



Wilms Tumour (Nephroblastoma) – Brief information

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Wilms Tumour (Nephroblastoma) – Brief information

1. General information on the disease

A Wilms tumour or nephroblastoma (nephro- for kidney, -blastoma for tumour), is a malignant *solid tumour* of the kidney. It is named after the German surgeon Dr. Max Wilms, who first described this tumour in the 19th century.

Wilms tumour arises from malignantly transformed *primitive* tissue. It resembles *embryonal* kidney tissue and is comprised of different tissue types. Usually, it mostly contains precursor kidney cells (*blastema*), but different developmental stages of various other tissue types, such as connective tissue, muscle, cartilage or *epithelial tissue*, to name a few, may also be present. This is why Wilms tumours are also called „mixed tumours“.

Wilms tumours are considered as malignant, because they grow fast and spread (metastasise) early. About 15 % of Wilms tumour patients (in Germany only 11% thanks to the scheduled routine check-ups) present with metastases [see *metastasis*] at tumour diagnosis. Most of these metastases can be found in the *lymph nodes* close to the kidney as well as in lung and liver. About 5 % of children with Wilms tumour have tumours in both kidneys (bilateral disease) at the time of diagnosis. These usually arise from so-called nephrogenic remainders, immature (embryonal) kidney tissue, which is known to be a precursor of Wilms tumour.

Wilms tumour is associated with other developmental disorders and/or with hereditary cancer syndromes more frequently than other cancers (see *chapter "Causes"*).

2. Incidence

Wilms tumour is the most common malignant kidney tumour of childhood. According to the German Childhood Cancer Registry and depending on the age group (0–14 years or 0–17 years), it accounts for approximately 4.8 % or 4 %, respectively, of all malignant diseases in children and adolescents, thereby representing one of the relatively frequent *solid tumours* in these age group. In Germany, about 95 children and teenagers under 18 years of age are newly diagnosed with a Wilms tumour each year. Hence, 8 or 9 out of 1,000,000 children and adolescents are diagnosed with the disease before they turn 18 years old.

As Wilms tumours are *embryonal* tumours, they occur mostly in young children: about 60 % of the patients are between 1 and 4 years old at diagnosis, 15 % are babies. The average age of the patients is 3 years, with girls being slightly more affected than boys. Nevertheless, older children and adolescents, adults rather seldomly, may also be affected.



3. Causes

The reasons why some children develop Wilms tumour, while others don't, are not completely understood. It is well-known, however, that alterations of certain *genes* and *chromosomes* contribute to Wilms tumour development. Best-known is the so-called Wilms tumour gene 1 (WT1-gene). It plays a key role in normal kidney development. If it is mutated, thus dysfunctional, it can result in tumour development and other disorders. Additional candidate *Wilms tumour genes* have been described to be located on chromosome 11 and other chromosomes. Also, other chromosomal modifications have been associated with an increased risk of developing Wilms tumour. According to current knowledge, multiple genetic changes (*mutations*) need to occur before a Wilms tumour develops.

Children with certain inherited diseases (such as *WAGR syndrome*, *Beckwith-Wiedemann syndrome* (BWS) and *hemihypertrophy*, *Denys-Drash syndrome* (DDS), or *Perlman syndrome*) have a higher risk of developing a Wilms tumour than their healthy peers. Since these genetic conditions are not only characterized by various kinds of developmental abnormalities, but also associated with an elevated risk for tumour development, they are also known as "*cancer predisposition syndromes*". About 10–15 % of all Wilms tumours are associated with such cancer predisposing syndromes.

In addition, there are families in whom Wilms tumours, but no associated *syndromes*, are diagnosed frequently, due to hereditary predisposition. This condition affects about 1-2 % of patients, particularly those with bilateral disease. In the majority of children, however, the tumour develops newly (sporadically), meaning that it is not associated with any underlying cancer syndrome or hereditary predisposition. According to current knowledge, environmental factors do not play a role in Wilms tumour development.

