Osteosarcoma (Brief information)

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1. General information on the disease

Osteosarcomas are rare malignant bone tumours. They are *solid tumour*s arising from malignantly transformed bone-forming *cell*s. Since osteosarcomas develop directly from bone tissue, they are also called *primary* bone tumours in order to distinguish them from cancers of other body parts that have spread to the bones (bone metastases). Most osteosarcomas grow and spread very quickly. Without an appropriate treatment, the disease is always fatal.

2. Incidence

Osteosarcomas are the most frequent malignant bone tumours in childhood and adolescence. According to the German Childhood Cancer Registry (Mainz, Germany), about 4 of 1,000,000 (in total approximately 60) children and adolescents under 18 years of age are diagnosed with osteosarcoma in Germany per year, which accounts for about 2.6 % of all paediatric malignancies in this age group.

Osteosarcoma can develop at any age. In childhood and adolescence (0-17 years), the frequency of this type of cancer peaks during the pubertal growth spurt in the second decade of life. The average age of patients within this age group is 14 years (when considering all patients, it is 16-18 years). Overall, boys are more frequently affected by the disease than girls (gender ratio: 1.3:1). Children under the age 5 are very rarely affected.

3. Localisation and spread

Most osteosarcomas arise in a long bone of a leg or an arm (for example in the thigh, shin or upper arm), usually in the areas that are close to the joints, the so-called metaphyses (*metaphysis*). In those bone areas (which include the so-called growth plates), longitudinal bone growth takes place, in particular during the pubertal growth spurt.

More than 50 % of all osteosarcomas are located around the knee (meaning above or below the knee joint). In general, osteosarcoma can develop in any bone. The tumour sometimes affects bone and/or *bone marrow* only, but it frequently also spreads (metastasizes) into adjacent tissue, such as connective, fat, muscle or nerve tissue. Rarely, an osteosarcoma does not arise from bone tissue, but from the surface of the bone (periosteal or parosteal) or even outside the bone (extraosseal or extraskeletal).

In about 10 to 20 % of children and adolescents with osteosarcoma, tumour spread (*metastasis*) is detectable at diagnosis. 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. Osteosarcomas primarily spread via the blood to the lungs (about 70 %), less frequently

to bones and other organs. Sometimes, metastases develop both in lungs and bones at the same time. Metastasizing into the lymph nodes is extremely rare.

Very rarely (in less than 5 % of the patients), tumours are found in various different bones from the very beginning. This is called “multifocal disease”.

4. Histologic characteristics and tumour types

One major characteristic of osteosarcomas is that the tumour cells – in contrast to healthy bone-forming cells – produce immature bone tissue (osteoid). This feature alone allows to distinguish osteosarcoma from other bone tumours. Apart from that, however, the histologic characteristics of osteosarcoma (i.e. the way the tumour cells look under a microscope) are diverse as is the biological behaviour of these tumours. Most osteosarcomas in childhood and adolescence are highly malignant, since they grow rapidly and spread fast. Specialists also call them grade 3- (G3-) tumours. Only a few subtypes of osteosarcoma may be considered to be of low or medium grade of malignancy (so-called G1- or G2-tumours, respectively).

The World Health Organization (*WHO*) differentiates between the following subtypes of osteosarcoma based on their typical histologic features (*WHO classification* of bone tumours):

- **conventional osteosarcoma** (high grade of malignancy, G3)
- **telangiectatic osteosarcoma** (high grade of malignancy, G3)
- **small-cell osteosarcoma** (high grade of malignancy G3)
- **low-grade central osteosarcoma** (low grade of malignancy, G1)
- **high-grade surface osteosarcoma** (high grade of malignancy, G3)
- **periosteal osteosarcoma** (medium grade of malignancy, G2)
- **parosteal osteosarcoma** (usually low grade of malignancy, G1)
- **secondary osteosarcoma** (usually high grade of malignancy, G3)

Conventional osteosarcomas are the most frequent. They account for about 80 to 90 % of all osteosarcomas and are subclassified according to the current WHO classification (2020). All other subtypes are rather rare (accounting for less than 5 % each). The grade of malignancy has a major impact on treatment planning.

Extraosseal osteosarcomas are classified under the soft tissue sarcomas according to the WHO and are thus treated as those (*see patient information on soft tissue sarcomas*).

5. Causes

The causes of osteosarcoma are only partially understood. Genetic, *epigenetic* and growth-related factors are currently being considered to all contribute to the risk of developing osteosarcoma.

