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Informationsportal zu Krebs- und Bluterkrankungen bei Kindern und Jugendlichen

Retinoblastoma (brief information)

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Retinoblastoma (brief information)

1. General disease information

Retinoblastoma is a rare eye cancer arising from the retina, the inner layer of the eye, which is specialised in colour and light perception. It almost only occurs during childhood. There is a hereditary (congenital) and a non-hereditary form of the disease. Patients with the hereditary form have an inherited predisposition for the development of this cancer, while in the second case, the cancer develops spontaneously, meaning, it is initiated by a new genetic alteration in a retina cell.

Retinoblastoma may affect one or both eyes. In the majority of patients (about 60 %), only one eye is affected (unilateral retinoblastoma); in approximately 40 % of the children, the tumour develops in both eyes (bilateral retinoblastoma). Bilateral disease is almost always seen with hereditary retinoblastoma, while most unilateral retinoblastomas are non-hereditary. Tumours may develop either at one site in the eye (unifocal) or at multiple sites (multifocal). About a third of the affected children present with bilateral, multifocal tumours at initial diagnosis, or they develop additional tumours while the disease is progressing.

In general, retinoblastomas grow fast. They can spread within the eyeball, into the orbit, and along the *optic nerve* into the *central nervous system* (CNS). In advanced stages, they may also spread into other organs via the blood and/or *lymphatic system*. If not treated appropriately, the outcome will be lethal. Only in very few patients (1 %), the tumour disappears without treatment (spontaneous regression).

2. Incidence

Retinoblastoma is the most common childhood cancer of the eye. According to the German Childhood Cancer Registry, Mainz (Germany), about 45 children under 18 years of age (corresponding to approximately 4 out of 1.000.000) are diagnosed with this type of malignancy in Germany each year. This means that there is one child with retinoblastoma among 18,000 children born alive. Overall, however, retinoblastoma is a rare disease; it accounts for approximately 2 % of all malignant diseases in children and adolescents.

Most retinoblastomas are diagnosed in infants and small children, i.e. before the age of five. Usually, children with a bilateral retinoblastoma are younger than children with unilateral disease. Beyond the sixth year of life retinoblastomas are extremely rare. The average age of disease is about 1 year, with boys being slightly more affected than girls (gender ratio: 1.1 : 1).



3. Causes

The causes for a retinoblastoma to arise in the eye include certain *genetic* alterations (mutations) in the precursor cells of the retina. Such alterations may occur spontaneously in single retina cells before or after the child's birth. Sometimes, however, the mutation may be present within the patient's *germ cells* (and, thus, in all body cells), meaning, the disease is hereditary and can be passed on to the offspring, too.

In more than 50 % of patients, the altered *gene* is only found in the tumour itself. They have the non-hereditary (sporadic) type of retinoblastoma. Almost 50 % of retinoblastoma, though, are congenital (hereditary), which means, the affected children have a predisposition for the tumour to develop. About one quarter of these children (10 to 15 % of all patients) are presenting with a family story of retinoblastoma, this means, other family members are known to have this type of cancer, too (familial retinoblastoma). In the remaining three quarters of patients with congenital retinoblastoma, the underlying genetical alterations are believed to have happened spontaneously.

Regardless of hereditary or non-hereditary, the mutations causing retinoblastoma are found in the retinoblastoma (RB1) gene, which is located on *chromosome* 13. Since in human cells chromosomes occur in pairs, there are also two *retinoblastoma gene* variants (so-called alleles) in each cell. Only when both retinoblastoma *alleles* are altered, the tumour will form. Since in hereditary retinoblastoma all retina cells initially contain one altered retinoblastoma gene variant already, "only" one additional *mutation* is required to induce tumour development. This is why the hereditary form presents at an early age, affects both eyes at (frequently) multiple sites (multifocal). Children who have inherited the altered gene have an almost 100% risk to develop retinoblastoma. Since there is a predisposition for developing additional cancers, hereditary retinoblastoma is also known as a *cancer predisposition syndrome*.

