Ewing sarcoma (brief information)

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1. General information on the disease

Ewing sarcomas are malignant, *solid tumour*s that mostly arise within the bone tissue. The disease is named after the American cancer researcher Dr. James Ewing (1866-1943), who first described this tumour in 1921. Most Ewing's sarcomas grow and spread very quickly. Without an appropriate treatment, the disease is always fatal.

In general, Ewing sarcoma can develop in any bone. However, pelvic bones, followed by the long bones of the upper or lower leg, the thoracic skeleton, the plate bones, and the spine are those most frequently affected.

The tumour may spread (metastasize) both within the bone and into the adjacent soft tissue. Rarely (about 15 %), Ewing sarcoma arises directly within *soft tissue*, that is to say, outside the bone and without the bone being involved. Such tumours are called extrasceletal or extraosseal Ewing sarcomas. Ewing sarcomas of pure soft tissue origin may be located in the kidneys, adrenal glands, lungs, or in the gastrointestinal tract.

Due to the rapid growth and spread of Ewing sarcomas, about 25 % of the children and adolescents with this disease already present with detectable daughter tumours (metastases) at the time of diagnosis, primarily in the lungs, but also in the bones and, less often, in the *bone marrow*. It has to be assumed for all other patients, too, that tumour cells have already spread elsewhere via the blood or lymphatic stream and, thus, have formed tiny metastases in other organs. These so-called micrometastases may not be detected at diagnosis due to their small size. Since Ewing sarcoma is thus considered a disease that may affect the whole body, it is also called a systemic disease.

2. Incidence

Following osteosarcomas, Ewing sarcomas are the second most common primary bone tumours in childhood and adolescence; they account for about 2 % of all pediatric malignancies. According to the German Childhood Cancer Registry (Mainz, Germany), approximately 50 children and adolescents under the age of 18 (about 3 of 1,000,000) are diagnosed with Ewing sarcoma in Germany per year.

Ewing sarcoma may develop at any age; however, the frequency of this type of cancer peaks in the second decade of life. In childhood and adolescence (age group 0-17 years), the median age at diagnosis is 13 years, with adolescents between 12 and 17 years of age being the most frequently affected. Nevertheless, Ewing sarcomas are also observed in babies, infants, and school children. Overall, boys and male adolescents are more frequently affected by the disease than girls (gender ratio: 1.3:1).

3. Histological characteristics and tumour types

Ewing sarcomas are *primitive* malignant tumours. It is still unknown as of today, from which precursor cell they arise. According to the most recent research, they develop from immature (undifferentiated) tissue cells, so-called *mesenchymal stem cells*, or from primitive *neuroectodermal* stem cells.

Ewing sarcoma cells are histologically assigned to the mesenchymal small-, blue- and round cell tumour types; they can only be differentiated from similar looking, *undifferentiated* tumour cells of other malignancies (such as *neuroblastoma*, *medulloblastoma*, *Non-Hodgkin lymphoma*, *soft tissue sarcoma*, small cell *osteosarcoma* and *retinoblastoma*) by *immunohistochemical* and *molecular genetic* analyses. Since these tumours are rare, the associated analyses are carried out in specialised laboratories (*see chapter "Diagnosis"*).

Until recently, different subtypes have been differentiated in the group of Ewing sarcomas, based on their histological features and the site of the primary tumour. These included the classic Ewing sarcoma (EWS), the peripheral malignant primitive neuroectodermal tumour (PPNET or pPNET), the Askin tumour of the chest wall and Ewing tumours of soft tissues. As per classification of the World Health Organization (*WHO classification*), all these tumours have been summarized to one entity, meaning that in general only the term "Ewing sarcoma" is used. All Ewing sarcomas are highly malignant.

4. Causes

The underlying causes for the development of a Ewing sarcoma are still unknown. Neither external factors, such as a previous *radiation therapy*, nor inherited *genetic* factors (genetic predisposition) seem to play a relevant role. However, the disease shows ethnical preference by developing more frequently in white-skinned people (Caucasians) than in people of colour (Asians or Africans).