Frequently, the tumour cells contain *DNA* changes, such as in so-called *tumour suppressor gene*s (like the *retinoblastoma gene* or the TP53 gene), which normally prevent tumour formation. In general, the genetic defects in osteosarcoma cells are characteristically quite complex, being associated with impaired cell cycle control, cell communication or differentiation of bone-forming cells, respectively. Since osteosarcoma preferably develops during *puberty*, it is assumed that the growth signals that are associated with puberty may play a role in the development and progression of osteosarcoma.

Apart from that, further factors are known to elevate the risk of osteosarcoma. These include *ionising radiation* as used, for example, in *radiation therapy*, as well as certain cellular poisons (cytotoxins), such as certain anticancer agents that are applied during chemotherapy (*cytostatics*, especially so-called *alkylants*). Radiation and cytotoxins are capable of causing genetic instability in bone-forming cells, thereby contributing to initiate osteosarcoma development.

Some osteosarcoma can also be associated with so-called *cancer predisposition syndrome*s, very rare hereditary diseases chararacterized by *mutation*s that (compared to healthy individuals) are connected with a higher risk of developing a malignancy at a younger age. Cancer predisposition that play a role in the development of osteosarcoma are, for example, the hereditary (mostly bilateral) type of *retinoblastoma* as well as *Li-Fraumeni syndrome* or *Bloom syndrome*. Also, children with chronic bone diseases, such as *Paget`s disease*, have an increased risik to develop osteosarcoma.

For most patients, however, no particular cause can be found.

6. Symptoms

The most frequent *symptom*s of osteosarcoma are pain in a bone or joint and/or a (progressive) swelling over a bone or bony part of the body. Occasionally, the pain is not directly experienced at the tumour site, but rather in a different area of the affected skeletal part.

Pain may be intermittant and activity-dependen, but frequently also occurs at rest. About a quarter of the patients complain about pain at night. With increasing tumour growth, the pain may be accompanied by a visible and / or palpable lump at the tumour site (frequently in the area of the knee joint). The swelling may be reddened and warm and may sometimes lead to impaired mobility, which initially may be mistaken for the result of a sports injury or bone inflammation. Sometimes, even a minor accident may cause a fracture at this site (pathological fracture). In about 5 to 10 % of patients, bone fracture is the first symptom of the disease.

The symptoms described above (such as pain, swelling, reddening) are caused by the tumour growth within the tender bone, which is very sensitive to pain, and adjacent soft tissue. Patients with advanced disease may also complain of general symptoms such as fever, weight loss and/or fatigue. 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 osteosarcoma 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.

7. 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 oncologist*s, 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 absolutely essential for optimal treatment planning and *prognosis*.

7.1. Clinical exams and laboratory tests

The caregiver team at the hospital will first take a thorough history followed by a physical exam, during which the location, size, consistency and range of motion of the affected site is being assessed. Lab tests rather play a secondary role in the diagnostics of osteosarcoma. However, serum levels of certain parameters may, if elevated, be indicative of an altered bone metabolism and, thus, a potential bone tumour. These include, for example, the *alkaline phosphatase* (AP) and the *lactate dehydrogenase* (LDH). Since elevated AP and LDH levels can be associated with different (bone) diseases, they only add to other diagnostic tests and are not specific for bone tumours.

7.2. Imaging tests for tumour detection

Based on their typical radiological features, most malignant bone tumours can already be diagnosed on an *X-ray examination* Additional imaging procedures such as *magnetic resonance imaging* (MRI) 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, nerves, tendons or joints). Nearby metastases (called skip metastases) are easily detectable by these methods, too. For imaging of affected soft tissue and bone marrow, MRI is superior to *computed tomography* (CT). Apart from plain *X-rays*, it is therefore considered as the gold standard in radiological diagnosis of osteosarcoma.

7.3. Tissue removal and analysis

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 bone tumours. 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 (thereby requiring limb amputation, for example). Also, suboptimally performed biopsy may be associated with an increased risk of recurrent disease. Hence, it is

recommended that, even prior to biopsy, all patients with a suspected bone tumour are referred to a bone tumour reference centre or a centre that belongs to an osteosarcoma network.

In order to obtain a sufficient amount of tumour tissue, open surgery, meaning the removal of tissue during the surgical procedure for tumour resection, is gold-standard. Needle biopsy may be considered for in single cases only. In these situations, special needles are used (tru-cut biopsy). The obtained samples are subsequently analysed both *histological*ly and *immunohistochemical*ly by specialists. These analyses serve to confirm the diagnosis of osteosarcoma and, once confirmed, to determine the subtype.