4. Symptoms

Very small retinoblastomas usually do not cause any complaints; the disease frequently progresses without any *symptoms* for a long period of time. Health problems usually occur with tumour growth into adjacent eye tissue. This can result in an impairment of vision or even loss of sight.

The most common and typical sign, which is found in about two thirds of patients, is a white flashing of the pupil (white pupillary reflex, leukocoria) under certain light conditions, for example, after a flash photograph was taken – in contrast to the well-known red or black appearance of the pupils in healthy eyes. This condition, also referred to as "amaurotic cat's eye" is caused by expansive tumour growth behind the lens. In addition, impairment of the visual axis may lead to crossed eyes (strabismus), depending on the source in up to almost 50% of patients. Less often, patients also complain about irritated, swollen, red or painful eye as a result of increased eye pressure caused by the growing tumour.

Warning signs indicative of retinoblastoma may be:

- "amaurotic cat's eye" (leukocoria)



- crossed eyes (strabismus)
- impairment of vision or loss of sight / visual disturbances
- different colour of each eye (due to impaired pigmentation of the iris in the affected eye)
- irritated eye (redness of the white part of the eye, bulging of the eye, eye pain, without infection)
- visual impairment (involuntary eye movement, *nystagmus*)
- no shrinking of the pupil when exposed to bright light (mydriasis)

Occurrence of one or more of these symptoms, however, does not necessarily prove underlying retinoblastoma or any other malignancy. Some of these symptoms may be caused by relatively harmless health conditions that are not associated with cancer at all. Nevertheless, it is recommended to consider these symptoms as warning signs and therefore to consult a physician promptly upon their appearance. If retinoblastoma (or another malignant disease) is present, early diagnosis is the best precondition for a successful treatment of the disease.

Good to know in case of known, hereditary predisposition: children from families with a hereditary risk should – as long as they are known or assumed to have inherited the disease – have regular eye exams, so that retinoblastoma can be diagnosed and appropriate management initiated at an early stage (*also see chapter „Diagnosis“*).

5. Diagnosis

If a child's medical history (*anamnesis*), presenting complaints and symptoms, as well as the *physical examination*, particularly the eye exam, are suggestive of retinoblastoma, the patient should immediately be referred to a children's cancer centre. There, diagnostics and treatment can be initiated and performed by specialists with the necessary expertise in childhood cancer. Close collaboration between various specialists (such as *paediatric oncologists*, eye doctors, surgeons, *radiologists*, radiation oncologists, to name a few) as well as special tests are required to confirm the diagnosis and to determine the type of retinoblastoma (hereditary or non-hereditary) and how the disease has spread. Knowing these details is absolutely essential for optimal treatment planning and *prognosis*.

5.1. Examination of the eye

The most important initial diagnostic procedure for a young patient presenting with suspected retinoblastoma is the examination of the eye (fundoscopy). This includes looking at the fundus of both eyes with an ophthalmoscope and bright light. In case of retinoblastoma, fundoscopy also helps to assess the extent of the disease, which serves as a basis for staging. This considers the number, size and site of tumours as well as the potential extent beyond the retina or within the glass body of the eye. For this eye exam, the patient is usually sedated and the pupils have been maximally dilated (mydriasis).



5.2. Imaging diagnostics and further tests

In order to assess the exact tumour extent (staging), fundoscopy is followed by diagnostic *imaging* such as *ultrasound* (sonography) and *magnetic resonance imaging* (MRI). Ultrasound serves to measure the tumour, for example. Using MRI of the eye-socket (orbit) and the brain helps to assess whether the disease is limited to the eye (known as intraocular retinoblastoma) or has spread into the eye layers, the *optic nerve* and/or the brain (extraocular retinoblastoma). Also, “trilateral” retinoblastoma (retinoblastoma plus brain tumour) can be diagnosed this way. For MRI, the patients are usually sedated. Also, a patient with first diagnosis of retinoblastoma should be seen by a paediatric oncologist.

Rarely, for example in patients with very advanced stages of the disease and/or prior to chemotherapy, additional tests may be performed, such as chest *X-ray examination*, spinal tap (*lumbar puncture*), *bone marrow puncture*, and/ or *skeletal scintigraphy* (bone scan).