Good to know: there are specific screening guidelines for patients who are genetically prone to potentially develop a Wilms tumour. Genetic counselling with a human geneticist is also necessary (see chapter "*Diagnosis*").

4. Symptoms

Wilms tumours do not cause any health problems or pain for quite a while. Children typically present with a rounded tummy, which may sometimes be misdiagnosed as a sign of good nutrition. In about 10 % of children, a painless abdominal mass is randomly felt by the doctor during a child health check-up, while no other *symptoms* are being noticed. Less common symptoms indicative of Wilms tumour may include tummy pain, blood in the urine, fever, nausea, vomiting and indigestion, as well as weight loss, hypertension and persistent cough as a result of lung *metastasis*. Also, concomitant physical abnormalities or hereditary syndromes can be associated with Wilms tumour (see chapter "*Causes*").

5. Diagnosis

If the doctor thinks that the young patient's history (*anamnesis*) and *physical examination* are suspicious of a kidney tumour like the Wilms tumour, he will refer the child immediately to a

hospital with a childhood cancer program (paediatric oncology unit), 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 kidney tumour 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 assessment of *prognosis*.

5.1. Diagnostic imaging

Besides physical exam, diagnostic *imaging* procedures such as abdominal *ultrasound*, *magnetic resonance imaging* (MRI) and *computed tomography* (CT) play a major role in Wilms tumour diagnostics. They help determine tumour size and extent as well as differentiate (with a certainty of over 95 %) between a Wilms tumour and other, rather rare, kidney tumours (such as clear-cell sarcoma, rhabdoid tumour of the kidney, renal cell carcinoma and congenital mesoblastic nephroma, to name a few). Other cancers, such as *lymphoma* and *neuroblastoma*, can be found in the kidney area as well.

For obtaining the accurate diagnosis by imaging, however, high-quality equipment is required as well as an experienced radiologist to analyse the results. This is crucial because in Europe (in contrast to North America) tumour tissue is usually removed and examined after cessation of a pre-operative chemotherapy, meaning, histological confirmation of the diagnosis is done after therapy has already started (see chapter “Obtaining a tumour sample”).

5.2. Further tests to confirm diagnosis and assess tumour spread

Sometimes, diagnostic imaging alone is not sufficient to accurately differentiate Wilms from other tumours, such as neuroblastoma. For those patients, the doctors may recommend special additional tests. For example, in order to differentiate from neuroblastoma, a *scintigraphy* with the low radio-labelled substance ¹²³Iodo-meta-iodobenzylguanidine (¹²³I-MIBG *scintigraphy*) may be indicated, or determining *tumour markers* characteristic for neuroblastoma, but not nephroblastoma, in a blood sample.

Other additional tests help determine whether the tumour has spread and, if so, where. For example, searching for lung metastases requires a chest X-ray or CT scan. In case of suspected liver, abdominal or brain metastases, magnetic resonance imaging is required.

5.3. 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. For example, prior to *chemotherapy*, the doctors will recommend an ultrasound of the heart (*echocardiography*), a hearing test (*audiometry*, *BERA hearing test* and/ or *otoacoustic emissions*) as well as special diagnostics for determining kidney function (renal scintigraphy). Any changes occurring during the course of treatment can be assessed and managed



better based on the results of those initial tests, which thus help to keep the risk of certain treatment-related side-effects as low as possible.

5.4. Obtaining a tumour sample (biopsy)

If it is possible to obtain accurate diagnosis by diagnostic imaging, the doctors will recommend to first proceed with chemotherapy (4 - 6 weeks) and obtain sample tumour tissue (biopsy) for microscopic and *molecular genetic* examinations later. The biopsy is then usually performed during surgical tumour removal. Only in a few situations, tumour tissue is required to be taken prior to chemotherapy (by means of punch biopsy or *fine needle biopsy*).

Good to know: Not all of the above-mentioned tests apply to 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.