7.4. Tests to assess tumour spread

Once the diagnosis of osteosarcoma has been confirmed, further *imaging* tests are required to find out if and to which extent the cancer has spread and which organs are involved. Since most metastases develop in the lungs, a chest x-ray as well as a chest-CT are indispensable. In order to assess or, respectively, rule out bone metastases, a *skeletal scintigraphy* (bone scan) using *radioactive* technetium (11mTc) is performed. In addition (or instead), *positron emission tomography* (PET) with radioactively labelled glucose (18F-fluoride-deoxyglucose, short FDG) may be an option. PET is either combined with computed tomography (PET-CT) or magnetic resonance imaging (PET-MRI).

7.5. 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.

8. 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

chance of recovery (*prognosis*) – called risk factors or prognostic factors – are being considered during treatment planning (risk-adapted treatment strategy).

Important *prognostic factors* are the type, the localisation, size and spread of the tumour, which are assessed before treatment starts. In the course of treatment, additional prognostic factors, such as the extent of tumour removal (incomplete versus complete) and the response of the disease to *chemotherapy*, are of major impact on how treatment is going to be continued. Taking into account all these factors aims at achieving the best outcome possible for each patient.

9. Treatment

Treatment of children and adolescents with osteosarcoma should take place in a children's hospital with a paediatric oncology program that is also part of a specialized osteosarcoma-network. 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 good cure rates while avoiding side effects as much as possible.

9.1. Treatment methods

Treatment of children and adolescents with osteosarcoma basically consists of **surgery** (local therapy) and **chemotherapy**. Only patients with the rare low-grade subtypes may benefit from surgery alone under certain conditions. **Radiotherapy** plays an inferior role. It is only considered when complete tumour removal is not possible. Overall, treatment takes about nine to twelve months.

Goal of *surgery* is to remove the tumour. Chemotherapy uses drugs (so-called cytostatic agents or *cytostatics*) that can kill fast-dividing cells, such as cancer cells, or inhibit their growth, respectively. High-dose *radiation therapy* is only required if gross total tumour resection is not an option and 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.

In order to prevent or adequately manage the side effects of the intensive therapy, specific supportive care regimens (see (*supportive therapy*) 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.

9.2. Course of treatment

The following treatment plan is currently the international standard for patients with highly malignant osteosarcoma: The first step includes a preoperative (neoadjuvant) chemotherapy for a total of about two to three months. The subsequent surgery for tumour removal is followed by another (adjuvant) chemotherapy,which lasts about six months (individual treatment plans may apply to

single patients). Requirement of radiotherapy is the exception and needs individually adjusted decision-making. Removal of lesions sus-picious of metastasis is usually done after surgery of the primary tumour. The different treatment phases will be outlined in the next paragraphs.

9.2.1. Chemotherapy prior to surgery

For most patients, therapy is initiated by a ten-week phase of *chemotherapy* (called *preoperative*, neoadjuvant or induction chemotherapy). 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 and prevent further tumour spread. This time is also used to prepare for surgery.

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 osteosarcoma. These agents include methotrexate (high dose, HD-MTX), adriamycin (ADR = doxorubicin) and cisplatin (DDP), abbreviated “MAP”. Chemotherapy is given as several courses over several days each (altogether two cycles of cisplatin/doxorubicin and four cycles of methotrexate), during which the patient needs to be inpatient. Between courses, patients can go home as outpatients. Only in case of severe side-effects, readmission is required.

9.2.2. Local therapy

Surgery is the gold standard for local therapy. (Additional) radiotherapy is an option only for tumours that cannot be completely removed due to their location or extent, respectively.

9.2.2.1. Surgery

Following chemotherapy and the shortest possible recovery period, patients undergo *surgery* with the goal of complete surgical tumour removal. Surgery aims at removing both tumour parts that have been identified by diagnostic imaging (macroscopic) as well as microscopically small ones, because gross total tumour resection is crucial for subsequent chances of cure. The term “gross total resection” is defined as the removal of all tumour parts including the biopsy scar, biopsy channel and a layer of surrounding healthy tissue.

Choice of the surgical technique depends on the site and extent of the tumour as well as the on response to chemotherapy and is adjusted to every patient individually. Also, metastases need to be removed to increase the chances of cure.

Thanks to major technical progress regarding limb-saving surgical procedures, tumour removal does usually not require amputation any more. Different techniques are available for limb reconstruction based on the location and the size of the tumour. For example, metal joint implants are frequently used; for children, also growing endoprotheses are available.

Following surgery, a pathologist examines the tumour tissue to find out how the disease has responded to the preceding chemotherapy. This response is assessed by measuring the amount of the tumour cells that are still alive. An amount of less than 10 % is considered as good response, which is achieved for about 50 % of all osteosarcoma patients. This response represents a very

important prognostic factor. However, changing the chemotherapy regimen in case of poor response is not required.