It is also known that tumour cells of Ewing sarcomas present with certain chromosomal aberrations, which all include a certain *gene* on *chromosome* 22 – the so-called Ewing sarcoma gene (EWS gene). These aberrations develop due to an exchange of chromosomal parts (*translocation*), mostly between the EWS gene on chromosome 22 and a gene on chromosome 11. Accounting for 85 %, the most frequent translocation (so-called [t(11;22) (q24;q12) translocation]) is so specific for Ewing sarcoma that it allows confirmation of the diagnosis. For many Ewing sarcomas, additional genetic alterations have been identified (for example increased numbers of chromosomes or loss or gain of genetic material, respectively). The genetic defects resulting from those aberrations promote that a healthy cell transforms into a tumour cell. In general, those genetic defects, which are found in tumour tissue only, are not inherited.

5. Symptoms

The most frequent *symptom*s of Ewing sarcoma are pain and a swelling in the tumour region.

Pain may be intermittant and is usually activity-dependent, but frequently also occurs at rest, for example during night time. With increasing tumour growth, the pain may be accompanied by a visible and/or palpable lump at the tumour site. The swelling may be reddened and may sometimes

lead to an impaired mobility, which initially may be mistaken for growing pains or a sports injury or some bone inflammation.

Since Ewing sarcomas may develop in any bone as well as in soft tissue, further symptoms are quite diverse, depending on the site and extent of the tumour. In case the spinal column and/or peripheral nerves (*peripheral nervous system*) are affected, deficits such as paralysis may be the major symptom. Tumours in the pelvic or chest region or in the thigh may remain unidentified for quite a while. About one third of patients complain of general symptoms such as fever, feeling of illness (malaise), weight loss and/or fatigue, which may be indicative of an advanced disease. For some patients, only a few weeks, for others up to several months may pass between first symptoms and the diagnosis of osteosarcoma.

Good to know: Not all children and adolescents presenting with the complaints described above suffer from Ewing sarcoma or any other malignant bone tumour. However, every type of musculoskeletal pain in a child or a teenager should be taken seriously and be dealt with by an experienced paediatrician in order to appropriately rule out an underlying cancer.

6. Diagnosis

If the paediatrician thinks that the young patient's history (*anamnesis*) and *physical examination* are suspicious of a malignant bone tumour, 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 surgeons, paediatric radiologists, to name a few) is required both to find out whether the patient really suffers from a malignant bone tumour and, if so, to determine the tumour type and the extension of the disease. Knowing these details is crucial for optimal treatment planning and *prognosis*.

6.1. Laboratory tests

The diagnosis of Ewing sarcoma requires, aside from a comprehensively taken history and physical exam, blood and urine tests. Although *tumour marker*s that are specific for Ewing sarcoma have not been identified yet, certain peculiarities indicative of the type of the disease and/or differential diagnoses do exist, and can be discovered via laboratory testing.

6.2. Imaging tests to confirm tumour existence

Based on their typical radiological features, most malignant bone tumours can already be diagnosed by *X-ray examination*. Additional *imaging* procedures such as *magnetic resonance imaging* (MRI) and/or *computed tomography* (CT) with a *contrast agent* subsequently help to define the exact tumour site and size as well as its demarcation with regard to adjacent tissue (such as blood vessels, muscles, tendons or joints). Nearby metastases (called skip metastases) are easily detectable by these methods as well.

For imaging of affected soft tissue and bone marrow, MRI is superior to CT. Apart from plain x-rays, it is, therefore, considered as the gold standard in radiological diagnosis of a Ewing sarcoma.

It also serves as a basis for planning subsequent surgery and for monitoring the course of the disease during chemotherapy. However, a CT may be additionally necessary in order to examine bone changes more closely.

6.3. Obtaining a tumour sample (biopsy)

For final confirmation of the diagnosis, tumour tissue is required to be removed (biopsy). The *biopsy* should only be performed by doctors who are specialized in surgery of sarcomas. This ensures that the access chosen for biopsy does not cause problems for subsequent treatment. An unfavourably planned biopsy may result in the requirement of a far more extensive subsequent surgery than initially necessary or, worst case scenario, in the inoperability of a tumour that would have been initially removable.