Once all necessary diagnostics are completed, the doctors will discuss the best treatment options with you.

5.3. Genetic testing

Since hereditary retinoblastoma cannot be ruled out in any patient, human genetics are consulted at primary diagnosis as well, and, following informed consent, the patient’s blood is analysed for *molecular genetics* (genetic testing). This includes a *DNA* analysis to identify genetic alterations (mutations) that are typical for retinoblastoma. Finding those mutations implicates that the child has hereditary retinoblastoma. In this case, the diagnostic procedures are not limited to the affected child only. Genetic testing and eye exams are also required for the patient’s siblings and parents in order to clarify the risk of the disease within the family and hence to be able to initiate appropriate early detection and monitoring measures, since it is possible that the siblings have inherited the abnormal gene as well.

Good to know: genetic consulting and testing are crucial parts of the care of children and families with retinoblastoma.

5.4. Early detection of known hereditary disease

As of today, children in families with retinoblastoma (familial retinoblastoma) can be tested for the defective *gene* immediately after birth (the probability of having inherited it is 50 %). Precondition is, that the *mutation* that is harboured in the family has been identified. This is not always possible, since the alterations within the retinoblastoma gene can be very heterogeneous. In case the child has inherited the mutations (or if this is uncertain), an eye exam is strongly recommended in order to detect and treat tumours as early as possible. Close monitoring should be maintained as long as the immature retina cells, which tend to degenerate, have fully differentiated, which means until about the child’s fifth year of life. Affected individuals will also be followed-up regularly until adulthood.

[Psychosocial Care](#)



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

6. Treatment planning

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).

Extent of retinoblastoma at the time of diagnosis is an important prognostic factor and hence a crucial criterion regarding the choice of the most feasible treatment. Also, unilateral versus bilateral disease is being considered. Knowing the extent of the disease helps the physicians to predict how the patient's disease might respond to a certain form of treatment, whether there is remaining vision of one or both eyes to be expected after therapy and how high the risk of progressive or recurrent disease is. Also, the patient's age and clinical condition as well as the knowledge about a *genetic* predisposition for the disease are integrated in treatment planning.

6.1. Stages of retinoblastoma

Based on the extent, retinoblastoma is divided into different stages (also known as classification). Consideration is primarily focussed on whether the retinoblastoma is intraocular, thereby affecting the eye(s) only, or if the disease has spread to other parts of the body (extraocular retinoblastoma). Tumour extent is always assessed separately for both eyes.

For staging of intra- and extraocular retinoblastoma, various classification systems have been developed:

- Classification of intraocular retinoblastoma is mostly based on the „International Classification of Retinoblastoma“ (ICRB, Philadelphia version). The ICRB staging system (also called ABC classification) considers size and site of the tumour as well as the existence and extent of spread within the vitreous body. This results in a classification of retinoblastoma into 5 stages (A to E).
- Extraocular retinoblastoma is classified according to the International Re-tinoblastoma Staging System (IRSS). This considers in particular whether the tumour has infiltrated the choroid, the dermis and/or the optic nerve, or whether it has spread into the orbit, the central nervous system (meningeosis) and/or even has distant metastases. Depending on the diagnosis, four stages are differentiated: IRSS I-IV. A retinoblastoma that won't be enucleated is assigned to stage 0.

Another classification, the TNM classification for retinoblastoma, merges information on intra- and extraocular disease.



For further details on the classification of intra- and extraocular retinoblastoma according to ICRB and ISSR, please see our information on „[Stages of retinoblastoma \(classification\)](#)“.

7. Treatment

Children with retinoblastoma should be taken care of in a children's cancer centre by specialists, because they provide the expertise necessary to manage this rare type of childhood malignancy.

Current treatment options for children with retinoblastoma include **surgery, chemotherapy** (local and systemic), **radiotherapy** (brachytherapy or percutaneous radiotherapy), **laser therapy, cryotherapy** and **thermotherapy**. For some patients with an advanced disease, **high-dose chemotherapy followed by autologous stem cell transplantation** may be an option, too.

