Neuroblastoma – Brief information

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1. General information on the disease

Neuroblastomas are malignant *solid tumour*s. They arise from degenerate immature cells of the *sympathetic nervous system*, which is part of the *autonomic nervous system*.

Neuroblastomas can occur at any site of sympathetic nervous tissue. They most frequently develop in the medulla of the adrenal gland (*adrenal medulla*, about 50 %) and within the nervous plexus on both sides of the spinal column, the so-called *sympathetic trunk*. If the sympathetic trunc is affected, neuroblastoma can occur at any spinal level, such as in the abdominal, pelvic, chest or neck region. In most cases (for about 75 %), the tumour can be found in the abdomen, about one fifth of tumours in the chest or neck region.

Some neuroblastomas are limited to their original site, others spread into close *lymph nodes*. At initial diagnosis, about half of the patients present with tumour spread (metastases) to the *bone marrow*, bones, distant lymph nodes or liver, less frequently with *brain*, lung or skin metastases. A typical feature of biologically favourable neuroblastomas is their ability to spontaneously regress (*see chapter „Courses of disease“*).

2. Incidence

Neuroblastoma accounts for approximately 5.3 % of all malignant diseases in childhood and adolescence, thereby representing one of the most frequent solid tumour type in this age group following tumours of the *central nervous system* (*CNS tumour*s, brain tumours). According to the German Childhood Cancer Registry (Mainz), about 120 children and adolescents under 18 years of age are newly diagnosed with a Neuroblastoma each year. Hence, 11 out of 1,000,000 children and adolescents between 0 and 17 years are diagnosed with this disease.

Since Neuroblastoma are *embryonal* tumours, they are most frequent in early childhood: 90 % of all affected patients are younger than 6 years old; about 46 % are newborns and babies in their first year of live. The average age of the patients at diagnosis is 15 months, with boys being (by 40 %) more affected than girls (gender ratio: 1.3:1). Nevertheless, older children, adolescents and, seldomly, adults may also be affected.

3. Causes

The underlying causes for the development of neuroblastoma are still not completely understood. It is known that the disease is initiated by a malignant transformation (degenerate) of immature cells of the *sympathetic nervous system*. The impaired development of not yet completely matured (embryonal) *nerve cells* most certainly starts before birth and can be a consequence of *chromosomal* aberrations and/or *genetic* changes (mutations).

Various genetic changes have been identified in neuroblastoma cells so far. However, these are very heterogenous, meaning that there is no specific genetic transformation that can be consistently observed in every tumour. Overall, a series of genetic and also *epigenetic* modifications may be responsible for the development of neuroblastoma. Hereditary transmission of the disease has, for most patients, not been proven yet.

However, families with increased incidences of neuroblastoma and related tumours over multiple generations have been described. About 1–2 % of patients have such a family history, and they often present with more than one *primary tumour*. Neuroblastoma can also be associated with so-called *cancer predisposition syndrome*s, congenital diseases characterized by *mutation*s that (compared to healthy individuals) are connected with a higher risk of developing a malignancy at a younger age. Cancer predisposition syndromes playing a role in the development of neuroblastoma are, for example, *Hirschsprung`s disease* or the *Undine syndrome*.

In most patients, however, the disease arises as a result of spontaneous mutations or other *genomic* changes in the cells' *DNA*. Whether external factors (such as environmental factors, parental exposure to stress factors at work, certain drugs, nicotin or alcohol abuse during pregnancy) play a role as well has not been elucidated yet.

4. Symptoms

Many patients with neuroblastoma do not complain about any health problems (*symptom*s). They are rather randomly diagnosed with the tumour, for example during a routine check-up or an *ultrasound* or *x-ray examination* that is being done for a different reason. Symptoms usually occur at advanced stages of tumour growth, when the tumour has spread (metastasis) or impairs adjacent tissue.

In addition, symptoms can vary dependent on the site of the tumour or the metastases [see *metastasis*]. Palpable tumours or metastases may be first symptoms, some children present with an abdominal or cervical swelling. Tumours of the abdomen or the adrenal gland can be associated with rather unspecific symptoms such as abdominal pain, constipation, bloating or diarrhea; compression of the ureter may lead to urine retention. Tumours in the chest can compress the lungs, thereby causing cough, pneumonia or shortness of breath. Neuroblastomas that are close to the spinal column (tumours of the *sympathetic trunk*) can grow into the spinal canal and subsequently result in *neurological* symptoms such as pain, impaired micturition or bowel incontinence.

High blood pressure (hypertension) as well as persistent diarrhea are, in rare cases, caused by the hormonal activity of the tumour. Tumours in the neck or upper chest region can result in the so-called *Horner`s syndrome*. This is defined by by one eye presenting with a very small pupil, a drooping eyelid and with the eyeball displaced backwards (also known as unilateral miosis, ptosis and enophthalmus). Further changes of the eyes may include small bruises of the eyelid (*eyelid ecchymosis*) as well as, in cases of advanced disease, bruises around one or both eyes (so-called monocular haematoma). A rare variant of the disease is neuroblastoma with a so-called *opsoclonus-myoclonus-ataxia syndrome* (OMAS).