The required tissue samples are either gained during the surgical procedure for tumour resection (open surgery) or by needle biopsy. The latter uses special needles to punch multiple samples of tumour tissue. The obtained samples are subsequently analysed *histological*ly, *immunohistochemical*ly and *molecular genetic*ally by specialists. Molecular genetic analysis has special relevance, since identification of genetic alterations that are typical for Ewing sarcomas confirm the diagnosis and allow ruling out other, similar tumour types (*see chapter „Causes“*).

6.4. Tests to assess tumour spread (staging)

Once the diagnosis of a Ewing sarcoma has been confirmed, further tests are performed to assess potential tumour spread into other organs (*metastasis*). In this context, diagnostic *imaging* plays a major role. At first, accurate measuring of the *primary tumour* is required (so-called volumetry), since its volume (and shrinking during treatment) has a major impact on the patient's probability of survival.

In order to assess or, respectively, rule out lung metastases, a computed tomography of the chest (chest-CT) is performed. A *skeletal scintigraphy* (bone scan) using *radioactive*ly labelled technetium (99mTc) serves to detect or rule out bone metastases. Increasingly, *positron emission tomography* (PET) with radioactively labelled glucose (18F-fluoride-deoxyglucose, short FDG) is performed instead of a bone scan. This very sensitive nuclear medical imaging procedure is either combined with magnetic resonance imaging or computed tomography. Regardless of whether bone scan or PET are chosen, an MRI is also done for all clinically and radiologically suspicious regions. Some patients benefit from a whole-body MRI.

To find out whether the bone marrow is affected, tissue samples are obtained by *bone marrow puncture* and *bone marrow punch biopsy* and, subsequently, analysed histologically and molecular genetically. If the central nervous system (brain and spinal cord) is suspected to be affected as well, it may even be necessary to take a sample of cerebrospinal fluid (*lumbar puncture*).

6.5. Tests before treatment begins

Before treatment begins, further tests are needed in order to assess the condition of different organs. Therefore, the doctors will recommend an *electrocardiography* (ECG) as well as an

ultrasound of the heart (*echocardiography*), a hearing test (*audiometry*), special diagnostics for determining kidney and lung functions as well as various blood tests. 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.

Good to know: Not all of the above-mentioned tests will be done for every single patient. On the other hand, additional tests not mentioned here may be required individually. Ask the doctor which diagnostics are necessary 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 before and during treatment (risk-adapted treatment strategy).

Important *prognostic factors* are the type, localisation, size and spread of the tumour (local or metastasised), which are assessed before treatment begins. In addition, the extent of surgical tumour/metastasis removal (imcomplete versus complete) as well as the response of the disease to *chemotherapy* have major impact on treatment planning. All these factors are included in treatment planning in order to achieve the best outcome possible for each patient.

8. Treatment

Treatment of children and adolescents with Ewing sarcoma 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. Treatment in a centre with assigned sarcoma focus is considered optimal. Alternatively, the paediatric oncology program should collaborate with such a centre, in particular regarding surgery and radiotherapy.

The goal of the treatment is to achieve higher cure rates while avoiding side effects as much as possible.

8.1. Treatment methods

Treatment of children and adolescents with Ewing sarcoma consists of **surgery** and/or **radiotherapy** (local therapy) as well as **chemotherapy**. For some patients, a high-dose chemotherapy followed by autologous stem cell transplantation may be an option, too.

Radiotherapy (*radiation therapy*) 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. Chemotherapy uses drugs (so-called cytostatic agents or *cytostatics*) that can kill fast-dividing cells, such as cancer cells, or inhibit their growth, respectively.

Surgery and radiotherapy aim at maximally possible local disease control. Additional *chemotherapy* is necessary, because it appeared that though *surgery* and radiotherapy alone are capable of eliminating the tumour, metastases will almost always develop later on. Therefore a treatment is required – such as chemotherapy – that affects the whole body (so-called systemic treatment). However, chemotherapy alone cannot replace local therapy. Some patients with a high risk of recurrent disease may benefit from *high-dose chemotherapy* and subsequent *autologous stem cell transplantation*.