9.2.2.2. Radiotherapy

For patients whose tumour and/or metastases [see *metastasis*] cannot be completely removed, *radiation therapy* might in some situations be an alternative or additional treatment option. However, radiotherapy is far less favourable than gross total tumour resection, and hence, all other options have to be carefully considered before. In general, osteosarcomas are not very sensitive to radiation, thereby requiring high radiation doses for treatment. Also, delivery of radiotherapy might me challenging depending on the tumour location.

The pros and cons of radiotherapy need interdisciplinary discussion and decision-making on an individual basis. In suitable cases, modern radiation techniques such as intensity modulated radiotherapy (IMRT), proton or heavy ion therapy may be used. The feasibility of heavy ion radiotherapy for children and adolescents is currently being investigated in the framework of a clinical study.

9.2.3. Chemotherapy after surgery

After surgery, chemotherapy with methotrexate, adriamycin and cisplatin (MAP) is continued for 18 weeks (postoperative chemotherapy). Treatment consists of 12 cycles (a total of two cycles cisplatin/doxorubicin, two cycles doxorubicin and eight cycles methotrexate) and takes about six to seven months including the treatment breaks.

9.3. Treatment of recurrent disease

About 20 to 40 % of patients with osteosarcoma develop recurrent disease. Like the primary disease, recurrent osteosarcoma (relapse) requires complete removal of the tumour in order to achieve cure. Subsequent treatment depends on the tumour sites and the timepoint of relapse (early versus late relapse).

Patients with single lung metastases, in particular if these occur later than two to three years after primary diagnosis, may benefit from surgery alone. Other patients with relapsed osteosarcoma will also need another round of *chemotherapy*, for example with carboplatin, etoposide and ifosfamide. In palliative settings, *radiation therapy* may be an option. Several clinical trials (phase I/II) are also investigating new agents (such as *tyrosine kinase* inhibitors). Overall, the *prognosis* for patients with relapsed osteosarcoma is not favourable.

10. Therapy optimising trials / registries

In the large paediatriac treatment centres, children and adolescents with osteosarcoma 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.

In Germany, patients with osteosarcoma had the option to be enrolled in the therapy optimising trial **EURAMOS 1** until June 2011. The study was conducted by the Cooperative Osteosarcoma Study Group COSS of the German Society for Paediatric Oncology and Haematology (GPOH) in collaboration with other renowned groups. Numerous children's hospitals and treatment centres all over Germany and other European as well as North American countries participated.

Since the EURAMOS trial has been closed for patient admission, children and adolescents with osteosarcoma are being registered in the so-called **COSS-Registry** until the subsequent trial is ready to be opened. The German headquarters of trial and registry are located at the Clinic for Paediatric Oncology, Hematology and Immunology of the Klinikum Stuttgart – Olgahospital, Germany. Principal investigator is Professor Dr. med. Stefan Bielack.

The registry does not provide protocols for diagnostics and therapy. However, the study centres recommend the current standard treatment (MAP chemotherapy prior and after surgery, *see chapter "Treatment"*) for all patients who are not participating in a trial. These recommendations also include the diagnostic standards, supportive treatment and long-term care. Having patients participate in open clinical trials is endorsed. Your caregiver team will inform you about the current options.

11. Prognosis

The chances of survival (*prognosis*) for children and teenagers with an osteosarcoma depend on various factors. In particular, the subtype and the site of the tumour, its extent at diagnosis, response to preoperative chemotherapy as well as the extent of surgical tumour/*metastasis* removal are of major prognostic importance.

During the last five decades, prognosis of children and teenagers with osteosarcoma has significantly been increased by major improvements of diagnostics and treatment in the framework of therapy optimising trials.

By combining different treatment methods and particularly by introducing intensive, standardised combination chemotherapy regimens, survival rates of approximately 70 % can be achieved today. Favourable prognosis usually requires complete tumour removal and good response to the chemotherapy that precedes surgery.

Patients with non-metastasised osteosarcoma of the arm or leg have the most favourable prognosis – cure rates may reach more than 70 %, depending on the response to chemotherapy. Patients with good response (that means less than 10 % of living tumour cells after chemotherapy) have

a much better prognosis than patients with poor response. The latter have a high risk of recurrent disease (relapse); the probability of disease-free survival is currently less than 50 %.