5.5. Screening for patients with genetically predisposed tumour risk

Patients with certain hereditary predispositions for developing cancer (cancer predisposition syndromes) (see *chapter "Causes"*) can present with Wilms tumour and/or with nephroblastomatosis, a preliminary stage of Wilms tumour. They also have an increased risk of developing bilateral tumours (bilateral nephroblastoma). In addition, certain predisposing syndromes (such as *Denys-Drash syndrome*) are associated with kidney function impairments or even early kidney failure.

For these reasons, patients with predisposing syndromes or with kidney malformations associated with an increased risk of developing Wilms tumour are recommended to undergo quarterly clinical exam and diagnostic imaging (*sonography*). Due to the additional risk of bilateral disease in patients with these syndromes, unilateral and bilateral nephroblastoma are treated the same (see *chapter "Course of treatment"*). For all patients with a cancer predisposition syndrome or familial nephroblastoma, molecular diagnostics following genetic counselling are recommended.

6. Treatment planning

After the diagnosis has been confirmed, therapy is planned. In order to provide a highly individual, risk-adapted treatment regimen for the patient, the doctors consider certain individual factors that can influence the patient's *prognosis* (risk factors or prognostic factors).



The most important *prognostic factors* for patients with a Wilms tumour are:

- **the stage of the disease**, that is, the extent of the tumour at diagnosis and the extent of its surgical removal;
- **the type of Wilms tumour**, that is, the characteristics of the tumour cells seen under the microscope, which describe, for example, how fast the tumour is expected to grow, thereby providing insight into its degree of malignancy.

Also, the response of the disease to *preoperative* therapy has major impact on prognosis. This response is partially dependent on stage and type of the disease. Scientists have also found out that, in addition to the microscopic characteristics of a Wilms tumour, its *molecular genetics* can also influence the course of the disease. Thus, certain *gene* and *chromosome* alterations in tumour cells appear to correlate with comparably more unfavourable outcomes. According to the latest findings, the absolute volume of the residual *blastema* portion of a nephroblastoma following surgery also has an impact on the patient's prognosis.

When planning the treatment, the doctors consider all these individual factors in order to provide optimal therapy, thus best possible outcome for every patient.

6.1. Stages of Wilms tumour

The stage of the disease represents a major criterion for treatment planning. Aspects like tumour extent, involvement of one versus both kidneys, involvement of local *lymph nodes* and/or blood vessels, or even spread to distant organs are all included in the staging of a Wilms tumour.

The extent of surgical tumour removal is another essential staging criterion. Hence, accurate definition of the tumour stage is only possible after surgery. Prior to treatment, a preliminary classification, based on diagnostic imaging results at diagnosis, is done by differentiating between localized tumours in one kidney, tumours with metastases and/or bilateral tumours.

The staging system used in German treatment centres is according to the International Society of Pediatric Oncology (*SIOP*). It differentiates five stages of Wilms tumour (*see table below*).

Staging of Wilms tumour according to SIOP

Stage	Definition
Stage I	The tumour is limited to the kidney. The outer layer of the kidney (renal capsule) did not break open. The tumour can be extracted completely.
Stage II	The tumour is not limited to the kidney, but has spread to blood vessels in the renal sinus or outside the area of the kidney. The tumor can be removed completely. Lymph nodes are not involved.
Stage III	The tumour cannot be removed completely <i>or</i> it has spilled or spread to local lymph nodes



Stage	Definition
	or it broke open (rupture of the tumour tissue). There is no spread to distant organs.
Stage IV	The tumour has spread through the blood (metastasised) to distant organs, such as the lungs, liver, bones and/or brain.
Stage V	Cancer cells are found in both kidneys (bilateral nephroblastoma).

Notes to staging: a local stage (I-III) is also determined for stages IV and V, since this is decisive for choosing the appropriate post-surgical treatment. In case of bilateral tumours, the one with the highest local stage and the most unfavourable *histology* counts for the choice of post-surgical treatment.