In order to prevent or adequately manage the side effects of the intensive therapy, specific supportive care (*supportive therapy*) regimens have been established. Here you will find information on *supportive care* as well as *recommendations for home*, the latter of which may be helpful during or after chemo- and radiotherapy.

8.2. Course of treatment

Usually, local therapy is provided between two cycles of chemotherapy. Overall, treatment takes about ten months, but – depending on many different factors – may also require more time. The different treatment phases will be outlined in the next paragraphs.

8.2.1. Chemotherapy prior to local therapy

Therapy is generally initiated by an intensive *chemotherapy* of several weeks (called induction chemotherapy or induction therapy). The goal of this chemotherapy is to shrink the tumour and potential spread (metastases) in order to optimise the conditions for subsequent surgical tumour removal, thereby contributing to safety and efficacy of surgery. Also, chemotherapy helps eliminate micrometastases (the tiny metastases that cannot be detected by imaging diagnostics), thus preventing further tumour spread.

In order to eliminate as many tumour cells as possible, patients receive a combination of different chemotherapeutic agents (*cytostatics*) that have proven to be effective in the treatment of Ewing sarcoma. These agents, administered by *infusion*, include vincristine, doxorubicin (= adriamycin), cyclophosphamide, ifosfamide, and etoposide (abbreviated “VDC/IE”). Chemotherapy is given as several courses over several (currently nine) days each, during which the patient needs to be

inpatient. Between courses, patients can go home as outpatients. Readmission is only required in case of severe side-effects.

8.2.2. Local therapy – surgery and radiotherapy

Still during or latest after cessation of chemotherapy, local therapy is scheduled. The preferred treatment is *surgery* with the aim of gross total tumour removal. (This surgical procedure should definitely be performed in a specialised sarcoma centre.) A complete tumour removal, however, may not always be an option due to tumour location within functionally relevant body regions and, hence, *radiation therapy* will be considered instead or in addition. Some patients require a combination of surgery and radiotherapy, since the combined treatment lowers the risk of recurrent disease.

Which one of the two treatment methods is indicated or whether they will be combined depends on the patient and his / her disease condition and, thus, needs to be decided individually. Your caregiver team will inform you more in detail on the type and course of surgery or radiotherapy, respectively. Thanks to huge progress made for limb-sparing surgical techniques, it is fre-quently possible as of today to waive amputation for patients with large tu-mours of the arms or legs.

Following surgery, a *pathologist* examines the tumour tissue under the microscope to find out how the disease has responded to the preceding chemotherapy. This so-called histological response is assessed by measuring the amount of the tumour cells that are still alive. An amount of less than 10 % vital tumour cells is defined as good response, an amount of 10 % or more vital tumour cells as inadequate response. The grade of response (defined as grades 1-6) is considered when deciding on further treatment steps to be taken.

Good to know: as far as possible, metastases identified at the time of diagnosis are treated locally like the *primary tumour*, thus being surgically removed and/or irradiated.

8.2.3. Chemotherapy after local therapy

After local therapy,*chemotherapy* is continued (then called consolidation chemotherapy or consolidation therapy). Treatment intensity depends on tumour size and extent at diagnosis as well as on the tumour's response to the chemotherapy preceding local therapy (induction chemotherapy).

Patients with local disease and poor response to the induction chemotherapy (more than 10 % living tumour cells) or with a large tumour (more than 200 ml of volume) will receive, after consolidation chemotherapy, if possible, a *high-dose chemotherapy* (with busulfan and melphalan) followed by an *autologous stem cell transplantatio*n. It has been shown that this treatment results in more favourable outcomes, but requires complete regression of the tumour (*remission*) after consolidation therapy.

