Soft tissue sarcomas and rare soft tissue tumours – Brief information

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1. General information on the disease

The term soft tissue tumours includes a variety of very different diseases that all share having developed due to a malignant transformation (degeneration) of immature precursor cells of *soft tissue*s.

Soft tissues, however, include different tissue types such as muscles, fatty and connective tissues as well as blood vessels and tissue of the *peripheral nervous system*. Therefore, different types of soft tissue tumours exist. They differ with regard to their *histological* structure and the type of *cell*s they arise from, and they also have different frequencies and biological behaviour. This means, for example, that they present with different growth rates and spread patterns (metastasis), or respond to treatment, such as *chemotherapy*, differently.

Soft tissue tumours can be benign, malignant or medium grade (intermediate) malignant. Usually, malignant soft tissue tumours are called soft tissue sarcomas; the term “soft tissue tumour” is rather neutral and refers to any type of tumour behaviour. “Soft tissue tumours“ and "soft tissue sarcomas“ summarize at least 150 different histological tumour types (entities).

Most soft tissue sarcomas are highly malignant; they grow and spread rapidly and, hence, are lethal within a few weeks or months, if not treated appropriately. The majority of the less frequent soft tissue tumours, however, is of intermediate malignancy or partially even benign. The growth pattern of these tumours varies; they can do both, spontaneously regress or locally grow very aggressively.

2. Incidence

Soft tissue tumours account for about 6 % of all malignant diseases in childhood and adolescence, thereby representing one of the most frequent *solid tumour* types in this age group, following tumours of the *central nervous system* (CNS tumours, brain tumours). According to the German Childhood Cancer Registry (Mainz), about 10 out of 1,000,000 (a total of approximately 125) children and adolescents between 0 and 17 years are diagnosed with a soft tissue tumour each year. More than half of these patients present with *rhabdomyosarcoma*, the most frequent soft tissue sarcoma in childhood and adolescence.

Soft tissue tumours are most frequent in children younger than five or six years of age. The average age at diagnosis is 8.5 years. Boys are slightly more affected than girls (gender ratio: 1.3 : 1). However, both age distribution and gender ratio differ very much depending on the type of soft tissue tumour.

The most frequent soft tissue sarcomas – that is to say, malignant soft tissue tumours – in children and adolecents under 18 years of age are:

- rhabdomyosarcoma (RMS): 61 %
- extraosseal tumours of the Ewing-group: 16 %
- synovial sarcoma (SySa): 7 %
- fibrosarcoma (FS): etwa 3 %
- leiomyosarcoma (LMS): etwa 2 %
- undifferenciated sarcomas (UDS): 2 %

All other soft tissue sarcomas are rather rare in childhood and adolescence.

3. Tumour types

There are multiple variants of soft tissue tumours, including more than 20 different types of soft tissue sarcomas.

As per currently valid clinical classification, soft tissue tumours are divided into three large groups:

- rhabdomyosarcomas (RMS)
- non-rhabdomyosarcoma soft tissue sarcomas (NRSTS)
- rare soft tissue tumours

Note: the „Cooperative Weichteilsarkom-Studiengruppe (CWS, German for „Cooperative Soft Tissue Sarcoma Study Group“) of the Society for Paediatric Oncology and Haematology (*GPOH*) differentiates within the CWS Guidance (status 2014) an additional group based on their clinical behaviour and treatment approach: the so-called rhabdomyosarcoma-like (RMS-like) soft tissue sarcomas. Two tumours assigned to this group (synovial sarcomas and undifferentiated sarcomas) are now included in the NRSTS group – both in Europe and the CWS Study Group.

According to the *WHO*, extraosseal tumours of the Ewing group (Ewing sarcomas originating from soft tissues) – which were previously also called “RMS-like” tumours – belong to the main group of Ewing sarcomas and are being treated as per therapy concepts of the Ewing group. Due to the identification of multiple (new) genetic markers, the classification of soft tissue tumours and sarcomas is currently in transition and hence, the term “RMS-like” is being abandoned.

The following paragraphs will provide more information on the three groups of soft tissue sarcomas.

3.1. Rhabdomyosarcoma (RMS)

For a long time, *rhabdomyosarcoma*s (RMS) have been divided into two major groups based on their microscopic (histological) appearance: embryonal RMS (ERMS) and alveolar RMS (ARMS). Aside from their different *histological* features, the two RMS types usually also show different characteristics regarding their growth pattern (localisation, extent, spread) as well as regarding age distribution and prognosis: embryonal RMS particularly affect children under 10 years of age and are mostly associated with a favourable outcome when compared to alveolar RMS, the incidence of which increases in children older than 10 years.

It is well-known by now that the course of the disease is mainly impacted by the *molecular genetic* characteristics of the tumour cells. Hence, there are genetic alterations, so-called fusion genes, whose presence is associated with an unfavourable *prognosis*. This is, for example, the case for a typical fusion in the *PAX-FOXO* gene, which can be found in the majority of alveolar RMS (but not in embryonal RMS); the affected ARMS are also called fusion-positive RMS, whereas RMS lacking this specific *PAX-FOXO* gene fusion are called fusion-negative. However, in the meantime, additional alterations have been identified that can cause high malignancy in fusion-negative RMS, too.

Important to know: today, RMS are not primarily assessed based on their histological features, but rather on the presence or lack of genetic alterations. Genetic characterization of the tumours therefore plays a major role when assessing the probability of survival and choosing the appropriate treatment approach.