6.2. Histological classification of Wilms tumour

Wilms tumours may look very different under the microscope (*histologically*), depending on which types of tissue they consist of and how mature (*differentiated*) the tumour cells are. The histology of the tumour determines the patient's response to treatment and, hence, also affects *prognosis*. Therefore, it is crucial for appropriate treatment planning to determine the tumour's histology, thus differentiating not only between Wilms tumour and any other type of kidney tumours, but also between different histological subtypes of Wilms tumour.

Based on how they appear under the microscope, Wilms tumours are classified into the following three histological groups reflecting the disease's degree of malignancy:

- nephroblastoma – low grade malignancy (favourable histology)
- nephroblastoma – intermediate grade of malignancy (standard histology)
- nephroblastoma – high grade of malignancy (unfavourable histology)

Certain subtypes of Wilms tumour are assigned to each of these groups. The exact way of assignment (classification) is based on whether tumour tissue is examined and assessed before or after chemotherapy. In Germany and other European countries, the removal and examination of tumour tissue usually (i.e. with the majority of patients) occurs after *preoperative* chemotherapy.

7. Treatment

Treatment of children and adolescents with Wilms tumour should take place in a children's hospital with a paediatric oncology program. Only such a childhood cancer centre provides highly experienced and qualified staff (doctors, nurses and many more), since they are specialised and focussed on the diagnostics and treatment of children and teenagers with cancer according to the most advanced treatment concepts. The doctors in these centres collaborate closely with each other. Together, they treat their patients according to treatment plans (protocols) that are continuously optimised.



The major **goal of treatment** is to eliminate the cancer while keeping the risk of side-effects and late sequelae as low as possible.

7.1. Treatment methods

Treatment of children and adolescents with Wilms tumour mainly consists of a combination of **surgery** and **chemotherapy**. Only a few patients receive additional **radiotherapy**.

Most patients with Wilms tumour receive *chemotherapy* first. The goal is to shrink the tumour to make it more easily removable by *surgery*. Some patients undergo surgery first. Surgery aims at complete removal of the tumour and possible metastases [see *metastasis*]. Usually, it is followed by another round of chemotherapy. Depending on the tumour staging after surgery and on possible spread, *radiotherapy* is required as well.

The individual treatment choice is based on the special features the tumour reveals under the microscope (subtype of Wilms tumour) as well as on the tumour extent after surgery (tumour stage). Taken together, the higher the degree of malignancy and the more advanced the tumour stage, the more intensive therapy will be. Since treatment of Wilms tumour can be associated with acute adverse effects, patients receive *supportive therapy* during cancer treatment in order to prevent and/or treat those side effects. Here you will find information on [supportive care](#) as well as [recommendations for home](#), the latter of which may be helpful during or after chemo- and radiotherapy.

7.2. Course of treatment

The international and national (German) paediatric cancer societies (*SIOP* and *GPOH*) recommend the following treatment strategies:

7.2.1. Chemotherapy prior to surgery

In Germany as well as in several other European and non-European countries, treatment for all patients between six months and 16 years of age begins with *chemotherapy* (*preoperative* or *neoadjuvant* chemotherapy). The reason for this strategy is that chemotherapy usually helps to reduce tumour size, thereby making it easier for the surgeon to later remove the tumour. Also, the risk of tumour spill during surgery, thus spreading tumour tissue in the abdomen, is lower when the tumour is smaller. Also, radiotherapy after surgery may be waived.

In order to eliminate as many cancer cells as possible, patients receive a combination of agents that have proven to inhibit Wilms tumour growth (cytostatic agents). Some of these are vincristine and actinomycin D, to name a few. For some patients, for example children with metastases or highly malignant tumours, additional chemotherapy with an anthracycline (doxorubicine) is recommended. Preoperative chemotherapy usually takes four weeks, for patients with metastasised disease six weeks and for patients with bilateral tumour up to a total of twelve weeks.