If lung metastases exist already at the time of diagnosis and if these regress completely during consolidation (complete remission), additional *radiation* of both lungs is given. High-dose chemotherapy followed by autologous stem cell transplantation did not reveal any benefit compared to standard treatment in the context of studies. This also applies for patients with metastases other than lung metastases at diagnosis. They will therefore receive conventional chemotherapy; just for

a subgroup of children under 14 years of age, high-dose chemotherapy with autologous stem cell transplantation may be of benefit.

Good to know: in some cases, additional radiation may be given after chemotherapy or high-dose chemotherapy.

8.3. Treatment in case of progressive or recurrent disease

Despite of optimised treatment methods, 30 to 40 % of patients with Ewing sarcoma will experience recurrent disease (relapse). There is no standardised treatment recommendation for these patients. Depending on the disease situation, multi-drug chemotherapy (for example with *topoisomerase inhibitors* such as etoposide, irinotecan or topotecan or alcylating agents (*alkylants*) like ifosfamide, cyclophosphamide and temozolomide), radiation therapy, surgical measures or a combination of these may be considered. Also, a high-dose chemotherapy may be an option after achievement of complete *remission* after relapse treatment.

When therapy with the goal of a cure is not an option any longer, maintenance of the patient's life quality is of major importance, for example by providing pain control and maintaining functions (*palliative care*). In the context of phase-I/II studies it is attempted to improve the probabilities of survival for these patients, for example by introducing and testing new agents.

9. Therapy optimising trials and registries

In the large paediatriac treatment centres, children and adolescents with Ewing sarcoma receive therapy according to standardised treatment plans (protocols). These protocols are designed by experts and aim at steadily improving the patients' survival rates while also reducing the risk of therapy-related late effects. Therapy according to such treatment protocols is usually carried out within *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 centre 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.

Since 2020, children and adolescents (as well as adults) with first diagnosis of Ewing sarcoma in Germany, who may not be treated in the context of any trial, can be registered with the **International Euro Ewing Registr**y. The registry represents a continuation of the EWING 2008 registry, which was closed mid 2019. The study coordination centre for Germany is located at the Children's Hospital of the University of Essen (principal investigator is Prof. Uta Dirksen, MD).

Since the end of 2018, patients with relapsed Ewing sarcoma are given the opportunity to participate in the international **phase-II study rEECur**. The rationale of this randomised controlled study is

to compare four different chemotherapy regimens (topotecan and cyclophosphamide, irinotecan and temozolomide, gemcitabine and docetaxel; high-dose ifosfamide) in order to identify the most efficient one. Principal investigator of this trial is Dr. Martin McCabe (Birmingham). Study coordination centre for Germany is located at the Children's Hospital of the University of Essen (principal investigator: Prof. Uta Dirksen, MD).

Aside from participating in this study, patients with recurrent disease can also register with the **INFORM-Registry**. The registry systematically records genetic changes in tumours with the goal to be able to offer individually tailored therapies, thereby improving outcomes for relapse patients. The abbreviation "INFORM" stands for INdividualised Therapy FOr Relapsed Malignancies in Childhood. The study coordination centre is located at the Hopp-Childhood tumour centre in Heidelberg (KiTZ) under supervision of Prof. Olaf Witt, MD, PhD.

10. Prognosis

The chances of survival (prognosis) for children and teenagers with Ewing sarcoma depend on various factors. In particular, the tumour's response to *preoperative chemotherapy* as well as its site, size and extent at diagnosis are of major prognostic importance.

During the last decades, prognosis of children and teenagers with Ewing sarcoma has significantly been increased, thanks to modern diagnostic procedures and standardised combination therapies in the framework of therapy optimising trials.

While the probability of survival after *radiation therapy* alone was about 10 % in the 1960s, an average of more than 80 % of patients with local disease, meaning without visible metastases [see *metastasis*], can achieve long-term cure by a combination of local and chemotherapy today. Favourable prognosis usually requires complete tumour removal and good response to the chemotherapy that precedes surgery.

