Ependymoma – Brief information

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1. General information on the disease

Ependymomas are *tumour*s of the *central nervous system* (CNS). They are *solid tumour*s arising from malignantly transformed *cell*s of the *brain* or *spinal cord*. Since they develop directly from CNS cells, they are also called *primary* CNS tumours in order to distinguish them from cancers of other body parts that have spread to the CNS (*metastasis*).

There are different types of ependymomas – some of which grow rather slowly, while others expand fast. Nevertheless, since for a growing mass the room in the bony skull is limited, even slow-growing ependymomas can become life threatening.

2. Localisation and spread in the central nervous system

Ependymomas arise from malignantly transformed cells of the ependyma. Ependyma cells are the cells that form the inner coat of the brain's cavities (ventricles) as well as of the spinal canal. Therefore, most ependymomas are situated in the *cerebral ventricles* or the spinal canal.

The majority of ependymomas (about 60 %) are found in the fourth ventricle, which is located in the lower back of the skull (*posterior cranial fossa*). From there, they tend to grow toward the *cerebellum*, the *brainstem* and the cervical spine. The doctors call this infratentorial growth. About 30 % of ependymomas grow in the area of the so-called lateral ventricles in the *cerebrum* (supratentorial growth); 10 % are located in the *spinal cord* (intraspinal).

In less than 5 % of children with either supra- or infratentorial ependymoma, the tumour has already spread within the central nervous system (CNS) at the time of first diagnosis. Tumour spread (*metastasis*) outside the CNS, for example into the lung and/or *lymph nodes*, is rare.

It is well-known by now that ependymomas that grow in different parts of the central nervous system differ regarding their biological characteristics and the health problems they cause in a patient. This particularly applies to spinal ependymomas (*see chapter „Treatment planning"*).

3. Incidence

Accounting for barely 2 % of all malignancies in children and adolescents, ependymomas are overall rare. They comprise about 7 % of all primary central nervous system tumours in childhood and adolescence. In Germany, about 40 children and adolescents under the age of 18 years are newly diagnosed with ependymoma each year. This corresponds to an incidence rate of about 3 per 1,000,000 children / adolescents.

Although mostly affecting children in the first three to four years of life, ependymomas can generally occur in any age group. The patients' average age at diagnosis is about five years. Boys are a

slightly more affected than girls (gender ratio: 1,4 : 1). Spinal ependymomas are an exception, since they affect mostly adolescents: the mean age at diagnosis is 14 years.

4. Causes

The causes for the development of ependymoma are still unknown. In general, individuals who received radiotherapy of the brain when they were young, for example children with acute *leukaemia* or *retinoblastoma*, have an increased risk of developing a brain tumour later.

Ependymomas can also be associated with so-called *cancer predisposition syndrome*s, hereditary diseases characterized by *mutation*s that, compared to healthy individuals, are associated with a higher risk of developing a malignancy at a younger age. An example for such a hereditary cancer predisposition is *neurofibromatosis* type II (NF-2): children with this inherited disease have a higher risk of ependymoma in the spinal canal than their healthy peers. In addition, it has been shown that ependymoma are frequently associated with certain aberrations of *gene*s or *chromosome*s 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. It has not been shown yet that children can inherit these types of genetic changes in tumor cells from their parents.

5. Symptoms

Similar to those of other tumours of the *central nervous system* (CNS), the presenting *symptom*s of ependymoma primarily depend on the patient's age, tumour site and size as well as pattern of spread within the CNS. The following general (nonspecific) and local (specific) symptoms can occur:

5.1. 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). Elevated ICP may be caused by the growing, thus more and more space-occupying tumour within the bony skull, but also by the tumour blocking the regular flow of the *cerebrospinal fluid*, 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.

5.2. Local (specific) symptoms

Local symptoms may indicate the tumour location and, thus, which functional regions of the CNS may be affected. Therefore, an ependymoma in the *cerebellum* can cause dizziness and gait disturbances, whereas such a tumour in the hemispheres of the *cerebrum* can be associated with

seizures and/or motor deficits and a tumour of the *spinal cord* with different kinds of *neurological* impairments such as motor and sensory deficits as well as typical gait disturbances. Also, impaired vision, mental and sleep problems may, although to a lesser extent, be indicative of tumour location.

Good to know: Not all patients presenting with one or more of the symptoms mentioned above do have an ependymoma 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 an ependymoma or some other brain tumour, treatment should be started as soon as possible.

6. Diagnosis

If the paediatrician thinks that the young patient's history (*anamnesis*), *physical examination* and possibly even results from diagnostic *imaging* 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 planning and *prognosis*.

6.1. 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 diagnostic, such as *magnetic resonance imaging* (MRI) or (less often) *computed tomagraphy*. These tests help to 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 laboratory 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.