For patients with bilateral Wilms tumour, treatment duration is determined individually with the major goal to save both kidneys. Hence, intensification of the pre-operative chemotherapy using additional agents (such as etoposide and carboplatin) may be indicated. The same concept applies for patients

with cancer predisposition syndromes: the goal is to salvage as much functional kidney tissue as possible.

Infants under the age of six months as well as teenagers older than 16 years do not receive preoperative chemotherapy. This is because most kidney tumours in these age-groups are not nephroblastoma, but other types of kidney tumours (such as renal cell carcinoma or congenital mesoblastic nephroma), which require a different type of treatment than Wilms tumour patients. Therefore, obtaining tumour tissue by surgery first is crucial for choosing the appropriate treatment strategy for these patients.

7.2.2. Surgery

The major aims of *surgery* are complete tumour removal as well as obtaining tissue samples for microscopic and *molecular genetic* analyses and assessing the extent of tumour growth.

The surgical approach is mainly dependent on whether only one or both kidneys are affected:

Patients with a Wilms tumour in only one kidney (unilateral tumour) usually undergo removal of the kidney with the tumour. Accordingly, this method is called tumour nephrectomy. As a result, the remaining kidney will enlarge over the following weeks and months, thereby becoming capable of fully taking over the removed one's function. Therefore, it is important to protect the remaining kidney from any damage (for example chronic inflammation) later in life. Kidney-preserving surgery can be sometimes achieved by an experienced surgeon, who is capable of completely removing the tumor out of the kidney. This applies mostly to stage I disease (see chapter „Therapy planning“).

If a patient presents with tumours in both kidneys (bilateral Wilms tumour) or has a high risk of developing a bilateral disease (for example, due to a hereditary cancer predisposition syndrome), the doctors will assess treatment options individually with the goal to at least save one of the affected organs.

For patients who developed lung metastases after chemotherapy, surgical removal of those is a feasible approach as long as it is performed by paediatric surgeons or urologists with expertise.

7.2.3. Chemotherapy after surgery

Following surgery, treatment usually carries on with chemotherapy for most patients (*postoperative* or adjuvant *chemotherapy*). Only for children with a tumour of low-grade malignancy that was limited to the kidney and could be completely removed (stage I and favourable histology), treatment is over after surgery. All other patients will receive a more or less intensive chemotherapy, depending on tumour type and weight at surgery as well as on local tumour stage.

For children with tumours of intermediate grade of malignancy that have not spread to other parts of the body (standard *histology*, stages I-III), therapy is usually continued by giving only two different *cytostatics* (vincristine and actinomycin D). If the disease has been classified as highly malignant and is at high stage, a combination of up to four different agents will be recommended (for example doxorubicine, carboplatin, etoposide and cyclophosphamide). The duration of therapy may be between one month (for patients with stage I tumours and standard histology) and eight to ten

months (for patients with tumours of unfavourable histology or distant spread after surgery). For bilateral tumours, treatment may last up to one year in case of nephrogenic remainders (pre-stages of Wilms tumour) have been diagnosed by a *pathologist*.

7.2.4. Radiotherapy

Due to the development of efficient combination chemotherapy regimens as well as the introduction of preoperative (neoadjuvant) chemotherapy, most patients can do without *radiotherapy* (radiotherapy). For a few children, however, radiotherapy following surgery and chemotherapy is still recommended. These include patients with tumours of intermediate grade of malignancy (stage III) and of high grades of malignancy (stages II and up) (see *chapter "Treatment planning"*).

Radiotherapy is usually carried out with doses between 15 and 30 *gray* (Gy) to the tumour site, depending on *histological* diagnosis (microscopical features) after surgery. Patients with residual tumours after surgery and chemotherapy usually receive an extra "boost" to the tumour site. For children with tumours that ruptured during surgery, radiotherapy of the whole abdomen is recommended with doses of 20 or 30 Gy, again depending on histology. Patients with tumour spread to the lungs usually receive chest irradiation as well. Patients with remaining lung metastases after pre-operative chemotherapy and surgery will also receive chest irradiation. In case of bilateral tumours, remaining kidney tissue and intermediate degree of malignancy, decreased radiation doses may be given (below 12 Gy) in order to maintain the remaining kidney function as long as possible.