3.2. Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS)

The non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) represent a rather heterogenous group of soft tissue sarcomas, which differ regarding multiple aspects, such as their growth behaviour, sensitivity to chemotherapy (chemosensitivity) and outcomes.

For example, alveolar soft tissue sarcoma, epitheloid sarcoma, malignant peripheral nerve sheath tumour, fibrosarcoma and leiomyosarcoma all belong to the group of NRSTS. Since these tumours may develop in adults, too, they are also known as „adult type NRSTS“. NRSTS also include those tumours that were previously called “RMS-like soft tissue sarcomas” by the CWS Study Group), based on their chemosensitivity and thus treatment, which are similar to that of rhabdomyosarcoma: the synovial sarcomas and the undifferentiated sarcomas (*see chapter “Tumour types”*).

3.3. Rare tumours

The group of the "rare soft tissue tumours” includes tumour types with malignant, medium-grade (intermediate) malignant or benign biological behaviour. Due to their extreme rarity, they are summarized, despite of their different growth patterns and degrees of malignancies. Rare soft tissue tumours are myofibromatosis, desmoid-type fibromatosis (DTF), inflammatory myofibroblastic tumour (IMT), gastrointestinal stromal tumour (GIST) and many more. Based on the tumour type, there are individual treatment concepts for each of these rare diseases.

4. Localisation and spread

Soft tissue tumours may generally develop anywhere in the human body, since there is soft tissue everywhere. The tumours usually spread along certain anatomical structures, for example along muscle sheaths, ligaments or blood vessels. In the course of this, single cells may detach from the *primary tumour* and spread to other body sites via the blood and/or lymph stream. They can settle there and start multiplying again; daughter tumours are developing (*metastasis*). Metastases of soft tissue sarcomas particularly occur in the lungs, in adjacent *lymph nodes* and in the bones. Other organs can be affected as well.

Origin and growth behaviour of soft tissue tumours are strongly associated with the tumour type.

Rhabdomyosarcomas, for example, can generally develop in almost every organ, however, most frequently, they are found in the head-and-neck area, the urinary tract and reproductive organs as well as the extremities. Usually, fusion-positive alveolar rhabdomyosarcomas (ARMS) show a more aggressive behaviour compared to embryonal rhabdomyosarcomas (ERMS), meaning that they frequently grow and spread faster via the blood and/or lymph stream. Also, fusion-positive ARMS are associated with a higher risk of recurrent disease than most ERMS.

Extraossear tumours of the Ewing group – which, according to their naming, grow outside any body tissue – mostly develop in the area of the trunc and extremities. Synovial sarcomas occur most frequently close to joints in the extremities as well as in the head-and-neck area. All these tumour types tend to metastasize early. About 20 % of patients with a soft tissue sarcoma present with distant metastases already at the time of diagnosis.

5. Causes

The causes for the development of soft tissue tumours are not completely understood as of today. The assumption is that they originate from precursor cells of the connective tissue (soft tissue). In medical jargon, these cells are called „*mesenchymal stem cells*“. The malignant transformation is most certainly initiated by *genetic* and/or chromosomal aberrations in these cells.

Different genetic and chromosomal aberrations have already been identified in the malignantly transformed cells, however, these happen to be quite heterogenous, do vary depending on the type of soft tissue tumour and are not regularly found in all tumours after all. Overall, multiple genetic alterations are most certainly responsible for the development of a soft tissue tumour. According to current research, most patients do not have any hereditary predisposition.

However, there are families presenting with high incidences of rhabdomyosarcoma in multiple generations. Also, children present with rhabdomyosarcoma more frequently in families with a frequent history of *carcinoma*. These observations indicate that those patients have a genetic predisposition to develop this disease, a so-called *cancer predisposition syndrome* (CPS). These are complex diseases which are characterized by various kinds of developmental abnormalities and an elevated inherited risk to develop cancer. Cancer predisposition syndromes that are known to play a role in the development of a soft tissue tumour are, for example, *neurofibromatosis*, the

Beckwith-Wiedemann syndrome, the *Li-Fraumeni syndrome*, the *Gorlin-Goltz syndrome* and the *Werner`s syndrome*.

Also, there are indications that certain external factors increase the risk to develop soft tissue tumour. These include *radiation exposure* of the unborn (for example by *X-rays* or *radiation therapy* received by the mother), alcohol or other parental drug abuse prior to or during pregnancy, respectively, as well as early radiotherapy of the child. Associations with viral *infection*s have been reported as well. Hence, *HIV*-positive, thus immunosuppressed children have an increased risk of developing leiomyosarcoma following an infection with the *Epstein-Barr virus* (EBV).

For most patients with soft tissue tumour, no risk factors have been identified yet.

6. Symptoms

The symptoms of patients with soft tissue tumour depend on the site and the extent of the tumour and are therefore quite diverse. To name only a few of the frequent, representative symptoms here:

- **Soft tissue tumours developing close to the surface** often cause a continuously increasing swelling and/or pain. Both are not infrequently wrongly referred to as, for example, exercise-induced trauma. Also, they may cause a dysfunction of the affected organ, such as limited range of motion in arms and legs.

- **A soft tissue tumour of the orbita** may initially present with a painless bulging of the eye anteriorly out of the orbit (*exophthalmus*) and a swelling of the eyelid; later it usually causes pain because of the increased local pressure. Vision impairment is also possible.

- **Soft tissue tumours of the nose** are often associated with a long history of congestion or sniffle at the timepoint of diagnosis.