6.2. Tests to assess spread of disease

Once the diagnosis of an ependymoma 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, 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.

6.3. 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.

7. Treatment planning

After the diagnosis has been confirmed, therapy is planned. In order to design a highly individual, risk-adapted treatment regimen for the patient, certain individual factors influencing the patient's *prognosis* (called risk factors or prognostic factors) are being considered during treatment planning (risk-adapted treatment strategy). One important prognostic factor is the type (subtype) of ependymoma, which defines its grade of malignancy and is assessed by *histological* and *molecular genetic* analysis of a tumour sample. The currently used classification of ependymomas will be outlined later.

Further *prognostic factors* are the size, localization, and spread of the tumour, 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, the patient's age at the time point of diagnosis and his overall physical condition play an important role. All these factors are included in treatment planning in order to achieve the best possible outcome for each patient.

Classification of Ependymoma

There are various subtypes of ependymoma: they look different under the *microscope*, meaning *histological*ly, and also present with different molecular characteristics.

Until recently, the classification of ependymomas was exclusively based on their histology. Classification according to the World Health Organization (*WHO*) histologically differentiated low-grade ependymomas (WHO grade I), which grow slowly, since their cells hardly ever divide, and higher-grade ependymomas (WHO grades II and III) with more frequently dividing cells and other typical characteristics of aggressive growth. 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. Tthe molecular subtype of a tumour will, therefore, increasingly impact the choice of optimal treatment.

As per current classification of the World Health Organization (*WHO classification*) for tumours of the central nervous system, the following subtypes of ependymoma have been defined (regarding histological and molecular genetic criteria):

- **Subependymoma WHO grade I**: slowly growing, low-grade tumour
- **Myxopapillary ependymoma grade I**: slowly growing, low-grade tumour (mostly found in the spinal canal)
- **Ependymoma WHO grade II**: usually slowly growing tumour with only a few features of aggressive growth
- **Ependymoma fusion-positive WHO grade II oder III**: tumour with partly aggressive growth behaviour
- **Anaplastic ependymoma WHO grade III**: tumour with aggressive behaviour.

Most ependymomas in children and adolescents are grade II- or grade III-tumours: WHO grade II-ependymoma as well as anaplastic ependymoma WHO grade III are dominating in the cerebellar region; in the hemispheres, ependymoma *RELA* fusion-positive WHO grade II and III are most common. The myxopappillary ependymoma WHO grade I is restricted to the spinal canal. Subependymomas WHO grade I are rare in childhood and adolescence.

Note: The cut-off between grade II- and grade III-tumours cannot always be clearly determined. Therefore, this classification cannot be used to precisely predict the growth behaviour of an

individual tumour. However, there is no difference between WHO grade II- and III-ependymomas regarding treatment and prognosis.

8. Treatment

Treatment of children and adolescents with ependymoma should take place in a children's hospital with a paediatric oncology program. Only such a childhood cancer centre provides highly experienced and qualified staff (doctors, nurses and many more), since they are specialised and focussed 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 high cure rates while avoiding side effects as much as possible.

Current treatment concepts for children and teenagers with ependymoma include **surgical tumour removal**, **radiotherapy** and, for some patients, **chemotherapy**. Very young children receive chemotherapy prior to radiotherapy to delay the beginning of radiation.

8.1. Surgery

Surgical tumour removal plays an important role in the treatment of ependymoma, because the extent of tumour resection has a major impact on the subsequent course of the disease: complete tumour resection is usually associated with a more favourable prognosis than partial resection, which may be the only option in some patients with advanced disease, for example.

If complete resection was not achieved during primary *surgery*, the doctors will recommend a second attempt of resection as long as the risk of the procedure is justifiable. However, some ependymomas are located in parts of the brain that make complete resection impossible. In particular, tumours in the area of the fourth brain cavity (*cerebral ventricle*) and in the so-called *cerebellopontine angle* usually allow only partial removal. Complete resection would be associated with a high risk of damaging healthy, vitally important brain tissue.

8.2. Additional treatment (adjuvant therapy)

The decision-making regarding additional, non-surgical treatments is based, above all, on the histological tumour type (WHO grade) and the extent of surgical tumour removal. While a completely removed WHO grade I-ependymoma usually does not require additional therapy, patients with ependymomas WHO grade II or III located in the brain (intracranial ependymomas) are considered for adjuvant treatment, which usually includes *radiation therapy* of the tumour region. Some patients also receive *chemotherapy* (*see below*).

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 tumour.