8. Therapy optimising trials / registries

In the large paediatric treatment centres, children and adolescents with Wilms tumour receive therapy according to standardised treatment protocols, which are designed and controlled by experts. They aim at continuously increasing survival rates while also reducing the risk of therapy-related late effects. Treatment according to such treatment protocols usually occurs within so-called *therapy optimising trials*.

In German-speaking countries, the long-standing therapy optimising trial SIOP WT 2001 came to an end in August 2011 and continued as a registry until early 2022. German, Austrian and Swiss treatment centres had participated in this study. It had been conducted under the roof of the *GPOH* by the study centre for nephroblastoma, as part of the International Nephroblastoma trial of *SIOP*. The key finding of the study was that, in patients with stage II and III nephroblastoma of intermediate malignancy, the intensity of treatment could be reduced by avoiding *anthracyclines* (which can damage the heart) without this adversely affecting the patients' prognosis.

The following clinical trials for patients with nephroblastoma are currently available in Germany (with international participation):

- **UMBRELLA SIOP-RTGS 2016:** Based on the results of previous national and international trials, a new SIOP study for children and adolescents with kidney tumours has been developed: UMBRELLA SIOP-RTGS 2016. The trial has been open for recruitment in Germany since late 2021 (in a few European countries already since 2019). The German headquarters of trial and



registry are located in the Children's Hospital of the University of Homburg/Saar, Germany. Principal Investigator is Prof. Dr. med. Norbert Graf.

- **RANDOMET 2017:** For patients with metastasized disease, the randomized trial RANDOMET 2017 has been available since beginning of 2022. The study analyses preoperative chemotherapy with the question whether a combination of vincristine, carboplatin and etoposide is as effective as the standard treatment with vincristine, actinomycin and doxorubicin. The goal is to reduce doxorubicin-induced cardiotoxicity in patients with metastatic disease, too, without jeopardizing cure rates. The trial is under the direction of PD Dr. med. Rhoikos Furtwängler (Children's Hospital of the University of Homburg/Saar, Germany, and Children's Hospital of the University of Bern, Switzerland).

9. Prognosis

Long-term survival rates of children and teenagers after treatment of Wilms tumour are high. About 90 % of all Wilms tumour patients survive their disease today, thanks to modern diagnostic procedures and standardised combination therapies, which are continuously improved.

However, individual *prognosis* depends, above all, on the tumour subtype and the stage of disease. The lower the grade of malignancy of the tumour and the lesser advanced its stage, the more favourable the outcome. For example, the chances of survival for patients with a non-metastasised nephroblastoma of favourable or standard histology are currently higher than 90 %, while the outcomes of patients with highly malignant tumours are less favourable.

Nevertheless, under certain conditions, even patients with Wilms tumours of higher stages may have a good chance of survival. For example, prognosis for children whose disease has spread to other parts of the body (nephroblastoma stage IV) highly depends on how it responds to treatment: if *preoperative chemotherapy* and subsequent surgery result in complete elimination of the tumour and its metastases, survival rates of more than 80 % can be achieved.

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.