- **In case the skull base is involved**, cranial nerve impairments may occur, which present as facial nerve palsy or double vision.

- **Tumours of the urinary tract and reproductive organs** may present with general malaise, constipation and/or impaired urination, vaginal bleeds, blood in the urine and pain, however, usually once the tumour is already quite large

As for other parts of the body, soft tissue tumours are often getting noticed only because of their palpable or visible tumour mass, for example during a routine physical exam at the paediatrician or by *imaging* diagnostics such as an *ultrasound*. They often do not cause any complaints, meaning that the patients feel good.

Children and adolescents with complaints as described above do, of course, not always necessarily have soft tissue tumour or any other malignant tumour. Nevertheless, it is strongly recommended to have the cause of such *symptom*s be evaluated by an experienced paediatrician.

Good to know: in case of suspected soft tissue tumour, the paediatrician should refer the patient to a treatment centre that is specialized on cancer in children and adolescents (paediatric oncology / haematology program). Initial diagnostic tests (imaging procedures or biopsy, respectively) that are done elsewhere often turn out insufficient and, thus, may negatively impact appropriate treatment and also the patient's prognosis (chance of cure).

7. Diagnosis

If the doctor thinks that the young patient's history and physical exam are suspicious of a soft tissue tumour, the child should immediately be referred to a hospital with a childhood cancer program (paediatric oncology unit), where further diagnostics can be initiated and performed by childhood cancer professionals. Very close collaboration between various specialists (such as *paediatric oncologist*s, paediatric surgeons, paediatric radiologists, to name a few) is required both to find out whether the patient really suffers from a soft tissue tumour and, if so, to determine the tumour type and the extension of the disease. Knowing these details is absolutely essential for optimal treatment planning and *prognosis*. Diagnostic management follows the European guidelines as well as the trial recommendations of the CWS Study Group, the Society of Paediatric Oncology and Haematology (*GPOH*), and the "European pediatric Soft tissue Sarcoma Study Group" (EpSSG), the latter of which is the merger of the European study groups.

7.1. Diagnostic imaging

Apart from comprehensive medical history taking (*anamnesis*) and *physical examination*, *imaging* procedures – preferably a *magnetic resonance imaging* (MRI) with and without *contrast agent* – play a major role in soft tissue tumour diagnostics. First of all, they serve to assess or rule out a tumour. Also, the localization, size and volume of a tumour as well as its demarcation with regard to adjacent tissue (such as organs, blood vessels and nerves) or any tumour-induced changes of the bone system can be diagnosed by such imaging techniques very well.

7.2. Tissue extraction (biopsy) to confirm diagnosis

For final confirmation of the diagnosis, tumour tissue is required to be removed (biopsy), even if the tumour may be benign (as is the case with a *lipoma* or *haemangioma*, for example). The *biopsy* should only be performed by doctors who are specialized in surgery of sarcomas.

The obtained samples are subsequently analysed *histological*ly, *immunohistochemical*ly and *genetic*ally by specialists, with *molecular genetic* tests becoming more and more important. The analyses serve to confirm the diagnosis of a soft tissue tumour and, once confirmed, to determine the subtype. For this, a very comprehensive characterization of soft tissue tumours will be available soon, which will make individualized (meaning tailored) therapies for single patients possible. Hence, analysis and research on tumour tissue is crucial.

Since the disease is overall rare, the obtained tissue samples should not only be studied by the local *pathologist*, but should also be sent to a reference centre for paediatric pathology – such as the reference pathologist of the CWS Study Group of the *GPOH* in Bonn. Such a centre receives tissue

samples of a certain tumours from all over Germany and therefore provides special experience with the assessment. The diagnosis is further confirmed by an additional molecular genetic analysis promoting superior tumour characterization, thereby providing relevant directions for the treatment.

Note: for molecular genetic analysis, fresh frozen tumour tissue is implicitly required. Therefore, it is crucial that the biopsy is taken in a centre that is specialized in paediatric oncology, where both the expertise and the facilities to process the tumour samples are adequately given. Remaining samples will be stored in the tumour bank and may be used for research aiming at treatment optimisation of these tumours.

7.3. Tests to assess spread of disease (staging)

Once the diagnosis of "soft tissue sarcoma" or "(intermediate) malignant soft tissue tumour" has been confirmed, further tests are required to find out if and to which extent the cancer has spread and which organs are involved. Since especially soft tissue sarcomas predominantly develop metastases in the lungs [see *metastasis*], a chest *X-ray examination* as well as a *computed tomography* (CT) of the chest are indispensable. In addition, a *magnetic resonance imaging* (MRI) is performed to assess or, respectively, rule out metastases in the abdominal and pelvic region or the brain.

For all high-grade malignant soft tissue sarcomas (G3 sarcomas), a *bone marrow puncture* is done to rule out *bone marrow* involvement. Depending on the disease and treatment situation, additional tests to diagnose and/or further assess metastases may be done, such as an *ultrasound* or a *lumbar puncture* (to analyze the *cerebrospinal fluid* when dealing with skull base or spinal tumours), a total body MRI and/or a *positron emission tomography* (PET).

The positron emission tomography with 18-fluorodeoxyglucose (FDG-PET) is meanwhile increasingly used – combined with MRI (PET-MRI) or CT (PET-CT) – for children and adolescents with suspected metastases. Its advantage is that, aside from bone, it can also detect soft tissue metastases. So far, PET has not been established in every treatment centre, and its benefits for soft tissue sarcomas are still being examined.