Patients with metastasised disease at primary diagnosis still have an unfavour-able prognosis despite of intensive chemotherapy (5-year survival rates are an average of about 20-25 %). Prognosis is more favourable for patients with single lung metastases that can be surgically removed, when compared to patients with bone or *bone marrow* metastases. Prognosis for patients with recurrent disease is similarly unfavourable. Most unfavourable is the prognosis for patients who develop early metastases after intensive frontline treatment. Currently active and future trials should help to improve the outcome of those patients as well.

Note: The survival rates mentioned in the text above are statistical values. Therefore, they only provide information on the total cohort of patients with osteosarcoma. They do not predict individual outcomes. In the context of cancer, the term „cure" should rather be referred to as „free of cancer", be-cause current treatment regimens may help to destroy the tumour, but they are also frequently associated with numerous 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

alkylants	artificially produced (synthetic) substances that are used as cytostatics to prevent cancer cells from multiplying; basically, alkylants act by forming strong bonds with DNA and/or certain proteins in the cell nucleus, thereby destroying the genetic material and preventing its replication during cell division.
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.
audiometry	method of studying auditory function using special tone generators that produce individual frequencies at a specific volume; it is used, among other things, to diagnose diseases of the hearing organs. A distinction is made between subjective and objective audiometric methods. An example of a subjective audiometric method is the tone audiogram. It requires the assistance of the person whose hearing is to be examined.
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.
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).
bone marrow punch biopsy	removal of bone marrow tissue for the purpose of examining the cells; with the help of a special hollow needle, a tissue cylinder about 2 cm long is punched out of the bone. The examination is always carried out under anesthesia. A bone marrow punch biopsy may be necessary in addition to or instead of a bone marrow puncture if the latter does not provide sufficient tissue for a

	reliable examination. Like the bone marrow puncture, it is usually performed from the posterior iliac crest bone. There, the bone marrow is only separated from the skin by a relatively thin layer of bone, so that the removal can take place without significant risk.
bone marrow puncture	removal of bone marrow tissue to examine the cells; during the puncture, a few milliliters of liquid bone marrow are drawn from the pelvic bone or sternum into a syringe with the help of a thin hollow needle. The puncture is performed under local anaesthesia in older children; a sedative may also be administered (sedation). For smaller children, a short period of anesthesia may be appropriate.
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.
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.
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
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.
genetic	concerning the (level of) inheritance or genes; inherited
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).
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
immunohistochemical	in an immunohistochemical or immunohistological examination, proteins or other cell or tissue structures are visualized with the help of labeled antibodies (e.g. bound to dyes).
infusion	introduction of fluids into the body, usually over a long period of time and via a central venous catheter; an infusion is given, for example, to supply water, electrolytes, proteins and/or medication as part of intensive treatment.

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.
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.
medulloblastoma	malignant embryonic (primitive) tumour of the cerebellum; it occurs mainly in infancy and childhood and, at almost 20 %, is the most common malignant solid tumour in childhood and adolescence.
mesenchymal stem cells	stem cells of connective tissue; they are found in various types of tissues (such as bone marrow, bones, skeletal muscles, cartilage, blood, adipose tissue, connective tissue of the skin) and can develop into different types of cells (including bone, cartilage, muscle, fat cells).
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.
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.
neuroblastoma	malignant solid tumour of the sympathetic nervous system; occurs more frequently before the age of 5, mainly in infants and newborns; neuroblastoma is one of the most common solid tumours in childhood and adolescence (accounting for about 5.5% of all malignant diseases) after CNS and soft tissue tumours.