Bone metastases – which particularly occur in the long bones of arms and legs as well as in the skull and the bones around the eyes – can result in bone pain. Some patients with bone pain present with a limp. In case of severe *bone marrow* involvement, patients may present with low red blood cell counts (*anaemia*) low platelet counts (*thrombocytopenia*) and low white blood cell counts (*leukopenia*) and, subsequently, an increased risk of infection and bleeding.

General symptoms that are suspicious of, mostly advanced stage of, neuro-blastoma are:

- fatigue, listlessness, decreased performance levels, frailty, pallor
- persistent fever with unknown cause, sweats
- tumours or swelling in the abdominal or neck region; lymph node swellings
- distended abdomen
- constipation or diarrhea, abdominal colics
- loss of appetite, nausea, vomiting and subsequent weight loss
- bone pain
- bruises around the eyes

Good to know: the occurrence of one or more of these symptoms does not necessarily mean that a person has neuroblastoma. Many of these symptoms can have rather harmless causes. Nevertheless, any of these complaints should be reported to a doctor in order to find out what causes them.

5. Diagnosis

If the doctor thinks that the young patient's medical history (*anamnesis*) and *physical examination* are suspicious of a neuroblastoma, he will refer the child immediately to a hospital with a childhood cancer program (paediatric oncology clinic), where further diagnostics can be initiated and performed by childhood cancer experts. Close collaboration between various specialists (such as paediatric oncologists, paediatric neurosurgeons, paediatric radiologists, to name a few) is required, both to find out whether the patient indeed suffers from a neuroblastoma and, if so, to determine the tumour type and the extent of the disease. Knowing these details is absolutely essential for optimal treatment planning and *prognosis*.

5.1. Laboratory tests

Aside from comprehensive medical history taking and physical exam, laboratory tests play a major role in confirming the diagnosis. Most patients with neuroblastoma present with elevated levels of certain bodily substances in the blood or urine, which are used as "*tumour marker*s" to confirm the diagnosis (and, in particular, to monitor the treatment efficacy during the course of the disease).

Relevant tumour markers for neuroblastoma are certain *catecholamines* or their metabolites, respectively (vanillinic acid, homovanillinic acid), as well as the *neuron-specific enolase* (NSE).

5.2. Diagnostic imaging

Additional tests to establish the diagnosis and to rule out other diseases (such as *Wilms tumour*, *phaeochromocytoma*) include diagnostic *imaging*: *ultrasound* is usually sufficient to determine both site and size of most abdominal or cervical neuroblastomas. *X-rays* help to check on chest and lungs.

In order to identify very small tumours and their impact on adjacent structures, *magnetic resonance imaging* (MRI) with and without *contrast agent* is used. Sometimes, *computed tomography* (CT) is applied instead. In general, however, MRI is the preferred imaging technique, since it does not involve *ionising radiation* but magnetic fields, thereby not causing radiation exposure.

5.3. Tests to assess tumour spread

To assess or, respectively, rule out metastases [see *metastasis*] and also to determine additional features of the *primary tumour*, total body scintigraphy is performed using the low *radioactive* agent ^{123}-Iodo-metaiodobenzylguanidine (short ^{123}I-*MIBG scintigraphy* or MIBG scan). This substance accumulates in catecholamine-producing tissues and thus in almost all neuroblastomas (with the exception of so-called MIBG-negative neuroblastomas). If the MIBG scan is negative, i.e. shows no abnormalities (as MIBG has not been taken up), other scintigraphic techniques can serve as alternatives, such as a *positron emission tomography* (PET) with radioactively labelled glucose (18F-fluoride-deoxyglucose, short FDG). Both techniques are combined with CT or MRI, respectively.

Since scintigraphy is not sufficient to identify very mild bone marrow involvement, obtaining a *bone marrow* sample is required for all patients. Bone marrow is obtained via *bone marrow puncture* or *bone marrow punch biopsy* from at least two different sites, while the patient is sedated or under short anaesthesia, and subsequently analysed under the *microscope* using techniques that are specific for looking at cancer cells. Patients with metastases also undergo an MRI of the brain to rule out central nervous system involvement. A total body MRI may be indicated for patients with advanced disease in order to identify potential bone metastases.

5.4. Obtaining a tumour sample (biopsy)

In general, final diagnosis can be established only by microscopic (histological) analysis of tumour tissue. A tumour sample is usually obtained by *surgery*. Molecular genetic analyses [see *molecular genetics*] allow conclusions regarding the grade of the tumour's malignancy. In fact, certain genetic changes (mutations) in the tumour *DNA* (such as the so-called *MYCN amplification* or *1p deletion*) as well as the existence of certain genetic variants (experts call it unfavourable genetic signature) correlate with unfavourable *prognosis*, while lack of these changes or other *mutation*s can be associated with a favorable outcome.

Additional genetic changes were identified in neuroblastoma cells a few years ago (for example changes of the *ALK gene* or the so-called telomerase activation), which can be used therapeutically in case of relapse as long as they were identified in the initial tumour. ALK alterations can also be used therapeutically in case of relapse, provided they have been detected in the patient's initial tumour.