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Glossary

anamnesis	medical interview, a patient's history, development of signs of illness; the type, onset and course of the (current) symptoms as well as any risk factors (e.g. hereditary diseases) are evaluated during a medical interview.
anthracyclines	substances derived from certain types of bacteria or artificially produced; used as cytostatics, they prevent cell division in various ways; they can also damage the cell membrane and cause the cell to die. Anthracyclines include, for example, daunorubicin, doxorubicin, epirubicin, idarubicin and mitoxantrone.
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.
Beckwith-Wiedemann syndrome	congenital or acquired clinical condition, characterized in particular by a pathologically increased one-sided growth of the body (hemihypertrophy), enlargement of the liver, spleen or kidneys, considerably enlarged tongue, umbilical (cord) rupture, maldevelopment of the auricles, kidney abnormalities and an increased risk to develop certain malignant diseases (especially Wilms tumours); BWS is one of the cancer predisposition syndromes and is caused by various genetic changes (on chromosome 11).
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.
blastema	undifferentiated germ tissue consisting of stem cells that are capable of dividing, from which differentiated tissue forms



		during embryonic development or regeneration processes; for example, an early embryonic organ (blastema) develops into a mature, functioning organ via cell proliferation and maturation (differentiation).
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.
chemotherapy		here: use of drugs (chemotherapeutic agents, cytostatics) for the specific inhibition of tumor cells in the organism
chromosome		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.
chromosome		
computed tomography		imaging, X-ray diagnostic procedure; it produces an image by computer-controlled evaluation of a large number of X-rays from different directions. This makes it possible to produce sliced images of body parts (tomograms, transverse or longitudinal sections of the human body)
cytostatics		drugs that inhibit cell growth; cytostatics can affect the metabolism of different types of cells, thereby destroying them and/or preventing them from multiplying. Cells that divide frequently are particularly affected.
Denys-Drash syndrome		rare disease characterized by severe genital malformations (pseudohermaphroditism), malformation of the gonads, kidney disease (proliferation of connective tissue cells in the renal corpuscles, mesangiosclerosis) with early renal failure and an increased risk of Wilms tumours and tumours of the gonads (gonadoblastoma); DDS syndrome is therefore also one of the cancer predisposition syndromes. In most patients with this disease, there is a change (mutation) in a gene on chromosome 11, called the Wilms tumour gene (WT1 gene). This gene probably



	<p>plays an essential role in the development of the genitourinary system. If it is present in mutated form, there is generally an increased risk (74–90%) of developing a Wilms tumour.</p>
differentiated	<p>here: mature, functional; differentiated cells/tissues are fully developed structures with special tasks; they have no or only limited ability to divide. The development from undifferentiated to differentiated cells and tissues (differentiation) takes place gradually, so there are many different stages of differentiation.</p>
echocardiography	<p>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.</p>
embryonal	<p>here: in an early stage of development, immature;</p>
epithelial tissue	<p>a closed group of cells that lines or borders the external or internal surfaces of the body in one or more layers; epithelial tissues include, for example, the skin, mucous membranes of the oral cavity, oesophagus, stomach and intestines, lining of the urinary bladder, renal pelvis, fallopian tubes, uterus and trachea. As covering and glandular tissue, epithelial tissue fulfils the following functions: protection, mass exchange and sensation/signal transmission. The epithelium is one of the four basic tissue types, along with muscle, nerve and connective tissue.</p>
fine needle biopsy	<p>diagnostic procedure in which cells are extracted from an internal organ for fine tissue examination with the help of a thin hollow needle; the insertion of the hollow needle can be carried out under the control of an imaging procedure (such as ultrasound).</p>
gene	<p>unit of genetic information in the genome of living organisms; a gene contains the genetic information – the blueprint – for a specific gene product (protein or RNA). In most organisms, the entirety of all genes, the genome, is present as a deoxyribonucleic acid chain (DNA), which forms the chromosomes in the cell nucleus. The information of a gene is mediated by a certain sequence of the nucleic acid building blocks adenine, guanine, cytosine and thymine.</p>
GPOH	<p>Society for Paediatric Oncology and Hematology (GPOH), the German professional society for childhood and adolescent cancers and blood diseases; in the GPOH, doctors, scientists, nurses and psychologists, among others, work together on the research, diagnosis, treatment and aftercare of malignant</p>