The appropriate type of treatment is individually assessed for each patient with retinoblastoma. It is generally based on whether one or two eyes are affected by the tumour, how far the disease has already spread (intraocular or extraocular retinoblastoma and exact stage of disease) and whether visual acuity can be expected for one or both eyes after treatment. The child's age at diagnosis is important for therapy planning, as well. **The major aim of treatment** is to completely destroy or remove the tumour and to cure the disease. In this context, survival has fundamental priority over preserving visual acuity.

In general, the following two treatment strategies currently exist:

- saving the eye by using radio-, laser-, cryo-, thermo, and/or chemotherapy
- surgical removal of the tumour by removal of the eyeball (enucleation) and sometimes also additional (adjuvant) forms of therapy for maintenance of the treatment success

Eye-preserving therapy is, whenever an option, preferred. For single, small retinoblastomas, a so-called ophthalmological local (focal) therapy is the gold standard. If tumours are already too large for this approach, *chemotherapy* for reducing tumour size may be an option (chemoreduction) in order to make subsequent local therapy feasible. The eye-preserving strategy aims at inactivating the tumour while preserving as much vision as possible, but also making sure that the treatment is efficient enough so the patient won't die from the disease.

If retinoblastoma has been diagnosed at an advanced stage, enucleation, i.e. the removal of the eyeball, is usually necessary. If the tumour has spread into other parts of the body (metastasised), treatment may also include chemotherapy and/or *radiation therapy* in addition to *surgery*. Some situations even require a *high-dose chemotherapy* followed by *autologous stem cell transplantation* to be performed.

The various therapy options will be explained below.



7.1. Eye-preserving therapy options (intraocular retinoblastoma)

Eye-preserving therapies include the ophthalmological focal therapies on the one hand and chemotherapy (systemic and/or local) on the other hand. Percutaneous radiotherapy (radiation from outside the body through the skin) is rarely indicated in case of intraocular retinoblastoma.

7.1.1. Ophthalmological local treatment options (focal therapy)

With the help of ophthalmological local therapies, smaller intraocular tumours (ICRB stages A and partially B) can be treated successfully in an eye-preserving manner. Possible treatment options are *laser therapy* (also called laser coagulation or photocoagulation), *cryotherapy* (or cryocoagulation), *thermotherapy* and local radiation therapy (*brachytherapy*). The individual treatment choice is based, above all, on the tumour's size and localisation:

- **Laser therapy** is particularly used for smaller tumours (smaller than 2 mm in height); it includes guiding a laser beam through the pupil onto the tumour, while the patient is under general *anaesthesia*. The tumour is being destroyed by the heat of the *laser beam*.
- **Cryotherapy** uses extremely low temperatures. The tumour is detected by using an ophthalmoscope and a metal probe and then frozen multiple times. The cold-sensitive tumour cells are thereby destroyed. This approach is feasible for tumours (up to 3-4 mm in height) that are located in the front part (periphery) of the retina. Local spread into the vitreous body can be treated this way as well.
- **Thermotherapy** (or thermochemotherapy) is a form of laser therapy that is combined with a systemically applied chemotherapy. It is particularly used for tumours in the back of the eye pole.
- **Brachytherapy** (short distance radiation) is used for single retinoblastomas (between 4-6 mm in height) located at easily accessible sites. It includes the surgical placement of a radioactive applicator (such as a Ruthenium applicator) onto the sclera in the area of the tumour and leaving it there until the desired radiation dose has been given (usually a few days). Radiation is targeting the tumour only. Therefore, a high total radiation dose can be applied to the tumour while protecting adjacent tissue. Over weeks, months or even years, the radiation-sensitive retinoblastoma is transformed into inactive scar tissue.
- Patients who have been diagnosed with small retinoblastoma in one eye may sometimes benefit from an **eye-preserving strategy**, such as local radiation therapy (brachytherapy). This type of treatment, however, is only recommended for patients with remaining preservable eye sight and for whom sufficient anti-tumour effects can be guaranteed. The benefits of this approach in comparison to enucleation still need to be determined.



All these treatment approaches may be used both alone and in combination with other therapies. They may also be feasible for consolidation in patients with retinoblastomas that could be reduced in size by systemic chemotherapy.