5.5. Tests before treatment begins

Depending on the type of treatment being considered, further tests are needed in order to assess the condition of different organs. These include, especially prior to chemotherapy, an examination of the heart (*electrocardiography*, *echocardiography*), a hearing test (for example, *audiometry*m *BERA hearing test* and/or *otoacoustic emissions*), special diagnostics for determining kidney function (kidney ultrasound, kidney nuclear medicine scan) as well as an *x-ray examination* of the hand to determine the child's bone age. In order to recognize certain treatment-related adverse reactions and subsequently manage them appropriately and as early as possible, many of these tests are regularly being repeated during the course of treatment and their results compared to those obtained by the initial tests.

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.

6. Treatment planning

After the diagnosis has been confirmed, therapy is planned. In order to design an individual, risk-adapted treatment regimen for the patient, certain 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).

The stage of the disease at the time of diagnosis is of major importance and, thus, a very significant prognostic factor. Aspects like the tumour's extent and the extent of its surgical removal are included in the staging of a neuroblastoma (*see table below*). Additional relevant prognostic factors include the patient's age as well as the *histological* and, particularly, the *molecular genetic* characteristics of the tumour, which reveal information on its growth and spread pattern (*see chapter "Diagnosis"*). All these factors are included in treatment planning in order to achieve the best outcome possible for each patient.

More information on the stages of neuroblastoma can be found in the following paragraphs.

6.1. Stages of neuroblastoma

The extent of the tumour within the body has usually a great impact on the chance of cure and is, therefore, an important criterion for choosing the feasible treatment strategy. The classification of neuroblastoma according to the stages of the disease considers the tumour size, lymph node involvement and existence of metastases [see *metastasis*]. Additional criteria that play a role in staging depend on the applied classification system. Two classification systems are currently in use: the INSS and the INRG classification.

- **INSS Classification:** following the traditional, international staging system, which has been used in Germany for a long time (International Neuroblastoma Staging System, INSS), the extent of surgery has been added to the factors mentioned above; hence, the exact assessment of the stage was only possible after surgery.

- **INRG Classification:** while the INSS classification is still being applied, the *International Neuroblastoma Risk Group Staging System* (INRG) is now the internationally valid classification system. The INGR system evaluates the stage of the disease prior to surgery based on established risk factors, which have been identified by diagnostic imaging (MRI or CT). Such a risk factor (called *Image Defined Risk Factor*, short: IDRF) is, for example, a walling-in of large blood vessels by the tumour. Aside from the surgical options, the patient's age, and the molecular characteristics of the tumour, the histology of neuroblastoma is also included in the staging.

Both classification systems are presented by the following tables. The INSS-classification differentiates between the localized stages 1-3, the metastatic stage 4 and the metastatic infant neuroblastoma stage 4S. The INGR staging differentiates the localized stages L1 and L2 under consideration of certain risk factors as well as the advanced (metastatic) stages M and (*see table below*).

Stages of Neuroblastoma according to the INSS and INRG Staging System, respectively

Tumour stages according to INSS	Description	Tumour stages according to INRG	Description
1	Localized, completely resected tumour	L1	Localized tumour not involving vital structures (as defined by the list of IDRFs) and confined to one body compartment
2a	Localized, incompletely resected tumour Involvement of only one side of the spinal column No lymph node involvement in the tumour region		
2b	Localized, completely or incompletely resected tumour	L2	Localized tumour with presence of one or more IDRFs

Tumour stages according to INSS	Description	Tumour stages according to INRG	Description
	Involvement of only one side of the spinal column Involvement of adjacent lymph nodes at the same side		
3	Incompletely resected tumour with extension to the other side of the spinal column or Involvement of lymph nodes on the contralateral side		
4	Distant metastases (for example in bone marrow, bone, liver, skin, distant lymph nodes and other organs)	M	Distant metastatic disease (except stage MS tumour)
4S	Only occurring in infants (0-18 months according to current criteria); metastases only in skin, liver and/or, minimally, in the bone marrow	MS	Metastatic disease in children younger than 18 months, with metastases confined to skin, liver, and/or bone marrow

With the exception of patients with stage 4S or MS, respectively, patients with less advanced disease usually have a more favorable prognosis than patients with advanced stages (such as stages 3 and 4). Patients with less favorable stages usually require a more intensive therapy than patients with more favourable prognosis (*see chapter "Course of treatment"*).

7. Courses of the disease

The courses of a neuroblastoma disease vary individually, particularly depending on the growth pattern of the tumour and its stage at initial diagnosis. Hence, neuroblastoma can be localized at diagnosis but also can have infiltrated other tissue and lymph nodes, either close or distant (*see paragraph "Stages of neuroblastoma" above*). A special feature of the biologically and clinically more favourable neuroblastomas is the fact that they can spontaneously turn into benign tumours (so-called *differentiation*) or spontaneously recede (spontaneous regression).

7.1. Tumour growth and spread

Particularly in children older than 18 months, neuroblastomas frequently grow fast and uncontrolled and spread within the whole body mostly via the bloodstream, but sometimes also via the *lymphatic system*. Metastases preferably develop in the *bone marrow* (in 90 % of the patients), bone (60 %),

distant *lymph nodes* (20 %) and liver (17 %), less frequently in the *brain* (9 %), skin (2 %) and lungs (1 %). These cases are considered as stage 4 or M, respectively.