7.4. Tests before treatment begins

Before treatment begins, further tests are needed in order to assess the condition of different organs. Therefore, the doctors will recommend an *electrocardiography* (ECG) as well as an ultrasound of the heart (*echocardiography*), an *electroencephalography* (EEC), a hearing test (*audiometry*), special diagnostics for determining kidney and lung functions as well as various blood tests. Any changes occurring during the course of treatment can be assessed and managed better based on the results of those initial tests, which thus help to keep the risk of certain treatment-related side effects as low as possible.

Psychosocial Care

A child's cancer is a stressful situation for the whole family. The psychosocial team of the clinic or later the aftercare facility provides advice and support to patients and their relatives from diagnosis to completion of treatment as well as during aftercare. Don't hesitate to take advantage of this offer.

It is an integral part of the treatment concept of all paediatric oncology centres in many countries. Here you will find comprehensive information on this.

8. Treatment planning

After the diagnosis has been confirmed and the spread of the disease has been assessed, therapy is planned. In order to design a highly individual, risk-adapted treatment regimen for the patient, certain individual factors influencing the patient's *prognosis* (called risk factors or *prognostic factors*) are being considered before and during treatment (risk-adapted treatment strategy).

Important prognostic factors are, for example, the type, the localisation, size and spread of the tumour. In addition, the patient's age has an impact on treatment planning.

- The type of the tumour (meaning its fine tissue features (*histology*) and *genetic* characteristics) impacts, amongst other factors, how fast the tumour grows and how the disease will respond to *chemotherapy* or another kind of *systemic* therapy (such as "new agent therapies"): there are, for example, chemosensitive and chemoinsensitive soft tissue sarcomas. The tumour type also impacts the risk of *metastasis* and the probability of relapse. Experts accordingly differentiate between soft tissue sarcomas with favourable and with unfavourable histology or genetics, respectively (*see also chapter "Tumour types"*).

- The site, size and extent of the tumour (including potential lymph node involvement and metastases) determine the options of surgical tumour removal and *radiation therapy* (radiotherapy).

- The patient's age is also considered for the decision with regard to systemic and/or radiotherapy. Hence, younger patients usually tolerate chemotherapy better than older children. For children under the age of three years (in particular under one year), radiotherapy is only rarely given, but still an option in individual cases.

All these factors are included in treatment planning in order to achieve the best outcome possible for each patient, while keeping the risks of side effects and long-term sequelae as low as possible.

Patients with rhabdomyosarcoma are — depending on whether their prognosis has been considered to be favourable or less favourable – assigned to different risk groups during therapy planning (low-risk group, standard-risk group, high-risk group), thus being treated according to different treatment plans. In Germany and other European countries, the differentiation according to risk groups with associated treatment plans is carried out according to the recommendations of the „European pediatric Soft tissue Sarcoma Study Group" (EpSSG) and the „Cooperative Weichteilsarkom Studiengruppe" (CWS Study Group).

9. Treatment

Treatment of children and adolescents with soft tissue 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 **goal of treatment** is to eliminate the cancer while keeping the risk of side effects and late sequelae as low as possible.

9.1. Treatment methods

Treatment options for children and adolescents with soft tissue sarcomas or rare soft tissue tumours include **surgery**, **radiotherapy**, systemic therapy (such as **chemotherapy** or a so-called **"new agent" therapy**) or a combination of those, respectively.

Individual treatment (meaning which types of therapy to be applied and in which order) depends in particular on the microscopical and *molecular genetic* tumour type, the localisation of the tumour, as well as on the patient's age. Treatment is also adapted to the extent of the tumour as well as to its surgical accessibility and sensitivity to chemotherapy (*see chapter „Treatment planning" above*). Since the treatment of soft tissue tumours can be associated with side effects, supportive treatment measures (*supportive therapy*) are also applied to prevent and/or treat these side effects. Here your will find further information on *supportive care* as well as on *recommendations for home*, the latter of which may be helpful during or after chemo- and radiotherapy.

9.1.1. Chemotherapy

Chemotherapy includes treatment with agents (so-called cytostatic agents or *cytostatics*), which inhibit cell growth, thereby contributing to eliminating the tumour and potentially existent metastases. In order to eliminate as many of the cancer cells as possible (even those that cannot be detected by diagnostic imaging techniques such as *magnetic resonance imaging*), a combination of cell and, thus, tumour growth inhibiting agents that have proven to be efficient in treating soft tissue sarcomas/tumours are used.

Frequently-used agents for rhabdomyosarcomas are, for example, actinomycin D (also known as dactinomycin), vincristine, cyclophosphamide, ifosfamide and doxorubicin (= adriamycin), in case of insufficient treatment response or in high-risk patients other agents, too. The combination of agents as well as their dosages and the duration of treatment vary depending on treatment or risk group. The cytostatic agents are given in multiple *chemotherapy* cycles with treatment pauses in between, which serve the patient's recovery.

9.1.2. Local therapy

In addition to chemotherapy, local tumour control is provided by *surgery* and sometimes *radiation therapy*. Surgical tumour removal may be performed both prior and after chemotherapy (primary or late resection, respectively), a potentially necessary radiotherapy either prior or after surgery (pre- or postoperative radiation). The CWS study centre and the CWS reference experts will help

the local caregiver team with decision-making regarding the treatment approaches for individual patients. For certain patient groups with rhabdomyosarcoma, the optimal treatment design will be evaluated in the framework of a new study (FaR-RMS).