7.1.2. Chemotherapy

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

7.1.2.1. Systemic chemotherapy for intraocular retinoblastoma (*chemoreduction*)

For retinoblastoma patients, systemic *chemotherapy* – a chemotherapy that can control tumour cells everywhere in the body (systemically) - is often applied in addition to other therapy methods to increase their efficiency or to consolidate treatment success. Usually, a combination of various agents is used (polychemotherapy). They are given via a *vein* (intravenous chemotherapy), from where they distribute in the whole body via the blood stream, thus also reaching the tumour's blood vessels.

While, in the past, systemic chemotherapy has primarily been used in advanced disease stages (tumour spread beyond the orbit) or following enucleation, it plays an important role today also for retinoblastomas with an extent that is limited to the eye (intraocular retinoblastoma). The goal of chemotherapy in the context of eye-preserving therapy is to reduce the size of existing tumours in the eye (so-called chemoreduction), so that they can subsequently be further controlled by ophthalmological local treatment forms. This approach is meant to avoid percutaneous radiotherapy as well as enucleation in as many patients as possible.

7.1.2.2. Local chemotherapy

In order to accumulate high concentrations of chemotherapy directly within the eye while also minimizing or avoiding the risk of adverse events of *intravenous* (systemic) chemotherapy (which typically affects the whole body), local chemotherapy has been used for eye-preserving therapy for some time, too. The necessity of percutaneous radiotherapy can be minimized by these relatively new treatment options as well.

- **For intra-arterial chemotherapy**, a cytostatic (for example melphalan) is given directly into an artery of the eyeball. This is done by the following procedure: After the child has been put to sleep by *anaesthesia*, the doctor inserts a *catheter* into a big artery in the child's groin and – monitored by *X-ray examination* – pushes it carefully through the con-nected arteries and past the heart all the way up into the region of the artery of the eye which is to be treated. From there, the substance distributes to the downstream blood vessels including those located in the retinoblastoma. Intra-arterial chemotherapy is very effective for eye-preserving therapy. It may be used during frontline treatment as well as following a preceding therapy.

- **Intravitreal chemotherapy (IViC)** is a therapy option for patients with retinoblastoma cells within the vitreous body (vitreous body spread). By giving melphalan or certain other agents, vitreous body spread can usually be well-controlled and hence the eye preserved.

7.2. Surgical removal of the eye (enucleation)

For a long time, the surgical removal of the affected eye (enucleation) was the most frequently applied and efficient treatment option for retinoblastoma patients and the only possibility for complete tumour removal and, thus, cure of the disease.

Still, enucleation is the therapy of choice for advanced intraocular disease (ICRB stage E, partly also stage D). Hence, it is indicated for patients who present with a retinoblastoma that, due to its size, does not allow local therapy and has already caused severe loss of vision at diagnosis, with no remaining preservable eye sight to be expected by eye-preserving treatment options. This is frequently the case in one-sided (unilateral) retinoblastoma, which are usually already advanced at the time of diagnosis. In bilateral retinoblastomas, tumours often have grown differently, and hence, both eyes present with different stages of the disease. In those cases, usually the more affected eye is being removed, as long as both eyes cannot be preserved.

For tumour removal, the complete eyeball needs to be removed along with a rather long part of the optic nerve. Patients who underwent complete surgical removal of the tumour usually do not require any additional treatment after surgery (adjuvant therapy). However, if histology of the removed eye reveals that the tumour has surpassed certain boundaries (extraocular retinoblastoma) or – due to various risk factors – bears an elevated risk for the development of metastases, respectively, further treatment (so-called adjuvant therapy) may be necessary (*see chapter “Treatment of patients with extraocular retinoblastoma” below*).

7.3. Treatment of patients with extraocular retinoblastoma

Patients who, following enucleation, present with certain histological risk factors (choroid coat-infiltration, involvement of the sclera or the optic nerve), thereby revealing tumour spread outside the eye, require additional (adjuvant) therapy in order to reduce the risk of further tumour spread via the bloodstream into distant regions of the body and/or via the optic nerve into the brain. Even in case metastases already exist, additional treatment is required. The more advanced the disease, the more intense and complex the treatment. Treatment options are: systemic *chemotherapy* alone, combined chemo- and *radiation therapy* (the latter locally limited to the orbit) as well as a multimodal therapy including chemotherapy, *high-dose chemotherapy* with *autologous stem cell transplantation*.

