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Informationsportal zu Krebserkrankungen bei Kindern und Jugendlichen

Medulloblastoma – Brief Information

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1. General information on the disease

Medulloblastoma is a highly malignant, *solid tumour* that develops due to a malignant transformation of *cell*s 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 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. Each year, about 60 children and adolescents under 18 years of age are newly diagnosed with medulloblastoma in Germany. 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 2 : 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 syndrome*s.

In addition, it has been shown that medulloblastoma are frequently associated with certain *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, *radiation therapy* 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, *symptom*s 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 *fontanelle*s), 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 oncologist*s, paediatric neurosurgeons, paediatric *radiologist*s, 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) 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 (*biopsy*) 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, such as *electrocardiography* (ECG) and *echocardiography* to check cardio function. 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. 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.

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,

since each subtype correlates with a different growth pattern and malignity. Further prognostic factors are the size, localization, and spread of the tumour (*metastasis*), for these factors have an impact on whether or not the tumour can be completely removed by means of an operation, thus influencing the patient's chances of survival.

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 (WHO grade IV). However, there are various subtypes of medulloblastoma: They look different under the microscope, meaning *histological*ly, 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 classification of the World Health Organization (*WHO classification*) for tumours of the central nervous system, the following subtypes of medulloblastoma have been defined:

- classic Medulloblastoma (CMB)
- desmoplastic/nodular Medulloblastoma (DMB)
- Medulloblastoma with extensive nodularity (MBEN)
- anaplastic Medulloblastoma (AMB)
- large cell Medulloblastoma (LC MB)

However, the appearance of the tumours under the microscope has turned out not to be 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. This additional consideration of molecular factors has shown to provide a more precise assessment of the tumour biology and, thus, is more feasible for optimal treatment planning. The WHO currently classifies four genetic (molecular) Medulloblastoma subgroups: WNT-activated, SHH-activated, group 3 and group 4.

Histological and/or molecular medulloblastoma subgroups with either favourable or unfavourable prognosis exist. For example, patients with desmoplastic/nodular medulloblastomas and medulloblastomas with extensive nodularity usually have a more favourable outcome than patients with other histological subtypes. Same for the WNT-activated medulloblastoma, which can be associated with a better prognosis when compared to a group 3 medulloblastoma, especially when the latter harbours a genetically unfavourable alteration (MYCC or *MYCN amplification*).

Every patient will be stratified – based on all prognostic factors (histological/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 *cerebrovascular 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 microsurgical 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 or, sometimes, even a permanent *drainage* system later.

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, *radiation therapy*.

Chemotherapy uses drugs (so-called cytostatic agents or *cytostatics*) that can kill fast-dividing cells, such as cancer cells, or inhibit their growth, respectively. 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. Aside from this so-called conventional radiotherapy, particle-radiation with protons (also known as proton therapy) can be an option for some patients as well. This type of radiotherapy provides the benefits of better targeting the tumour area, thus sparing more adjacent, healthy tissue from the effects of radiation. Proton therapy is gaining an increasing importance in the treatment of children and teenagers with solid tumours.

Decision upon which therapy is to be applied (treatment modalities and intensity) is based on the patient's age, the histological and molecular subtype of the tumour, certain biological risk factors as well as on the extent of both metastases and surgical tumour removal.

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 3-5 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. Radiotherapy is followed by a so-called maintenance chemotherapy, which includes a combination of cytostatic agents. Medulloblastoma patients of both risk groups can be enrolled in the *therapy optimising trial*s SIOP-PNET 5 MB (LR/SR-arm) (*see chapter "Therapy optimising trials and registries"*).

7.2.2. Treatment of high-risk Medulloblastoma in patients older that 3-5 years

Patients over 3-5 years with metastasised disease and/or who have been stratified to the high-risk group based on the biology of their tumour, will usually receive an intensified treatment. Depending on the individual risk factors, an intensified regimen may include radiotherapy with higher doses and, for some patients, even a so-called induction chemotherapy, which is given prior to radiotherapy. Either or, radiotherapy (of central nervous systems and tumour site) is always followed by maintenance chemotherapy. Since 2018, certain high-risk patients are eligible to participate in the therapy optimising trial SIOP-PNET 5 MB) (*see chapter Therapy optimising trials and registries*).