7.2. Tumour maturation (differentiation)

Neuroblastomas with a favourable biological profile may undergo tumour maturation (known as *differentiation*), either spontaneously or as a result of a mild *chemotherapy*. In this case, the tumours do not disappear during observation and may require further surgery later on. However, the prognosis for these patients remains very favourable. Even high-risk neuroblastomas with unfavourable biology can some-times mature under chemotherapy. However, these patients have a high risk of *recurrence*, so the planned intensive high-risk therapy must still be completed.

In addition, there are patients who, at the time of diagnosis, already have a fully matured neuroblastical tumour, known as a ganglioneuroma. These patients are generally older. Since ganglioneuromas do not respond to chemotherapy, they must always be removed surgically. The risk of recurrence is minimal, even following incomplete tumour removal.

7.3. Tumour regression (spontaneous regression)

A high number of neuroblastomas regress spontaneously (tumour regression). The tumour cells die by a form of self-initiated cell death, a process that scientists call *apoptosis*. The spontaneous tumour regression is particularly and almost regularly observed in neuroblastomas that are diagnosed in infancy or early childhood. This can affect localised tumours and even metastatic neuroblastomas.

A special case is stage 4S or MS in young patients. In these patients, in addition to the tumour itself, the liver is often enlarged due to extensive *metastasis*. These initially diagnosed metastases may still rapidly grow in the beginning, thereby pushing on abdominal organs and lungs and reaching a life-threatening extent, so that mild chemotherapy is required. Subsequently, however, they may regress.

However, spontaneous tumour regression does not only occur in stage 4S (MS) in infants, but are also observed in older children with localized neuroblastoma stage 1 to 3 or L1 to L2, respectively.

Information on the different stages of the disease can be found in the paragraph “Treatment planning” (*see above*).

8. Treatment

Treatment of children and adolescents with neuroblastoma should take place in a children's hospital with a paediatric oncology program. Only such a childhood cancer centre provides highly experienced and qualified staff (doctors, nurses, psychosocial support service), 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 treatment** is to eliminate the cancer while keeping the risk of side effects and late sequelae as low as possible.

8.1. Treatment methods

Therapy of a neuroblastoma patient is based on the individual situation of the disease and the probability of relapse. For some patients, surgery to remove the tumour or to obtain a tumour sample can be sufficient, while others require the combination of multiple treatment methods in order to improve the chances of cure.

The treatment methods described in the following paragraphs represent the current standard of treatment in Germany. New treatment concepts are continuously being evaluated in the framework of clinical studies, so the treatment may sometimes differ from this standard in single patients.

Treatment of neuroblastoma includes **surgery**, **chemotherapy** and **radiotherapy**. In addition, patients with a high risk of relapse usually undergo **high-dose chemotherapy with subsequent autologous stem cell transplantation** as well as **immunotherapy with antibodies**. Further treatment methods, such as the **MIBG-therapy**, a treatment with radioactively labelled metaiodobenzylguanidine, may be indicated in these patients as well.

The goal of *surgery* is to remove the tumour and/or to gain a tissue sample. Chemotherapy uses drugs (so-called *cytostatics*) that can kill fast-dividing cells, such as cancer cells, or inhibit their growth, respectively. Since one cytostatic agent alone may not be capable of destroying all tumour cells, a combination of cytostatics that function in different ways is given (polychemotherapy). The goal is to eliminate as many malignant cells as possible. A *high-dose chemotherapy* is even more intense: it is capable of eliminating resistant neuroblastoma cells. Since the high doses of cytostatics given according to this treatment strategy also lead to the destruction of the blood-forming cells in the bone marrow, the patient will receive *blood stem cells* in a second step. These stem cells are obtained from the patient's blood or bone marrow prior to high-dose chemotherapy and are given back right after this treatment (so-called autologous stem cell transplantation, SCT). Radiotherapy (*radiation therapy*), which is required in high-risk patients, 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.

The individual treatment choice is based on the tumour`s extent at diagnosis and after surgery as well as on is growth characteristics (tumour biology) and the patient's age. Taken together, the more advanced the tumour stage and the higher the risk of an aggressive tumour growth or a relapse after the end of treatment, the more intensive therapy will be.

Since treatment of neuroblastoma can be associated with side effects, supportive treatment measures (*supportive therapy*) are also applied to prevent and/or treat these side effects. Here you will find further 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

At the beginning of treatment, every patient is being assigned to a certain risk or treatment group. The current treatment guidelines consider three different groups of therapy: low-risk group, intermediate-risk group and high-risk group. Each of these treatment groups is associated with a different treatment plan. This strategy allows a risk-adapted therapy that is individually adjusted to the patient.