8. Trials and registries

Since retinoblastoma is a very rare disease (about 45 children are diagnosed in Germany per year), so far only few data have been acquired that can be used as a basis for treatment strategies which both consider a patient's individual risk of recurrent disease (risk-adapted therapy) and are statistically proven (evidence-based therapy).



In contrast to treatments of other childhood cancers, a standardised therapy plan (protocol) for the management of retinoblastoma still needs to be established, for example as a *therapy optimising trial*. Therefore, the Retinoblastoma Registry (**RB Registry**) was opened for patients in Germany and Austria by the end of 2013. This clinical registry aims at gathering various data on retinoblastoma over several years, such as incidences and clinical courses of the different types of the disease as well as their response to different treatment forms, in order to fill the information gap mentioned above and, thus, to optimise current therapy and outcomes.

All children and adolescents under the age of 18 years who have been diagnosed with retinoblastoma or have a germline mutation of the retinoblastoma (RB1) gene and who have not yet received any retinoblastoma-specific treatment can be included in the RB-Registry. The headquarters of the RB-Registry are located in the Childhood Cancer Centre of the University of Essen, Germany. The registry is coordinated by Prof. Dr. Petra Ketteler.

9. Prognosis

Due to continuously optimised diagnostic procedures and treatment forms, more than 95 % of children with retinoblastoma can be cured of their disease today. Children with unilateral retinoblastoma still have one completely unaffected eye with normal vision. Their life quality may not differ from that of their healthy peers at all. Also, most patients with retinoblastoma in both eyes will keep a certain amount of visual acuity in at least one eye.

The individual *prognosis* primarily depends on the patient's stage of disease at diagnosis as well as on whether they have the hereditary or non-hereditary type of retinoblastoma.

Patients with tumour growth limited to the eye(s) only (intraocular retinoblastoma) usually have a bigger chance of successful treatment and, thus, a more favourable prognosis than children whose disease is further progressed at diagnosis.

The overall prognosis of children with hereditary retinoblastoma is generally less favourable compared to the outcome of patients with the non-hereditary form, because, regardless of the treatment, hereditary retinoblastoma is associated with a higher risk of developing a second malignant tumour somewhere else in the body (for example a *soft tissue sarcoma* or an *osteosarcoma*). This risk increases if *radiation therapy* forms part of the treatment. About 5 % of children with hereditary, unilateral retinoblastoma develop the disease in the contralateral eye within one and a half years after diagnosis of the first tumour.

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Glossary

allele	The allele is the name given to the different expressions of a gene on the largely identical (homologous) chromosomes that are present in pairs. The two alleles of a gene are located in the same place (gene locus) of the homologous chromosomes; one comes from the father, one from the mother; a parent passes on only one of his or her two alleles to their offspring.
anaesthesia	a type of anaesthesia in which the patient sleeps and reflex activity is reduced (= general anaesthesia); it leads to a complete insensitivity to pain, temperature and touch stimuli. Due to the reduced reflex activity, the patient is required to be on a ventilator during surgery.
anamnesis	medical interview, a patient's history, development of signs of illness; the type, onset and course of the (current) symptoms as well as any risk factors (e.g. hereditary diseases) are evaluated during a medical interview.
autologous stem cell transplantation	(re)transfer of blood stem cells, e.g. after a chemotherapy or radiotherapy; the patient receives his own cells that were previously taken from their own bone marrow or blood. Autologous stem cell transplantation may be an option, for example, for certain patients with lymphoma, neuroblastoma, soft tissue sarcoma, or a brain tumour.
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.
brachytherapy	treatment of tumours with ionising radiation at short distances; usually a radiation carrier (iodine or ruthenium applicator) is surgically inserted into the tumour tissue to remain there until the desired radiation dose is reached. Since the radiation is only emitted in the direction of the tumour, adjacent, healthy tissue can be protected from radiation.
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