	diseases and blood diseases in children and adolescents. In the GPOH, doctors, scientists, nurses and psychologists, among others, work together on the research, diagnosis, treatment and aftercare of malignant diseases and blood diseases in children and adolescents.
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)
hemihypertrophy	one-sided growth of the body or individual parts of the body (e.g. limbs of one half of the body, half of the head, half of the face); organs can also be affected. In some cases, there are also abnormalities of the skin and teeth as well as hormonal imbalances. Hemihypertrophy can be congenital and present at birth or develop during childhood; however, it can also develop later in life. Hemihypertrophy is observed in the context of certain cancer predisposition syndromes (e.g. Beckwith-Wiedemann syndrome, neurofibromatosis), but can also occur on its own in otherwise normal individuals or as a separate syndrome.
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).
histology	study of the tissues of the body
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
lymph nodes	small lenticular to bean-shaped organs that are part of the body's 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.
lymphoma	collective term for lymph node enlargement of various causes
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 scintigraphy

imaging nuclear medicine technique applied specifically for the diagnosis of sympathetic nervous system tumours by using radiolabeled methyl iodine 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 body's 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.

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.



neuroblastoma	malignant solid tumour of the sympathetic nervous system; occurs more frequently before the age of 5, mainly in infants and newborns; neuroblastoma is one of the most common solid tumours in childhood and adolescence (accounting for about 5.5% of all malignant diseases) after CNS and soft tissue tumours.
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.
pathologist	a physician who identifies diseases and determines the malignancy of tumours by means of histological and molecular genetic examination of cells and tissues
Perlman syndrome	a very rare hereditary disorder associated with tall stature, high mortality in the early stages of life, kidney malformations, nephroblastomatosis and kidney tumours; the disease is inherited in an autosomal recessive manner and is one of the cancer predisposition syndromes.
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.
postoperative	following surgery
preoperative	prior to surgery
primitive	undeveloped, undifferentiated
prognosis	prediction of the course and outcome of a disease / prospect of recovery
prognostic factors	factors that allow an approximate assessment of the further course of the disease (i.e. the prognosis);
radiotherapy	controlled use of ionizing (high-energy) radiation for the treatment of malignant diseases
scintigraphy	a nuclear medicine examination procedure in which internal organs or tissues and their function (activity) can be visualized, for example on an X-ray film, by administering a radioactively



	<p>labeled substance; in cancer medicine, scintigraphy can be used to visualize tumours or metastases. There are different types of scintigraphy, depending on which organ is to be examined and the chemical substance used for it.</p>
SIOP	<p>International Society for Childhood and Adolescent Cancers; SIOP is the abbreviation for "Société Internationale d'Oncologie Pédiatrique" or "International Society of Paediatric Oncology".</p>
solid tumour	<p>solid, localized increase of the body's 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.</p>
supportive therapy	<p>supportive treatment measures to prevent, alleviate or treat disease and/or treatment-related side effects or complications; supportive therapy is designed to improve the patient's quality of life.</p>
surgery	<p>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.</p>
symptom	<p>sign of illness</p>
syndrome	<p>clinical presentation resulting from the coincidence of various characteristic signs (symptoms)</p>
therapy optimising trial	<p>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.</p>
tumour marker	<p>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</p>



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.

WAGR syndrome

abbreviation for a clinical condition associated with a predisposition to Wilms tumours, complete or partial absence of the iris of the eye (aniridia), malformations of the urinary and genital organs (genitourinary system) and mental retardation; there is also an increased risk of developing kidney disease (e.g. renal insufficiency) with chronic renal failure. It usually manifests itself between the first and fourth year of life and is due to the loss of a piece of chromosome 11. This activates the so-called Wilms tumour gene WT1.

Wilms tumour gene

genes that play a decisive role in the development of the Wilms tumour (as a result of tumour-specific changes in certain chromosomes); so far, despite indications of the existence of various Wilms tumour genes, only the Wilms tumour suppressor gene WT1 on chromosome 11 (gene locus 11p13) has been identified and decoded.