9.1.2.1. Surgery

Surgery aims at complete tumour removal. Hence, it is frequently scheduled later in the treatment plan, in fact, after the tumour volume has been decreased by chemotherapy (experts call this „late resection“). This particularly applies to soft tissue sarcomas that are known to be very responsive to chemotherapy, which hence allows to expect tumour shrinkage. These tumours include rhabdomyosarcomas and some other tumours behaving like RMS (therefore previously also called ”RMS-like soft tissue sarcomas“).

Surgery as the first treatment choice (primary tumour resection) is usually per-formed only when, based on diagnostic imaging results, total gross tumour resection is possible without damaging healthy tissue. This is limited to very small tumours with favourable location. For patients with tumours less responsive to chemotherapy, primary surgery may also be an option as long as it is doable.

Surgery is carefully planned in the local treatment centre by representatives of all participating disciplines (*paediatric oncologist*s, surgeons, radiotherapists, *radiologist*s). The CWS study centre and the CWS reference expert group are standing by for advice. Since soft tissue sarcomas are rare, surgical treatments should only be performed in a centre with long-standing sarcoma experience.

9.1.2.2. Radiotherapy

Radiotherapy 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.

Radiotherapy is a very efficient treatment method for patients with eventually remaining soft tissue tumour tissue following surgery. It is a particularly favourable approach when surgery is not an option, for example for patients with rabdomyosarcoma in the head and neck area. Also, patients with a site-associated high risk of tumour spread (for example patients with rhabdomyosarcoma close to the *meninges* or inside the orbita) should receive *radiation therapy*. Patients with rhabdomyosarcoma (RMS) or a non-RMS-like soft tissue sarcoma (NRSTS) whose tumour could be resected completely by primary surgery do not require radiotherapy.

The radiation dose is calculated based on the tumour type, its localisation and extent, its response to chemotherapy as well as its surgical resectability. Conventional treatment uses total radiation doses of about 40-50 *gray*, given in single daily doses of 1.8-2 Gy. For individual cases, modern radiation techniques such as the so-called intensity-modulated radiotherapy (imrt) may be favourable. For certain tumour sites or age groups, proton therapy is increasingly used.

9.1.3. New therapy options – "new agent“ therapies

The term “new-agent“ therapy summarizes new types of *systemic* therapies (system therapies). These include targeted treatments with new agents that work in a different way compared to

chemotherapy. There is already a variety of promising medications, however, their use within the childhood population is mostly still limited to individual treatment settings.

Example: an already licensed targeted therapy for soft tissue tumours is the use of the NTRK-*inhibitor* Larotrectinib for patients with a so-called NTRK-positive infantile fibrosarcoma (a non-rhabdomyosarcoma-like soft tissue sarcoma, NRSTS). These patients have a NTRK gene fusion (NTRK is the abbreviation for neurotrophic tyrosine receptor kinase), which can be inhibited by Larotrectinib. The agent is the treatment of choice for metastatic disease and is even an option for tumours that are not surgically resectable. However, since data regarding length of treatment, development of *resistance* and long-term sequelae are still limited, the use of these agents versus the option of chemotherapy requires careful consideration. Children with this disease have been treated with chemotherapy and surgery for many years and show excellent prognosis.

Good to know: future studies using these kinds of agents are being planned. The treatment of children according to such studies should definitely be given preference over any individualized treatment regimen. Only in this way can valid data be acquired that will serve to optimise future therapies.

9.2. Treatment of patients with rhabdomyosarcoma (RMS)

In Germany and other European countries, patients with rhabdomyosarcoma (RMS) are treated according to recommendations of the “European pediatric Soft tissue Sarcoma Study Group” (EpSSG) and the “Cooperative Weichteil-sarkom-Studiengruppe” (CWS).

Depending on the patient’s risk factors, rhabdomyosarcoma are divided into four different risk groups: one low-risk group, one standard-risk group and two high-risk groups. The upcoming European treatment guideline (ERN-Guidance) is considering a joint “very high risk-group” (VHR) for high-risk patients – such as patients with alveolar rhabdomyosarcoma with lymph node involvement (lymph node positive ARMS) or patients with metastasized RMS disease.

Treatment for the different risk groups is as follows:

- **Low-risk group:** for the low-risk group, treatment consists of total gross tumour resection and a chemotherapy with the agents vincristine and actinomycin D (dactinomycin) for about 22 weeks.
- **Standard-risk group:** in the standard-risk group, surgery and chemotherapy are also done; the latter includes, aside from vincristine and actinomycin D, additionally ifosfamide, and most patients also receive radiotherapy (time of therapy about 25 weeks). .
- **High-risk groups:** in both high-risk groups, surgical tumour removal is planned either prior to chemotherapy or later, depending on the site and extent of the tumour. All patients in these groups receive radiotherapy. Chemotherapy includes ifosfamide, vincristine, actinomycin D, and sometimes doxorubicin (adriamycin) and takes about 25 weeks. As mentioned above, RMS patients with metastases will be included in the one high-risk group according to the ERN Guidance in the future.

9.3. Treatment of patients with non-RMS soft tissue sarcoma (NRSTS)

The wide variety of tumours in the group of non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) is not only mirrored by their growth pattern, malignancy, operability and chemosensitivity; it also impacts the type of treatment to be considered for the individual patient:

There are NRSTS that are about as chemosensitive as rhabdomyosarcomas, for example the synovial sarcomas and the undifferentiated sarcomas. Patients with these tumour types (also called “RMS-like soft tissue sarcomas” in the past) are treated quite similarly to high-risk patients with RMS (*see chapter „Treatment of patients with rhabdomyosarcoma“*). The treatment takes about 25 weeks, depending on the therapy group.