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 trial*s 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-commital) 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 / registries are available for patients with medulloblastama in Germany:

- **Trial SIOP-PNET 5 MB for patients with medulloblastoma:** Since April 2014, patients with medulloblastoma can participate in the European-wide conducted study SIOP-PNET 5 MB. Initially open only for patients with low- or standard-risk and recurrent disease, the study has been offering different treatment arms also for certain high-risk patients since fall 2018. Aside from patients with WNT-activated medulloblastoma, who – due to age, metastasised disease and/or residual tumour – harbour a high risk of recurrent disease (WNT-HR), these also include patients with certain hereditary cancer predisposition syndromes (SHH medulloblastoma with

TP53-mutation). SIOP-PNET 5 MB also involves an open registry for patients who are not eligible to be recruited to one of the study arms, such as patients with other types of cancer predisposition syndromes. One of the eligibility criteria for both study and registry is an age of 3-5 years at diag-nosis (depending on the medulloblastoma subtype). The headquarters of the trial are located in 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:** Patients with medulloblastoma, who, for different reasons, cannot or do not want to participate in any currently available or open trial, can be en-rolled in this registry (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 study: Prof. Dr. med. Stefan Rutkowski).

- **HIT-REZ Registry:** Patients, whose disease does not respond to current treatments (therapy-resistant, progressive medulloblastoma) or with recurrent disease (relapse), respectively, can be enrolled in this registry, which has been open since January 2015. This registry does not serve to test new treatment regimens or drugs. However, the experts running the registry are providing treatment recommendations based on the most recent results obtained from national trials (for example from the HIT-REZ 2005 trial, which was closed in 2016) as well as international relapse trials. The headquarters of the registry are located in the Children's Cancer Centre at the University of Essen, Germany. The head of the study is Prof. Dr. med. Gudrun Fleischhack.

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 desmoplastic/nodular and WNT-activated medulloblastoma. Patients with unfavourable risk profile (such as with anaplastic or large-cell medulloblastoma or with MYCC or *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 irrepairable 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

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.
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.
biopsy	removal of a tissue sample for subsequent (mainly microscopic) examination; this can be done, for example, by puncture with a hollow needle, with the use of special instruments (such as forceps, punching instruments, probes) or surgically with a scalpel.
blood group	hereditary, usually stable, structural characteristics (blood group antigens) of blood components (e.g. AB0 blood groups) located on the cell walls of blood and other tissue cells;
blood transfusion	transfer of blood (whole blood) or blood components (e.g. red blood cells or platelets) from a donor to a recipient.
bone marrow	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).
brainstem	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.
cancer predisposition syndrome	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.
cell	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.
central nervous system	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 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)
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
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.
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 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.
fontanelle	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.

Gorlin-Goltz syndrome	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);
high-dose chemotherapy	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).
histological	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).
hydrocephalus	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.
imaging	diagnostic procedures generating images of the inside of the body, such as ultrasound and X-ray examination, computed tomography, magnetic resonance imaging, and scintigraphy
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 bodys 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	duplification 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 tumors. 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
neurosurgery	a branch of surgery that includes parts of the diagnosis and surgical treatment of diseases of the nervous system
paediatric oncologist	paediatrician who is specialized on the management of children and adolescents with cancer
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);
radiation therapy	controlled use of ionizing (high-energy) radiation for the treatment of malignant diseases
radiologist	a physician specialized in diagnostic imaging and radiotherapy
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 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.
solid tumour	solid, localized increase of the bodys 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.
spinal cord	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.
surgery	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.
symptom	sign of illness
therapy optimising trial	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.
WHO	abbreviation for World Health Organization; international federation for cooperation in the field of public health
WHO classification	international guideline developed by the World Health Organization (WHO) for classification, diagnosis and differentiation/grading of (malignant) diseases