Therapy options for patients with ependymoma WHO grade I

Patients with a myxopapillary ependymoma grade I of the spinal cord, whose tumour could be completely removed, usually do not need additional treatments. However, they are regularly seen by their caregiver team for physical exams and imaging controls. In case there is remaining tumour after surgery, radiotherapy of the tumour region has proven to be of benefit and is given upon decision on an individual basis.

Other WHO grade I ependymomas are rare in children. Hence, decision-making regarding optimal treatment is based on the patient's individual situation.

Therapy options for patients with ependymoma WHO grade II-III

For patients with ependymomas presenting with signs of malignancy such as ependymoma WHO grade II, anaplastic ependymoma WHO grade III or ependymoma RELA fusion-positive WHO grade II or III, respectively, additional treatments are indicated, even if complete tumour resection was achieved. The reason beyond this strategy is that, despite macroscopic (that means visible) total removal, remaining tumour cells, which are invisible to any surgeon's eye, may be left in the body. These remainders are associated with a high risk of recurrent disease at the original tumour site (local relapse). Recurrent disease at other sites of the brain or spinal cord is rather rare.

Radiotherapy, and, for some patients, additional chemotherapy, help reduce the risk of local (*recurrence*). Chemotherapy is particularly given to very young children, in order to delay or even completely avoid radiotherapy while they are so young. Also, treatment intensification (for example in case of *metastasis* or remaining tumour) can be a goal of chemotherapy.

The doctors will recommend the type of additional treatment based on the type of ependymoma, its grade of spread, the extent of surgical removal and the patient's age at diagnosis.

According to the current treatment recommendations of the HIT-MED study centre (HIT-MED-Guidance), patients 18 months old and older who neither have remaining tumour nor metastases after surgery usually receive radiotherapy of the tumour region. Younger patients without metastases or remaining tumour, respectively, receive an intensive chemotherapy, sometimes followed by radiation of the tumour region once they have turned one year old.

For patients with remaining tumour after initial surgery, the goal of non-surgical (adjuvant) treatment is to shrink the remaining tissue in order to fa-cilitate a second attempt of complete tumour removal. This can be achieved by an intensive chemotherapy. Depending on the outcome and the patient's age, more cycles of chemotherapy as well as radiotherapy of the remaining tumour are further options. Patients with metastases (which are rare at primary diagnosis) receive individual treatment under the supervision of the HIT-MED study centre.

Note with regards to intraspinal ependymas WHO grades II and III: patients with ependymomas WHO grade II or III located in the spine may also receive radiotherapy (with or without chemotherapy). However, there are no standardized treatment recommendations for these patients and decision-making is based on the individual situation.

Note to the trial SIOP-Ependymoma II
Note to the trial SIOP-Ependymoma II: The therapy optimising study SIOP-Ependymoma II, which has been active in Germany since August 2019 (*see next chapter on trials and registries*), examines whether certain modifications of the previous standardized therapy result in improved outcomes. Hence, patients (after having provided informed consent) are randomized into different treatment arms, which enable the comparison between the current treatment recommendations and new options (standard arms and examining arms). Therefore, treatment of your child might differ from above-mentioned treatment concepts.

9. Therapy optimising trials and registries

In Germany, almost all children and adolescents with first diagnosis or relapse of ependymoma are treated within *therapy optimising trial*s or registries. The term "therapy optimising trial" refers to a form of controlled clinical trial, which aims at improving current treatment concepts for 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 who do not meet the required inclusion criteria, respectively, may be included in a so-called **registry**. Such a registry pools scarce data in order to help with the planning of appropriate future clinical trials. To ensure optimal treatment for patients not registered in a study, experts from assigned trial panels usually provide recommendations and advice to the local caregiver team.

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

- **SIOP-Ependymoma II**: Since the beginning of 2019, children, adolescents and young adults with newly diagnosed ependymoma can be enrolled in the international, multi-centred trial SIOP-Ependymoma II. Approximately 60 paediatric oncology centres in Germany and numerous hospitals in other European countries are participating in this trial. The goal is to offer optimal and standardized diagnostics and treatment and to make research possible all over Europe.The German study centre is located at the Children’s Cancer Centre at the University of Hamburg. Principal investigator of the tral is Prof. Dr. med. Stefan Rutkowski.

- **I-HIT-MED Registry**: Patients with ependymoma, who for different reasons cannot or do not want to participate in any currently available or open trial, can be enrolled 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 ependymoma) 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 (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, Essen, Germany. The head of the study is Prof. Dr. med. Gudrun Fleischhack.

10. Prognosis

The *prognosis* of children and teenagers with ependymoma mainly depends on the tumour site and, thus, the extent of surgical tumour removal. Survival rates for patients after complete resection and subsequent radiotherapy are between 60 and 85 % after five years and between 50 and 70 % after 10 years, as long as the disease does not progress. After partial tumour removal, survival rates are far less favourable.