Patients with tumours of the trunk, which often cannot be completely removed because of their location, have a less favourable prognosis than patients with a tumour of the extremities (which generally can be removed more easily). The situation is similar for patients with large tumours that cannot be removed in total. In case of metastases, their number, localisation and *operability* are major prognostic factors. Patients with single, removable lung metastases have a better chance of survival than patients with bone metastases or multifocal disease. For patients with recurrent disease, prognosis is usually rather unfavourable (with a chance of survival of 20-25 %). However, cure of (even repetitive) *recurrence* is possible, as long as the tumours can be removed completely.

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", because 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.
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.
Bloom syndrome	rare hereditary disorder characterized by growth disorders, pigmentation defects, photosensitivity, fertility disorders, increased susceptibility to infections and increased risk of cancer (leukaemias and solid tumors); the affected patients develop several tumours in the first two years of life, which are rare in the rest of the population. Bloom syndrome is therefore one of the cancer predisposition syndromes.
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).
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.
chemotherapy	here: use of drugs (chemotherapeutic agents, cytostatics) for the specific inhibition of tumor cells in the organism
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.
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
epigenetic	epigenetics is a branch of biology that deals with molecular mechanisms that lead to stronger or weaker expression of genes without altering the information stored on the gene. Instead, certain biocatalysts (enzymes) mark certain sections on the genetic material (DNA). In contrast to genetic processes,

	epigenetic processes are reversible and do not influence the sequence of the DNA, but the way the sequence is being read by taking place on top of it, i.e. at a higher level ("epi-" - from Greek: "over"). Epigenetic processes are nevertheless heritable, meaning they are passed on during cell division. Through epigenetics, cells control, for example, which proteins they produce, in what quantities and when.
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).
ionising radiation	very high-energy radiation that can cause radiation damage when passing through a cell or organism; ionising radiation breaks chemical bonds and produces chemical radicals, which in turn trigger chemical reactions. This is where their biologically harmful effect lies. Ionising radiation includes electromagnetic radiation (such as X-rays, gamma rays and short-wave UV rays) as well as particle radiation (e.g. alpha, beta and neutron radiation).
lactate dehydrogenase	enzyme that plays a role as part of a metabolic process (lactic acid fermentation) in all cells and organs and is also detectable in the blood; an elevated LDH level in the blood can indicate cell damage in the body and (among other conditions) occur in many benign and malignant diseases or injuries.
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).
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.
metaphysis	the area in a long bone that is located (close to the joint) between the middle part (bone shaft, diaphysis) and the end piece (epiphysis) of the bone; during the growth phase, the longitudinal growth of the bone takes place in the so-called epiphyseal plate.
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.
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.
operability	feasibility of surgery as a treatment option; whether a patient is operated depends on their clinical condition and on whether the procedure is an appropriate and effective form of treatment in the respective case (indication). The operability of a tumour particularly depends on its location in the body and its growth behaviour.
paediatric oncologist	paediatrician who is specialized on the management of children and adolescents with cancer
Paget`s disease	here: bone disease the cause of which has not yet been clearly elucidated; it begins insidiously and is accompanied by curvature and thickening of one or more long bones, corresponding deformities and pain.
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
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);
puberty	the process of sexual maturation; the period during which adolescents reach sexual maturity and become capable of reproduction
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).
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.
retinoblastoma gene	tumour suppressor gene called RB1, which causes the development of a malignant retinal tumour (retinoblastoma) when

	genetically altered (mutated); it is located on the long arm of chromosome 13.
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.
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.
tumour suppressor gene	gene that controls cell division (via its gene product) and thus prevents the formation of uncontrollably growing tumour cells (e.g. TP53 gene or retinoblastoma gene, RB); the failure of a tumor suppressor gene, e.g. due to mutation, can promote tumour formation.
tyrosine kinase	enzymes from the protein kinase family; they particulalrly contribute to the transmission of signals within a cell and are important for embryonic development as well as the regeneration

	and maintenance of tissues. Functional disorders can play a role in the development of cancer, among other pathological conditions.
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
X-ray examination	imaging procedure that uses X-rays to visualize organs or parts of organs
X-rays	high-energy electromagnetic radiation, discovered by W. C. Röntgen in 1895; X-rays can partially penetrate matter, so that insights into the interior of the human body are possible, among other things. Since X-rays have an ionising effect (ionising rays), they can also change matter, e.g. damage cells and possibly cause cancer. In diagnostics, X-rays are used to examine certain parts of the body. Depending on the type of irradiated tissue, the radiation is intercepted (absorbed) to varying degrees and displayed on a film plate as a two-dimensional image. Since every X-ray examination is associated with a certain amount of radiation, particularly sensitive parts of the body (such as gonads) must be protected. In the context of X-ray therapy (e.g. radiotherapy), very high-energy X-rays are used to kill tumour cells.