A large group of the rare NRSTS, the so-called „adult-type“ NRSTS (named that way because they also appear in adults) are often not chemosensitive. New treatment options are currently tested for patients with these tumours, mainly in the framework of new trials (*see chapter “New agent therapy” above*). Some other of these rare NRSTS are rather benign; treatment in this case involves mainly a so-called extended resection, which is defined by surgical removal of the tumour with a certain safety distance, meaning removal of adjacent tissue surrounding the tumour. For some patients with NRSTS, the type of treatment also depends on the size of the tumour and the success of surgery.

Important to know: the treatment spectrum for this inhomogenous disease group is quite large, and new treatment options are being tested. Your caregiver team will explain to you, which therapy options exist for you/your child.

9.4. Treatment of patients with rare soft tissue tumours

Treatment of patients with a rare (frequently intermediate malignant or benign) soft tissue tumour mainly depends on its growth pattern. For tumours growing locally very aggressively (this can be the case for both benign and intermediate malignant tumours), surgery aiming at tumour removal is not always the first choice of treatment. For most of these tumours, the doctors will wait and see whether growth is ongoing, since spontaneous tumour regression is possible as well. If this does not happen or if the localisation of the tumour jeopardizes adjacent organs, a low-dose chemotherapy, depending on the tumor type, is indicated. By now, even newer, so-called targeted therapies (that consider the individual genetic alterations) are an option as well.

9.5. Treatment of RMS patients with metastases or relapse

According to the current CWS Guidance and the upcoming European ERN Guidance, patients with metastatic disease [see *metastasis*] of rhabdomyosarcoma receive chemotherapy. Local treatment (radiotherapy, surgery) plays an important role.

According to the current CWS Guidance and the upcoming European ERN Guidance, patients with metastatic disease of rhabdomyosarcoma receive chemotherapy. Local treatment (radiotherapy, surgery) plays an important role. These are either given as pills (orally) or *intravenous*ly once a week, so that treatment can almost exclusively be done on an outpatient basis. Total duration of

therapy takes about one year; the upcoming trial FaR-RMS is testing the efficacy of an extended maintenance to up to 24 months. In general, an oral-only maintenance therapy as per CWS Guidance with the agents trofosfamide and etoposide (in short: O-TIE) is an option, too; in this case, treatment will take about a year or even longer in individual situations.

Patients with a particularly unfavourable prognosis can participate in so-called experimental trials. Your caregiver team will inform you whether one of those experimental treatment approaches is an option for your child. For patients whose disease does not respond to chemotherapy or with a recurrent disease, treatment is based on the frontline therapy. Usually, different and partially new agents are given that are not necessarily part of the standard treatment plans, but allow hope based on most recent research results.

10. Therapy optimising trials and registries

In the large paediatriac treatment centres, children and adolescents with a soft tissue tumour receive therapy according to standardised treatment plans (protocols). These protocols are designed by experts and aim at steadily improving the patients' survival rates while also reducing the risk of therapy-related late effects. Therapy according to such treatment protocols is carried out within „*therapy optimising trial*s". These are controlled clinical trials, which have been developed, are being monitored and adjusted to the most recent research by the Society of Paediatric Oncology and Haematology ("Gesellschaft für Pädiatrische Onkologie und Hämatologie", *GPOH*).

For patients who are not being treated within a trial (such as the upcoming trial FaR-RMS), there is a registry („**SoTiSaR / from 2024 SoTiSAR 2.0**") to collect all relevant patient data. These patients receive the currently recommended standard treatment, so far as per CWS Guidance (guidance of the CWS Study Centre), in the future as per European guidance (ERN Guidance) for patients with rhabdomyosarcoma. In addition, a randomized study („CWS-2007 HR") had been available for certain patients until 30/06/2019. The opening of a new trial for patients with rhabdomyosarcoma or relapsed rhabdomyosarcoma (**FaR-RMS**) is considered to start in 2023/2024.

For further information on above-mentioned registries and guidelines, please see here. Details are available on the website of the CWS Study Group: *https://www.klinikum-stuttgart.de/cws/home*

11. Prognosis

Prognosis for children and adolescents with a soft tissue tumour depends on multiple factors. Most relevant are the type, localisation and size of the tumour, its spread, operability (resectability) and the patient's age.

Over the past four decades, *prognosis* for patients with soft tissue tumour has improved drastically due to standardised treatment based on *therapy optimising trial*s. At the end of the 70s, still only 30 to 40 % of all children survived, while the 10-year survival rate is now a bit over 70 % due to continuous treatment optimisation.

In favourable constellations, long-term survival can be observed in over 80 % of patients, while the chance of long-term cure decreases for patients with large, inoperable tumours at diagnosis. Similar, even more unfavourable outcomes have been reported for patients presenting with lymph node involvement and/or spread into other body sites at the time of diagnosis. For example, for patients with a metastasised RMS-like soft tissue sarcoma, the 5-year-survival rate is currently 30 %. Various studies aim at improving the prognosis for these patients as well.

Note: The above-mentioned numbers are statistical values. Therefore, they only provide information on the total cohort of patients with these types of tumour. They do not predict individual outcomes. Please ask the doctor, who is responsible for your child, for competent information on the 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.
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).
biopsy	removal of a tissue sample for subsequent (mainly microscopic) examination; this can be done, for example, by puncture with a hollow needle, with the use of special instruments (such as forceps, punching instruments, probes) or surgically with a scalpel.
bone marrow	site of blood formation; spongy tissue with a strong blood supply that fills the cavities inside many bones (e.g., vertebrae, pelvic and thigh bones, ribs, sternum, shoulder blade, and collarbone); in the bone marrow, all forms of blood cells develop from blood progenitor cells (blood stem cells).
bone marrow 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.