8.2.1. Treatment within the low-risk group (watch-and-wait group)

The low-risk group (watch-and-wait group) includes patients, who, due to localized tumour growth and/or their age, are not put at risk by the watch-and-wait approach of this treatment strategy. The proof of lack of unfavourable *molecular genetic* tumour characteristics (such as the *MYCN amplification* or, in part, also the 1p *deletion*) is crucial for the assignment of a patient to this watch-and-wait group. Hence, the watch-and-weight group includes patients with one of the following disease features:

- Stage 1 (INSS), age 0-21 years, no MYCN amplification
- Stage 2 (INSS), age 0-21 years, neither MYCN amplification nor 1p deletion
- Stage 3 (INSS), age 0-2 years, neither MYCN amplification nor 1p deletion
- Stage 4S (INSS), age-range is limited, but according to INRG stage MS extended to 0-18 months, neither MYCN amplification nor 1p deletion

Course of treatment: Treatment for patients with low-risk neuroblastoma is usually limited to surgical tumour removal, provided this can be done safely. Otherwise, given the high rate of spontaneous tumour regression, even an incomplete operation or a tissue sample (*biopsy*) is sufficient.

If the patient is in good clinical condition, no chemotherapy or radiotherapy is given. However, the patient is monitored closely (by regular physical exams, *ultrasound*, *magnetic resonance imaging* and *tumour marker*s). In the first year, patients undergo follow-up at least every six weeks, from the second to fifth year at least every three months, and after that at least every six to twelve months. The type of follow-up exam varies based on whether the patient has residual tumour and if the tumour is sufficiently assessable by ultrasound.

If the residual tumour starts to grow again during the watch-and-wait period, or if it progresses and/or starts causing symptoms that require treatment (such as reduced clinical status, nutrition problems, weight loss, hypertension, urine transport problems), usually a low-dose *chemotherapy* is indicated in order to initiate tumour regression. Treatment consists of up to four cycles of combination chemotherapy with doxorubicin, vincristine and cyclophosphamide. Alternatively, carboplatin and etoposide may be given as well.

Chemotherapy will be ended as soon as the tumour stops growing. If the tumour does not show a clear reduction in size as the condition progresses, further surgery may be required to remove

the tumour or to reduce symptoms. The latter applies in particular to patients with stage 4S, whose tumour has the potential to significantly grow before it regresses.

8.2.2. Treatment within the intermediate risk group

The intermediate risk group includes patients with a more advanced stage of the disease and/or older patients as well as patients with certain unfavourable *molecular genetic* characteristics (1p deletion). A *MYCN amplification* needs to be ruled out. Patients with the following disease constellations are assigned to the intermediate risk group:

- Stage 2 (INSS), age 0-21 years, with deletion in chromosome 1p, but no MYCN amplification
- Stage 3 (INSS), age 0-21 years, with deletion in chromosome 1p, but no MYCN amplification
- Stage 3 (INSS), age 2-21 years, neither MYCN amplification nor 1p deletion
- Stage 4 (INSS), age-range is limited, but according to INRG stage MS extended to 0-18 months, no MYCN amplification

Course of treatmment: treatment consists of *surgery* or, if not feasible, a *biopsy* first. After that, *chemotherapy* is given. It consists of six blocks of intensive chemotherapy (induction chemotherapy) and four blocks of a, slightly lower-dose, maintenance chemotherapy. In case only a biopsy could be performed prior to chemotherapy, surgical tumour removal is being strived for after the first cycles of induction chemotherapy because, frequently, the tumour shrinks during chemotherapy.

For induction treatment, the standard combination chemotherapy regimen contains doxorubicin, vincristine and cyclophosphamide or carboplatin, etoposide and vindesine, respectively, which are administered alternately and as *intravenous infusion*s over hours or days. Maintenance therapy consists of cyclophosphamide, which is mostly given as pills or as a solution.

If active tumour tissue is still found after the intensive chemotherapy, children older than 18 months will receive *radiation therapy* (with a radiation dose of 36 to 40 *gray*) of the residual tumour during maintenance chemotherapy. An initially residual tumour (for example in cases with initial biopsy only) may sometimes shrink so much during chemotherapy that complete surgical removal during or after this treatment phase becomes feasible. Total duration of treatment is about one year.

8.2.3. Treatment within the high-risk group

Patients with stages 1, 2, 3 or 4S whose tumour harbours a *MYCN amplification*, as well as all patients with stage 4 who are older than 18 months are assigned to the high-risk group. The treatment regimen for patients with high risk neuroblastoma is quite extensive.

Course of treatment: following *surgery* or *biopsy*, patients receive *chemotherapy* with multiple agents for about five months (so-called induction chemotherapy). The current standard induction regimen consists of six blocks of chemotherapy with alternating combinations of cisplatin, etoposide and vindesine or vincristine, dacarbacine, ifosfamide and doxorubicin, respectively. In between or after those cycles, a second-look surgery is usually performed, preferably with complete tumour removal. After that, patients undergo *high-dose chemotherapy* followed by *autologous stem cell transplantation* (duration: about six weeks). For patients with *MIBG*-positive residual

tumour, additional treatment with radioactively-labelled ^{123}-Iodo-metaiodobenzylguanidine, (^{123}I-*MIBG therapy*) is a feasible option. In these cases, the ^{123}I -MIBG therapy is given prior to the high-dose chemotherapy.

Following high-dose treatment, *radiation* of the tumour bed with a dose of 21 *gray* (Gy) and an *immunotherapy* with the *antibody* dinutuximab beta is given. The aim of this treatment phase (also known as maintenance or post-consolidation therapy) is to eliminate potentially residual tumour cells. In case of an active residual tumour, a total radiation dose of up to 36 Gy is recommended. The total duration of therapy can last up to two years.