neuroectodermal	The neuroectoderm refers to the tissue parts of the outer of the three embryonic germ layers (ectoderm) from which the nerve tissue develops.
Non-Hodgkin lymphoma	a large group of malignant diseases of the lymphatic system, which can provoke lymph node swelling as a main feature; like Hodgkin lymphoma, NHL is a malignant lymphoma. It accounts for about 7 % of malignant diseases in childhood and adolescence.
osteosarcoma	the most common bone tumour in childhood and adolescence; occurs mainly in the second decade of life during the pubertal growth phase
pathologist	a physician who identifies diseases and determines the malignancy of tumours by means of histological and molecular genetic examination of cells and tissues
peripheral nervous system	can be described as the receiving and executing organ of the central nervous system (CNS); it consists of the numerous nerves that run through the body; they carry impulses either from the periphery to the CNS (sensory nerve pathways) or from the CNS to the periphery (motor nerve pathways). The peripheral nervous system includes, for example, the cranial nerves, spinal cord nerves and peripheral nerve cells.
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.
positron emission tomography	an imaging, nuclear medicine procedure based on the principle of scintigraphy, which can be used in cancer medicine to visualize tumours or metastases. To detect tumour tissue, a radioactively labeled sugar compound is administered. Since tumours have a higher metabolism than healthy tissue, the radioactive substance is increasingly taken up and stored by the tumour cells. The tumour cells enriched with this substance emit signals that are captured by a special camera (PET scanner) and converted into an image (tomogram).
preoperative	prior to surgery
primary tumour	the tumour that developed first, from which metastases can originate
primitive	undeveloped, undifferentiated
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	controlled use of ionizing (high-energy) radiation for the treatment of malignant diseases
radiation therapy	controlled use of ionizing (high-energy) radiation for the treatment of malignant diseases
radioactive	the term „radioactive“ is used for substances with unstable atomic nuclei that spontaneously transform by releasing energy. The energy released is emitted as ionizing radiation (high-energy particles and/or gamma radiation).
remission	temporary or permanent decrease or disappearance of the signs of cancer.
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.
skeletal scintigraphy	an imaging, nuclear medicine procedure that is mainly used in cancer medicine to detect or exclude bone metastases; radioactive technetium (99Tc), which is bound to a phosphate compound, is used for the investigation. Since phosphate is a natural component of the basic substance of bones, the radioactive compound is taken up by the bone cells, especially in those with increased metabolism. A special camera locates the suspicious areas.
soft tissue	soft tissues include connective, fat, and muscle tissue, as well as blood vessels and peripheral nerve tissue (nervous system without the brain and spinal cord). The soft tissues thus include all non-epithelial tissues of the body with the exception of the supporting tissue (bone and cartilage). They connect, support and surround the other parts of the body and organs.
soft tissue sarcoma	a variety of very different malignancies that originate from soft tissues, e.g. connective, fat, muscle or peripheral nerve tissue; they account for about 6% of malignant diseases in childhood and adolescence; the most common soft tissue sarcoma in children and adolescents is rhabdomyosarcoma.

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.
supportive therapy	supportive treatment measures to prevent, alleviate or treat disease and/or treatment-related side effects or complications; supportive therapy is designed to improve the patients quality of life.
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.
topoisomerase inhibitors	substances used to treat cancer (cytostatics); they inhibit various enzymes (e.g. topoisomerase I and topoisomerase II) that are involved in the repair of breaks in the genetic material. This way, they block the bodys own repair mechanisms, on which rapidly dividing tumour cells depend. Topoisomerase inhibitors include, for example, the active substances etoposide, etoposiphosphate and teniposide from the group of epipodophyllotoxins as well as topotecan and irinotecan from the group of camptothecines.
translocation	exchange of gene segments between two chromosomes
tumour marker	biological substance (e.g. protein) in the blood or other body fluids, the increased concentration of which may indicate a newly developed tumour or tumor recurrence; tumor markers play a major role in monitoring the course of the disease in patients who presented with elevated concentrations of a certain tumour marker at the time of cancer diagnosis. Tumour markers are not proof of an existing cancer, because on the one hand, they also occur naturally in the body, and on the other hand they do not

	necessarily rule out a tumour if they are missing (i.e. not present in conspicuously elevated concentrations).
undifferentiated	here: immature, not yet functional and usually capable of unlimited division (e.g. stem cells); the development from undifferentiated to differentiated cells and tissues (differentiation) takes place in stages. Accordingly, there are many different degrees of differentiation.
WHO classification	international guideline developed by the World Health Organization (WHO) for classification, diagnosis and differentiation/grading of (malignant) diseases
X-ray examination	imaging procedure that uses X-rays to visualize organs or parts of organs