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.
carcinoma	malignant tumour resulting from degenerated epithelial tissue (e.g. skin, mucous membranes, glandular tissue);
cell	the smallest functional unit in organisms with the ability to perform metabolism, involuntary muscle movement and reproduction and to respond to stimuli; each cell contains a nucleus and a cell body (cytoplasm) and is externally bounded by the cell membrane.
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.
cerebrospinal fluid	fluid produced by cells of the cerebral ventricles; it floats around the brain and spinal cord to protect them from injury and provide them with nutrients.
chemotherapy	here: use of drugs (chemotherapeutic agents, cytostatics) for the specific inhibition of tumor cells in the organism
computed tomography	imaging, X-ray diagnostic procedure; it produces an image by computer-controlled evaluation of a large number of X-rays from different directions. This makes it possible to produce sliced images of body parts (tomograms, transverse or longitudinal sections of the human body)
contrast agent	substance that can be used to improve the visualization of structures and functions of the body in imaging techniques; contrast agents are mainly used in X-ray diagnostics (X-ray examination, computed tomography), magnetic resonance imaging (MRI) and ultrasound examinations.
cytostatics	drugs that inhibit cell growth; cytostatics can affect the metabolism of different types of cells, thereby destroying them and/or

	preventing them from multiplying. Cells that divide frequently are particularly affected.
DNA	abbreviation for deoxyribonucleic acid; it carries the genetic information and is found in all living beings. DNA contains the genes that provide the information for the production of ribonucleic acids (RNA) or proteins. It is a large molecule consisting of two nucleic acid chains twisted into a double helix. The individual chains consist of a sequence of four different building blocks (bases), the order (sequence) of which determines the genetic code.
echocardiography	ultrasound examination of the heart to check its performance (cardiac function); the position or structure of the heart valves and walls, the wall thickness of the heart muscle, the size of the heart and the ejected blood volume (pumping function of the heart) are examined and assessed, among other things.
electrocardiography	method of measuring the electrical activity of the heart
electroencephalography	method of recording the electrical activity of the brain; the electroencephalogram (also abbreviated EEG) is the graphical representation of this electrical brain activity. Its evaluation can provide evidence of brain dysfunctions.
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.
Epstein-Barr virus	causative agent of glandular fever;
exophthalmus	pathological protrusion of the eyeball from the eye socket on one or both sides;
genetic	concerning the (level of) inheritance or genes; inherited
Gorlin-Goltz syndrome	a hereditary disease associated with a number of developmental disorders and a predisposition to various cancers, the most common being a form of skin cancer (basal cell carcinoma);
GPOH	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 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)
haemangioma	benign neoplasms of blood vessels (sometimes also referred to as blood sponges) mainly in the skin, but also, depending on the type of haemangioma, in other organs; haemangiomas develop in the first few weeks of life or are already present at birth, but usually regress on their own within a few years.
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
HIV	abbreviation for "human immunodeficiency virus"; HIV belongs to the retrovirus family. After an incubation period of varying lengths, usually several years, an infection leads to AIDS (acquired immunodeficiency syndrome), an immunodeficiency disease that is currently still incurable.
imaging	diagnostic procedures generating images of the inside of the body, such as ultrasound and X-ray examination, computed tomography, magnetic resonance imaging, and scintigraphy
immunohistochemical	in an immunohistochemical or immunohistological examination, proteins or other cell or tissue structures are visualized with the help of labeled antibodies (e.g. bound to dyes).
infection	penetration of the smallest organisms (e.g. bacteria, viruses, fungi) into the body and subsequent multiplication within it. Depending on the characteristics of the microorganisms and the immune system of the infected person, various infectious diseases can occur after infections.
inhibitor	the term derives from „inhibition“ (= hindering); a substance that influences one or more biochemical reactions thereby slowing it down or completely preventing it
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.

Li-Fraumeni syndrome	cancer predisposition syndrome characterized by the increased occurrence of various solid tumours within a family; in childhood and adolescence, tumours of the adrenal glands, as well as soft tissue sarcomas, leukaemias and CNS tumours are most commonly observed, in adulthood mainly bone tumours (osteosarcomas), breast cancer and lung tumours. In most cases, there is a change (mutation) of the so-called tumour suppressor gene TP-53 (protein p53).
lipoma	benign tumour that develops from cells of adipose tissue
lumbar puncture	puncture of the spinal canal in the lumbar spine, e.g. to remove cerebrospinal fluid (CSF) or for the purpose of administering medication (so-called intrathecal treatment); in the case of cancer, a sample and examination of cerebrospinal fluid can be used to detect malignant cells; in the case of increased intracranial pressure due to a CNS tumour, cerebrospinal fluid removal (CSF) is also used to relieve pressure.
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.
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.
meninges	layers of connective tissue that protectively envelop the brain; the three meninges are joined to the outside by the skull bones. In the area of the spinal cord, the meninges merge into the three-layered spinal cord membrane, which surrounds the rest of the central nervous system.
mesenchymal stem cells	stem cells of connective tissue; they are found in various types of tissues (such as bone marrow, bones, skeletal muscles, cartilage, blood, adipose tissue, connective tissue of the skin) and can develop into different types of cells (including bone, cartilage, muscle, fat cells).
metastasis	1. tumour spread from the primary site of tumour to other parts of the body; characteristic feature of malignant tumours (cancer). 2. collective term for a disease process characterized by malignant