Note on trial HR-NBL2 for patients with high-risk neuroblastoma: As part of the study for high-risk patients, which has been open since 2023, patients are receiving a different induction chemotherapy regimen to the standard one (COJEC). For high-dose chemotherapy and radiotherapy, two different treatment regimens are being compared in each of the two treatment arms. Patients are randomised to the treatment arms if the respective treatment is eligible [see *randomisation*].

9. Trials and registries

In Germany, the majority of the children and adolescents with neuroblastoma receive therapy according to the treatment plans of clinical trials or registries. The aim of clinical trials is to gradually improve treatments under strictly controlled conditions, so that the risks to participants are kept to a minimum.

Regardless of whether patients take part in a clinical trial or not, they are all recorded in a so-called **registry**. Such a registry serves primarily to accompany the patients‘ therapy scientifically. 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 trial.

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

- **Trial HR-NBL2** (high-risk neuroblastoma trial 2.0): international, multicentre, randomisid therapy trial (phase III studies) for patients with high-risk neuroblastoma; the SI-OP Europe Neuroblastoma (SIOPEN) study has been open for patient recruit-ment in Germany since 2023. The German headquarters are located at the Department of Paediatric Oncology and Haematology at the Charité in Berlin (principal investigator: Prof. Dr. med. Hedwig E. Deubzer). The study analyses different treatment concepts of induction *chemotherapy* as well as *high-dose chemotherapy* and *radiotherapy* with the aim of further improving the prognosis of patients. Numerous paediatric oncology centres throughout Germany as well as in other European and non-European countries participate in this trial.

- **NB Registry 2016:** Registry for newborns, infants, children and adolescents (as well as adults with a newly diagnosed or recurrent neuroblastic tumour (neuroblastoma, gan-

glioneuroblastoma, ganglioneuroma); the registry was opened in 2017 after the end of therapy trials NB2004 und NB 2004-HR. Its major aim is to gather knowledge about the incidence, disease courses and long-term sequelae, thereby improving prognosis. Decision-making on the treatment regimen is done by the attending physician with the support of the therapy recommenda-tions from the study centre. Registering for the registry does not exclude future recruitment for a clinical study. The registry centre is located at the University Children's Hospital in Cologne with Prof. Dr. med. Thorsten Simon as acting head.

Note on trials for patients with relapse: For patients with relapsed or refractory high-risk neuroblastoma, several phase I/II studies do exist, on which further, up-to-date information can be obtained by contacting the *study headquarters in Berlin, Cologne and Greifswald*).

10. Prognosis

Appraising the probability of cure from neuroblastoma remains a challenge. Both the extent of the disease and the aggressiveness of the tumour play a role. Children with stage 4S neuroblastoma as well as most patients with localized disease (stages 1 and 2) have a very good *prognosis* with 10-year survival rates of partially more than 90 %. Also, younger children (under 18 months) with stage 3 tumours have a favourable prognosis, as long as they don't present with unfavourable molecular tumour features. For older children with metastatic neuroblastoma (stage 4), cure rates are, with only 50 % or less, still unfavourable, despite the intensive therapy regimen.

Note: The above-mentioned numbers are statistical values. Therefore, they only provide information on the total cohort of patients with this type of tumour. They do not predict individual outcomes. Please ask the doctor, who is responsible for your child, for competent information on her individual prognosis.

Further information

The information provided in this chapter are primarily based on the references cited below, are considering the current guidelines and treatment protocols for children and adolescents with neuroblastoma and have been created in collaboration with the study centre for neuroblastoma. Please contact your attending physician in case of further questions.