	<p>change or cancer predisposition syndrome. Cancer predisposition syndromes include Louis Bar syndrome (= ataxia telangiectatica), Beckwith-Wiedemann syndrome, Down syndrome, Hippel-Lindau syndrome, Li-Fraumeni syndrome, MEN syndrome, neurofibromatosis and WAGR syndrome. The familial form of retinoblastoma is also part of it.</p>
catheter	<p>tubular, rigid or flexible instrument for insertion into hollow organs, vessels or specific body cavities (e.g. bladder), e.g. for examination, drainage, sample collection, monitoring of vital parameters and/or administration of medication</p>
central nervous system	<p>comprises the brain and spinal cord and is separated from the so-called peripheral nervous system; as a central organ of integration, coordination and regulation, it serves to process external sensory impressions as well as stimuli produced by the organism itself.</p>
chemotherapy	<p>here: use of drugs (chemotherapeutic agents, cytostatics) for the specific inhibition of tumor cells in the organism</p>
chromosome	<p>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.</p>
cryotherapy	<p>here: treatment of a tumour using low temperatures; the tumor is frozen repetitively, and the cold-sensitive tumour cells will subsequently be destroyed.</p>
cytostatics	<p>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.</p>
DNA	<p>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.</p>
gene	<p>unit of genetic information in the genome of living organisms; a gene contains the genetic information – the blueprint – for a</p>



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
germ cells	mature cells capable of sexual fertilization (eggs in women, sperm cells in men)
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).
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
intravenous	means located within a vein or given into a vein; here: e.g. administration of a medication or fluid/suspension into the vein by an injection, infusion or transfusion.
laser therapy	melting of tissue by the heat effect of the laser beam; is used in the removal of tissue parts and in the obliteration of vessels.
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.
lymphatic system	collective term for lymphatic vessels, lymphatic vessel trunks, lymph nodes, lymphatic tissues (lymphocytes in connective tissue, mucous membranes, glands) and lymphatic organs (spleen, pharyngeal tonsils, bone marrow, thymus gland).
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



	<p>of the body are generated, which usually allow a very good assessment of the organs and many organ changes.</p>
molecular genetics	<p>a branch of genetics and biology that investigates the inheritance, structure, metabolism, differentiation and interactions of cells at the molecular level; the focus is on the analysis of the genetic information of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and their processing in the context of protein synthesis as well as gene regulation.</p>
mutation	<p>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.</p>
nystagmus	<p>involuntary, rhythmic eye movements; "eye tremors"</p>
optic nerve	<p>first section of the visual pathway that starts from the retina in the eye and leads to the visual center of the cerebral cortex; the optic nerve consists of the processes (axons) of the nerve cells of the retina and thus contains a total of about one million nerve fibers. The optic nerve, which has an average length of 4.5 cm, can be divided into three parts: one in the eyeball, one in the eye socket (orbit) and one part in the skull.</p>
osteosarcoma	<p>the most common bone tumour in childhood and adolescence; occurs mainly in the second decade of life during the pubertal growth phase</p>
paediatric oncologist	<p>paediatrician who is specialized on the management of children and adolescents with cancer</p>
physical examination	<p>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.</p>
prognosis	<p>prediction of the course and outcome of a disease / prospect of recovery</p>



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
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.
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.
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.
thermotherapy	here: targeted overheating of a tumour using laser beams with the aim of destroying the tumour cells and/or enhancing the effect of concomitant chemotherapy/radiation
ultrasound	an imaging technique used to examine organs, in which ultrasound waves are sent through the skin into the body; at tissue and organ boundaries, the sound waves are reflected



back, picked up by a receiver (transducer) and converted into corresponding images with the help of a computer.

vein

blood vessel that carries the blood circulating in the body to the lungs and heart. the veins of the bodys circulation carry oxygen-depleted blood from the organs to the lungs and heart; the veins of the pulmonary circulation transports oxygen-rich blood from the lungs to the heart.

X-ray examination

imaging procedure that uses X-rays to visualize organs or parts of organs