspecialty discipline of psychology that deals with the diagnosis and therapy of cognitive disorders after acquired brain damage; it deals with the functions of the brain, such as thinking (intelligence), attention, memory, language and motor skills.
neurosurgery	a branch of surgery that includes parts of the diagnosis and surgical treatment of diseases of the nervous system
otoacoustic emissions	very quiet sounds that the inner ear emits when hearing sounds (sound waves hitting the ear); these can be registered by highly sensitive microphones. The measurement of OAE is used to check the function of the inner ear; the patients assistance is not required (objective hearing test). This form of hearing test is therefore also suitable for infants and toddlers. During the examination, tiny measuring microphones are inserted into the external ear canal. The supplied sound waves cause the outer hair cells in the inner ear to vibrate, i.e. move mechanically. This generates the quiet but measurable otoacoustic emissions.



paediatric oncologist	paediatrician who is specialized on the management of children and adolescents with cancer
photon	from ancient Greek light; smallest unit of electromagnetic radiation; each photon transports energy.
physical examination	an important part of diagnostic examinations; includes palpation and listening to certain body organs as well as testing reflexes to obtain indications of the nature or course of a disease.
posterior cranial fossa	part of the bony skull that includes the cerebellum, part of the brainstem (the back of the bridge = pons), the 4th cerebral ventricle, and the confluence of the venous blood ducts (confluens sinuum)
prognosis	prediction of the course and outcome of a disease / prospect of recovery
prognostic factors	factors that allow an approximate assessment of the further course of the disease (i.e. the prognosis);
proton radiation	three-dimensional irradiation using protons; proton radiation is used for the treatment of tumours. In this process, the majority of the radiation energy is emitted precisely at the tumour site; the surrounding healthy tissue is spared due to low energy dispersion.
proton therapy	modern form of radiotherapy using protons for the treatment of malignant tumours; compared to conventional radiotherapy with photons, this type of radiation can specifically target the tumour area, thereby sparing adjacent, healthy tissue from the effects of radiation.
radiologist	a physician specialized in diagnostic imaging and radiotherapy
radiotherapy	controlled use of ionizing (high-energy) radiation for the treatment of malignant diseases
randomisation	(statistical) random distribution of patients to treatment and control groups in a study; the strict random distribution is intended to eliminate systematic errors in the evaluation of therapy studies.
recurrence	relapse, recurrence of a disease after recovery
rehabilitation	medical, social, psychosocial and occupational measures after an illness for reintegration into society, work and private life, which may include, among other things, the restoration of abilities through exercise treatment, protheses and other measures
retinoblastoma	a rare malignant tumour of the retina that occurs almost exclusively in children; there are hereditary and non-hereditary



	<p>forms of the disease. Either one or both eyes can be affected (unilateral or bilateral retinoblastoma). In very rare cases, hereditary retinoblastoma can also occur together with a brain tumour (e.g., pineoblastoma); in this case, it is called trilateral retinoblastoma.</p>
solid tumour	<p>solid, localized increase of the body's own tissue; solid tumours can originate from various tissues and can be benign or malignant; only the malignant ones are considered as cancers. Solid tumours include all cancers that do not affect the haematopoietic or lymphatic system. The latter are systemic malignancies. The most common solid tumours in childhood and adolescence are brain tumours, followed by neuroblastoma and soft tissue sarcomas.</p>
spinal cord	<p>part of the central nervous system; its main function is to transmit messages between the brain and other organs of the body. The spinal cord is protectively enveloped by the three spinal cord membranes and the bony spinal canal.</p>
surgery	<p>surgical intervention on or in the body of a patient for the purpose of treatment, less often also in the context of diagnostics; the surgical intervention is carried out with the help of special instruments, generally with the patient under anesthesia.</p>
symptom	<p>sign of illness</p>
therapy optimising trial	<p>a controlled clinical trial (study) that aims to provide the best possible treatment for patients and at the same time to improve and develop treatment options; therapy optimisation is aimed not only at improving the chances of recovery, but also at limiting treatment-related side effects and long-term effects.</p>
ultrasound	<p>an imaging technique used to examine organs, in which ultrasound waves are sent through the skin into the body; at tissue and organ boundaries, the sound waves are reflected back, picked up by a receiver (transducer) and converted into corresponding images with the help of a computer.</p>
WHO	<p>abbreviation for World Health Organization; international federation for cooperation in the field of public health</p>
WHO classification	<p>international guideline developed by the World Health Organization (WHO) for classification, diagnosis and differentiation/grading of (malignant) diseases</p>