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Glossary

adrenal medulla	tissue of the adrenal gland, which is made of various nerve cells, especially cells of the sympathetic (autonomic) nervous system
ALK gene	gene that codes for the anaplastic lymphoma kinase (ALK), a protein in the group of tyrosine kinases; the protein is mainly produced during embryonic development until shortly after birth and is thought to play an important role in the development and function of the nervous system. Through various mechanisms, the ALK gene can become an oncogene that promotes the development of malignant tumours.
anaemia	„lack of blood“; reduction of the red blood pigment (haemoglobin) and/or the proportion of red blood cells (haematocrit) in the blood below the normal value typical for a given age. Signs of anaemia include palor, headache, dizziness, and fatigue.
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.
antibody	Antibodies are proteins from the group of globulins, which the bodys immune system forms as a defensive reaction to invading foreign substances or foreign structures (antigens). The antibodies bind specifically to these antigens and lead (in various ways) to the elimination of the pathogen. Antibodies are produced by a group of white blood cells, so-called B lymphocytes, which are known as "plasma cells" at the stage of antibody production.
apoptosis	programmed cell death; form of cell death, which is triggered by various mechanisms in the cell itself; this can happen naturally in the context of cellular aging, but also, for example, in response to cell damage (e.g. caused by cytostatics, radiotherapy).
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.
autonomic nervous system	part of the nervous system, consisting of two parts, the sympathetic nervous system and the parasympathicus; it is used for the unconscious and involuntary (i.e. largely independent of the will) control of the internal organs and thus numerous vital processes, e.g. breathing, digestion, blood pressure regulation, and fluid balance. Nerve fibers of the autonomic nervous system are found in almost all organs of the body.
BERA hearing test	ENT examination to determine hearing damage; it essentially measures the electrical activity of the auditory nerve and the auditory pathways to the brain stem and does not require the patients assistance (objective hearing test). In the BERA test, certain auditory stimuli (sounds) are emitted via headphones: with the help of an electroencephalogram (EEG), the reaction (in the form of brain waves, so-called acoustically evoked potentials) is measured. This is the brainstems response to the acoustic stimulus. The measurement of these brain waves makes it possible to detect hearing disorders or abnormalities in the cranial nerve or brainstem.
biopsy	removal of a tissue sample for subsequent (mainly microscopic) examination; this can be done, for example, by puncture with a hollow needle, with the use of special instruments (such as forceps, punching instruments, probes) or surgically with a scalpel.
blood stem cells	precursor cells of all blood cells, which give rise to red blood cells (erythrocytes), white blood cells (leukocytes), platelets (thrombocytes) and some other cells. This process is called blood formation. The various blood cells are formed in the bone marrow before they enter the blood stream.
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.
brain	the part of the central nervous system (CNS) located in the head; the brain is protected by the skull and the meninges and consists mainly of nerve tissue.
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.
catecholamines	collective term for the bodys own substances dopamine, adrenaline and norepinephrine, which are messenger substances (hormones) of the sympathetic nervous system and have a stimulating effect on the cardiovascular system (they lead to an increase in heart rate and blood pressure); catecholamines are formed in the adrenal glands and nervous system. There are also artificially produced catecholamines that are used as medicines.
central nervous system	comprises the brain and spinal cord and is separated from the so-called peripheral nervous system; as a central organ of integration, coordination and regulation, it serves to process external sensory impressions as well as stimuli produced by the organism itself.

chemotherapy	here: use of drugs (chemotherapeutic agents, cytostatics) for the specific inhibition of tumor cells in the organism
chromosomal	referring to the chromosomes, carriers of the genetic material (see chromosomes)
CNS tumour	tumour of the central nervous system; a primary CNS tumour is a solid tumour that originates from brain or spinal cord tissue. Secondary CNS tumours are metastases of tumours located in other organs or tissues.
computed tomography	imaging, X-ray diagnostic procedure; it produces an image by computer-controlled evaluation of a large number of X-rays from different directions. This makes it possible to produce sliced images of body parts (tomograms, transverse or longitudinal sections of the human body)
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.
deletion	gene or chromosome aberration in which genetic material is lost; single nucleic bases (point mutation), larger base sequences, or even entire chromosomes may be affected (deleted).
differentiation	here: development of immature cells / immature tissue into mature tissue with specialised tasks; differentiation is based on a hereditary blueprint.
DNA	abbreviation for deoxyribonucleic acid; it carries the genetic information and is found in all living beings. DNA contains the genes that provide the information for the production of ribonucleic acids (RNA) or proteins. It is a large molecule consisting of two nucleic acid chains twisted into a double helix. The individual chains consist of a sequence of four different building blocks (bases), the order (sequence) of which determines the genetic code.
echocardiography	ultrasound examination of the heart to check its performance (cardiac function); the position or structure of the heart valves and walls, the wall thickness of the heart muscle, the size of the heart

	and the ejected blood volume (pumping function of the heart) are examined and assessed, among other things.
electrocardiography	method of measuring the electrical activity of the heart
electromagnetic	electromagnetic rays (also known as electromagnetic waves) consist of coupled electric and magnetic fields; examples of electromagnetic radiation are X-rays and gamma rays as well as radio waves, thermal radiation and light.
embryonal	here: in an early stage of development, immature;
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.
eyelid ecchymosis	extensive bleeding in the area of the eyelids
genetic	concerning the (level of) inheritance or genes; inherited
genomic	concerning the entire genetic material (genome) of a living being; the largest part of the genome is located on the chromosomes, a small part outside the cell nucleus in the so-called mitochondria.
gray	unit of measurement for the dose of energy caused by ionising radiation (e.g. in the context of radiotherapy) and absorbed by a given mass (kilogram of body weight)
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).
Hirschsprung`s disease	congenital disease of the large intestine in which nerve cells are missing in part of the colon; the malformation can lead to impaired bowel movements such as severe constipation as well as enlargement of the large intestine (megacolon), bloating