The overall prognosis for patients with intraspinal ependymoma is more favourable than for patients with ependymoma of the brain. However, remaining tumour as well as young age at diagnosis may have a negative impact on their prognosis.

When patients suffer from a recurrent ependymoma, opportunities for another surgery and/or radiation therapy will be evaluated. There is evidence that special irradiation techniques (such as *stereotactic* radiosurgery) can increase the average time of survival. Recurrent ependymomas are also sensitive to chemotherapy so that this form of treatment can improve the outcome for relapse patients.

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

In the context of cancer, the term „cure" should rather be referred to as „free of cancer", because current treatment regimens may help getting rid of the tumour, but they are also frequently associated with numerous late-effects. Early detection and appropriate management of these long-term sequelae typically requires intensive rehabilitation and thorough long-term follow-up care, although a patient may have been cured of 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.
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.
brain	the part of the central nervous system (CNS) located in the head; the brain is protected by the skull and the meninges and consists mainly of nerve tissue.
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.

cerebellopontine angle	niche in the posterior region of the brain and part of the cerebellum; this is where the roots (nuclei) of ten of the twelve cranial nerves are located in a very small space.
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.
cerebrum	largest and most highly developed section of the brain; it consists of two hemispheres connected by a thick bundle of nerves (corpus callosum). Each hemisphere of the brain is specialized on specific tasks. The outermost layer of the cerebrum, the cerebral cortex, houses the ability to learn, speak and think, as well as consciousness and memory, amongst other things. This is also where the processing centres for information from the sensory organs (e.g. eyes, ears) are located.
chemotherapy	here: use of drugs (chemotherapeutic agents, cytostatics) for the specific inhibition of tumor cells in the organism
chromosome	chromosomes are the carriers of the genetic material, i.e. the genetic information of a cell; chromosomes consist mainly of DNA and proteins and are components of the cell nucleus. The shape and number of chromosomes are species-specific. Humans have 46 chromosomes (23 pairs of chromosomes) per cell in the body.
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.
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.
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.
gene	unit of genetic information in the genome of living organisms; a gene contains the genetic information – the blueprint – for a specific gene product (protein or RNA). In most organisms, the entirety of all genes, the genome, is present as a deoxyribonucleic acid chain (DNA), which forms the chromosomes in the cell nucleus. The information of a gene is mediated by a certain sequence of the nucleic acid building blocks adenine, guanine, cytosine and thymine.
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.
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.
mutation	alteration of genetic material; it can arise without any identifiable external cause (so-called spontaneous mutation) or be caused by external influences (induced mutation). External influences include, for example, ionizing radiation or certain chemical

	substances (mutagens). If somatic cells are affected, it is referred to as a somatic mutation, and if germ cells are affected, it is referred to as a generative mutation. Somatic mutations are not heritable, while germ cell mutations can lead to hereditary damage. Depending on the extent of the change (single or multiple genes, larger chromosome segments or complete chromosomes), a distinction is made between point and block mutations as well as numerical and structural chromosomal aberrations.
neurofibromatosis	hereditary disease that leads to tumours of the nerve sheaths, meninges and glia (the "connective tissue" of the nervous system). Clinically and molecular-genetically, two forms of neurofibromatosis can be distinguished, which are caused by different genetic defects: 1. Peripheral neurofibromatosis (NF1, also known as Recklinghausens disease): this is characterized by so-called café-au-lait spots on the skin and a predisposition to various tumours (including neurofibromas, gliomas of the optic nerve, iris hamartomas as well as astrocytomas and pheochromocytomas). 2. Central neurofibromatosis (NF2): it is characterized by mostly (bilateral) neuromas of the auditory nerve (acusticus), which can lead to deafness, facial paralysis and mental disturbances. There is also an increased risk of tumours (e.g. astrocytomas, spinal ependymomas). Neurofibromatosis is one of the so-called phacomatoses.
neurological	referring to the function of the nervous system / nerve tissue
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
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.
seizures	uncontrolled electrical activity between nerve cells in the brain; a distinction is made between focal and generalized seizures. Focal seizures are limited to a specific area of the brain; depending on the area of the brain, the symptoms vary: e.g. twitching of one side of the body, an arm or a leg. Generalized seizures spread over large areas of the brain and lead, for example, to twitching of the limbs, sudden absence and loss of consciousness.
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.
stereotactic	touching or reaching a specific region of the body with pinpoint accuracy using imaging techniques (e.g. computed tomography, magnetic resonance imaging) and computer calculation, e.g. to targetedly remove tissue or as part of a treatment;
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.
tumour	groups of abnormal cells forming a growing lump, both benign and malignant
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