	cells spreading from their primary site to other areas of the body via the bloodstream and/or the lymphatic system.
molecular genetic	referring to structure, formation, development, function and interactions of cells and cell building blocks (e.g. nucleic acids, proteins) at the molecular level; the focus is on the analysis of the genetic information stored in the nucleic acids (DNA and RNA) and its processing in the context of protein synthesis as well as gene regulation.
neurofibromatosis	hereditary disease that leads to tumours of the nerve sheaths, meninges and glia (the "connective tissue" of the nervous system). Clinically and molecular-genetically, two forms of neurofibromatosis can be distinguished, which are caused by different genetic defects: 1. Peripheral neurofibromatosis (NF1, also known as Recklinghausens disease): this is characterized by so-called café-au-lait spots on the skin and a predisposition to various tumours (including neurofibromas, gliomas of the optic nerve, iris hamartomas as well as astrocytomas and pheochromocytomas). 2. Central neurofibromatosis (NF2): it is characterized by mostly (bilateral) neuromas of the auditory nerve (acusticus), which can lead to deafness, facial paralysis and mental disturbances. There is also an increased risk of tumours (e.g. astrocytomas, spinal ependymomas). Neurofibromatosis is one of the so-called phacomatoses.
paediatric oncologist	paediatrician who is specialized on the management of children and adolescents with cancer
pathologist	a physician who identifies diseases and determines the malignancy of tumours by means of histological and molecular genetic examination of cells and tissues
peripheral nervous system	can be described as the receiving and executing organ of the central nervous system (CNS); it consists of the numerous nerves that run through the body; they carry impulses either from the periphery to the CNS (sensory nerve pathways) or from the CNS to the periphery (motor nerve pathways). The peripheral nervous system includes, for example, the cranial nerves, spinal cord nerves and peripheral nerve cells.
physical examination	an important part of diagnostic examinations; includes palpation and listening to certain body organs as well as testing reflexes to obtain indications of the nature or course of a disease.
positron emission tomography	an imaging, nuclear medicine procedure based on the principle of scintigraphy, which can be used in cancer medicine to visualize

	tumours or metastases. To detect tumour tissue, a radioactively labeled sugar compound is administered. Since tumours have a higher metabolism than healthy tissue, the radioactive substance is increasingly taken up and stored by the tumour cells. The tumour cells enriched with this substance emit signals that are captured by a special camera (PET scanner) and converted into an image (tomogram).
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 exposure	the dose of ionising radiation to which humans are exposed from natural, civilised or artificial sources of radiation; natural sources of radiation include cosmic, terrestrial and natural radioactive substances produced by the decay of natural radioactive substances, which are absorbed into the body with drinking water, food and breathing air. Artificial sources include radiation produced by the technical and medical use of nuclear and atomic forces, such as X-rays.
radiation therapy	controlled use of ionizing (high-energy) radiation for the treatment of malignant diseases
radiologist	a physician specialized in diagnostic imaging and radiotherapy
resistance	here: insensitivity of cancer cells to certain cell growth-inhibiting drugs (cytostatics)
rhabdomyosarcoma	the most common soft tissue sarcoma in childhood and adolescence
soft tissue	soft tissues include connective, fat, and muscle tissue, as well as blood vessels and peripheral nerve tissue (nervous system without the brain and spinal cord). The soft tissues thus include all non-epithelial tissues of the body with the exception of the supporting tissue (bone and cartilage). They connect, support and surround the other parts of the body and organs.
solid tumour	solid, localized increase of the bodys own tissue; solid tumours can originate from various tissues and can be benign or malignant; only the malignant ones are considered as cancers. Solid tumours include all cancers that do not affect the haematopoietic or

	lymphatic system. The latter are systemic malignancies. The most common solid tumours in childhood and adolescence are brain tumours, followed by neuroblastoma and soft tissue sarcomas.
supportive therapy	supportive treatment measures to prevent, alleviate or treat disease and/or treatment-related side effects or complications; supportive therapy is designed to improve the patients quality of life.
surgery	surgical intervention on or in the body of a patient for the purpose of treatment, less often also in the context of diagnostics; the surgical intervention is carried out with the help of special instruments, generally with the patient under anesthesia.
symptom	sign of illness
systemic	covering/includiing the entire body
therapy optimising trial	a controlled clinical trial (study) that aims to provide the best possible treatment for patients and at the same time to improve and develop treatment options; therapy optimisation is aimed not only at improving the chances of recovery, but also at limiting treatment-related side effects and long-term effects.
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.
Werner`s syndrome	very rare, genetic disease associated with premature aging and an increased risk of cancer; the first symptoms appear in early puberty (short stature; weak, high-pitched voice), the full manifestation of the disease presets around the age of 30 years. Symptoms include, for example, characteristic skin changes, whitish and sparse scalp hair, bilateral cataracts, type II diabetes mellitus, arteriosclerosis, muscle breakdown and osteoporosis. In addition, patients with Werner syndrome have an increased risk of malignant tumours. The disease is inherited in an autosomal recessive manner and is one of the cancer predisposition syndromes.
WHO	abbreviation for World Health Organization; international federation for cooperation in the field of public health
X-ray examination	imaging procedure that uses X-rays to visualize organs or parts of organs

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