	(meteorism), vomiting and intestinal obstruction. Inflammatory complications are also possible.
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).
Horner`s syndrome	combination of signs of a disease in one eye based on eye muscle paralysis of various causes; signs of illness include, for example, the recession of the eyeball into the eye socket (enophthalmus), a narrowing of the pupil (miosis) and drooping of the upper eyelid (ptosis).
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
immunotherapy	a form of treatment that affects the immune system with the aim of fighting off or fighting tumours or other diseases
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.
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.
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).
leukopenia	decreased white blood cells (leukocytes) in the blood to levels below the age-appropriate norm;
lymph nodes	small lenticular to bean-shaped organs that are part of the bodys immune system and are located in many parts of the body; they serve as filter stations for the tissue water (lymph) of a region of the body and contain cells of the immune system.
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 of the body are generated, which usually allow a very good assessment of the organs and many organ changes.
metastasis	1. tumour spread from the primary site of tumour to other parts of the body; characteristic feature of malignant tumours (cancer). 2. collective term for a disease process characterized by malignant cells spreading from their primary site to other areas of the body via the bloodstream and/or the lymphatic system.
MIBG	a weakly radiolabeled substance that resembles a neurotransmitter of the sympathetic nervous system, the stress hormone norepinephrine (a catecholamine), in its chemical structure.
MIBG scintigraphy	imaging nuclear medicine technique applied specifically for the diagnosis of sympathetic nervous system tumours by using radiolabeled methyliodine benzylguanidine (123I-MIBG). In children and adolescents, these include, for example, neuroblastoma and phaeochromocytoma as well as their metastases. MIBG is a substance that has similar chemical structure to the bodys own catecholamines (specifically the hormone norepinephrine, a messenger substance of the sympathetic nervous system). It typically accumulates in tumours that can produce catecholamines. Since weakly radioactive iodine is coupled to the MIBG, the tumour cells enriched with this substance emit signals that can be recorded by a special camera and processed into an image.
MIBG therapy	treatment with radiolabeled methyliodine benzylguanidine (MIBG; 123-I-MIBG), a substance that accumulates primarily in catecholamine-producing tumours of the sympathetic nervous system (e.g. neuroblastoma). The radioactive dose is chosen so high for treatment purposes that the tumour tissue is irradiated "from the inside" by the MIBG accumulation and is subsequently destroyed.
microscope	an instrument that allows you to magnify objects or certain structures of objects that are not visible to the human eye
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.
molecular genetics	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.
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.
MYCN amplification	duplification of the MYCN oncogene, a cancer-causing gene that can be detected in various types of tumours (for example, some neuroblastomas and medulloblastomas); amplification of oncogenes (such as MYCN) is associated with the development and/or spread of some tumours. Tumor cells with the MYCN oncogene are particularly resistant to chemotherapy and radiotherapy.
nerve cells	components of the nervous system of higher organisms that are mainly responsible for transmitting messages in the organism (by transmitting, processing and receiving signals);
neurological	referring to the function of the nervous system / nerve tissue
neuron-specific enolase	enzyme of glucose metabolism, which is found in nerve cells in the brain as well as peripheral nerves, among others; elevated levels of NSE in the blood may indicate certain cancers (e.g. neuroblastoma).
otoacoustic emissions	very quiet sounds that the inner ear emits when hearing sounds (sound waves hitting the ear); these can be registered by highly

	sensitive microphones. The measurement of OAE is used to check the function of the inner ear; the patients assistance is not required (objective hearing test). This form of hearing test is therefore also suitable for infants and toddlers. During the examination, tiny measuring microphones are inserted into the external ear canal. The supplied sound waves cause the outer hair cells in the inner ear to vibrate, i.e. move mechanically. This generates the quiet but measurable otoacoustic emissions.
phaeochromocytoma	rare tumour, in about 10 % of cases malignant; it predominantly develops in the adrenal medulla, less often in the area of the sympathetic trunk. It occurs more frequently in connection with familial disease syndromes such as multiple endocrine neoplasms (MEN syndromes), neurofibromatosis and Hippel-Lindau disease.
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).
primary tumour	the tumour that developed first, from which metastases can originate
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
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).

radiotherapy	controlled use of ionizing (high-energy) radiation for the treatment of malignant diseases
randomisation	(statistical) random distribution of patients to treatment and control groups in a study; the strict random distribution is intended to eliminate systematic errors in the evaluation of therapy studies.
recurrence	relapse, recurrence of a disease after recovery
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.
sympathetic nervous system	part of the autonomic nervous system and antagonist of the parasympathetic nervous system (parasympaticus); the sympathetic nervous system manages demanding and stressful situations. Its excitation leads, for example, to an increase in blood pressure, an acceleration of heartbeat and breathing, dilation of the pupils and increased sweating, while at the same time dampening the activities of the stomach and intestines and their glands.
sympathetic trunk	a chain of numerous nerve nodes (ganglia) of the sympathetic nervous system on both sides of the spine; the sympathetic nervous system is part of the autonomic nervous system.
symptom	sign of illness
thrombocytopenia	decreased platelets (thrombocytes) in the blood to levels below the age-appropriate norm (less than 150,000 platelets per microliter of blood); thrombocytopenia is associated with impaired haemostasis, which in turn may lead to increased bleeding tendencies (e.g. nose or gum bleeds, bleeding into the skin (petechiae, bruising) and/or prolonged bleeding time (e.g. after

	injury). A transfusion of platelets (platelet concentrate) may sometimes be necessary.
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).
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.
Undine syndrome	a rare congenital disease of the central nervous system associated with a disorder of respiratory regulation; in addition, there are other dysregulations (such as cardiac arrhythmias, swallowing disorders, body temperatures that are too high or too low, formation of tumours). About a quarter of children with this syndrome also suffer from Hirschsprungs disease.
Wilms tumour	embryonic, malignant solid tumour of the kidney, most common in children between 1 and 5 years of age, especially in the presence of various syndromes or congenital abnormalities; Wilms tumour accounts for 6% of all malignancies in childhood and adolescence.
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.