Hepatoblastoma (Brief information)

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1. General information on the disease

Hepatoblastomas are highly malignant solid tumours of the liver. Since they develop directly in the liver, they are also called *primary* liver tumours in order to distinguish them from cancers of other body parts that have spread to the liver (liver metastases). Already before birth, hepatoblastomas arise from degenerated precursor cells of liver tissue. Since degeneration of these precursor cells can happen during different phases of liver development, various histological types of hepatoblastoma exist (for example fetal or embryonal hepatoblastoma); some hepatoblastomas can also include differently matured precursors of other tissues. The various tumour types partially also differ with regards to their growth patterns.

Hepatoblastomas preferably develop in the right lobe of the liver. They are mostly single, large, well-perfused tumours that are limited to one area of the organ (unifocal). Only about 15 % of the patients present with tumours in multiple liver areas (multifocal), thereby indicating aggressive growth behaviour. Very rarely, hepatoblastoma extends beyond the liver (extrahepatic). Tumour spread via the blood stream with development of daughter tumours (distant metastases) is mostly seen with progressive disease; the lungs are frequently affected. Hence, about 10 to 20 % of patients present with lung metastases at the time of diagnosis. Metastasis via the lymphatic system is rather rare.

2. Incidence

Hepatoblastoma is the most frequent primary liver tumour in childhood and adolescence and the third most frequent abdominal tumour in this age group (following neuroblastoma and nephroblastoma). According to the German Childhood Cancer Registry (Mainz, Germany), about 2 of 1,000,000 (in total approximately 25) children and adolescents under 18 years of age are diagnosed with hepatoblastoma in Germany per year, which accounts for about 1 % of all paediatric malignancies in this age group. The incidence of hepatoblastoma has increased globally during the last few decades, assumably in the context of the increasing number of premature births and low birth weight (*see chapter „Causes“*).

As hepatoblastomas are embryonal tumours, the mostly occur in newborns, infants and toddlers, that is, in early childhood: The majority of patients is between six months and three years old. The average age of patients at diagnosis is 1.5 years. Children over the age of four are very rarely affected. Overall, boys are more frequently affected by the disease than girls (gender ratio: 1.4:1).

3. Causes

The underlying causes for the development of hepatoblastoma are still not completely understood. A prenatal trigger is being assumed. It is known, that premature babies and children with very low birthweight have an increased risk of developing hepatoblastoma later in life. Both of these factors

are increasing in first world countries and hence, a higher global incidence of hepatoblastomas is being recorded.

Some hepatoblastoma can also be associated with so-called cancer predisposition syndromes, rare hereditary diseases characterized by mutations that (compared to healthy individuals) are connected with a higher risk of developing a malignancy. Cancer predisposition syndromes that play a role in the development of hepatoblastoma are, for example, Beckwith-Wiedemann syndrome (BWS), Edwards' syndrome (trisomy 18) and Familial adenomatous polyposis (FAP).

Furthermore, various genetic and chromosomal changes have been identified in the majority of hepatoblastoma cells. These modifications are known or supposed to be at least partly responsible for tumour development, even in patients without a tumour predisposition syndrome. In these patients, the disease arises as a result of spontaneous mutations or other genomic changes in the cell's DNA.

4. Symptoms

Like other abdominal tumours, hepatoblastomas usually present as visible and palpable, painless abdominal tumours, for example during a routine physical exam. Aside from that, particularly in case of progressed disease, patients may show general symptoms such as fever, fatigue, loss of appetite and unintended weight loss as well as abdominal pain and nausea. The tumour may also cause fluid retention in the abdomen (ascites) and / or anaemia.

Impaired liver function, for example presenting as a yellowing of the skin, mucous membranes and the white in the eyes (jaundice) or as an increased risk of bruising and bleeding, is less frequent. Also, tumour rupture and precocious puberty are rather rare presenting symptoms.

5. Diagnosis

If the doctor thinks that the young patient's history and physical exam 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. Clinical exams and laboratory tests

The caregiver team at the hospital will first take a thorough history followed by a physical exam. In addition, there will be blood tests. Of particular interest are certain substances in the blood (so-called tumour markers), which – if their levels are increased – can be indicative of hepatoblastoma. 80 to 90 % of patients with hepatoblastoma present with severely increased levels of a substance called alpha-1-fetoprotein (α-Fetoprotein, AFP). The tumour marker β-HCG is increased in about 60 % of patients.

5.2. Imaging tests for tumour detection and the assessment of tumour spread

Using ultrasound (sonography) of the abdominal organs, the location, extent, structure and blood supply of a hepatoblastoma can be visualized. In order to obtain a more comprehensive and detailed diagnosis, additional diagnostic imaging such as magnetic resonance tomography/imaging (MRI) and, less frequently, computed tomography (CT) are required. They are done using contrast medium and provide better assessment of the tumour with regard to its extent within the liver and adjacent tissue as well as a possible invasion of a large vein or lymph node involvement, respectively. Furthermore, these methods may give hints regarding tumour type. Since the patients are young, those scans are done in sedation. For identifying potential metastases, lung x-rays and CT, also with contrast medium and in sedation, are performed.

5.3. Tissue removal (biopsy)

For final diagnosis, histological examination of tumour tissue is needed. The required sample can be obtained via abdominal surgery (laparotomy), which also aims at tumour removal (so-called open biopsy). Alternatively, percutaneous punch biopsy is an option. This approach involves the sampling of multiple tissue cylinders from the tumour, guided by ultrasound and done mostly in sedation. A laparoscopy is done rarely. The choice of biopsy technique depends on multiple factors, including the size and operability of the tumour.

Good to know: children aged between six months and three years may be spared from biopsy, when imaging shows a liver tumour accompanied by elevated AFP-levels in the patient's blood (higher than 1.000 ng/ml), and when this level is also three times as high as the normal reference at that age. According to experience, it is well-known that these scenarios are in accordance with the diagnosis of hepatoblastoma. In the framework of research studies, however, a biopsy might be recommended for obtaining more detailed histological information as well as for molecular genetic testing.

5.4. 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) 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.

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.

6. Treatment planning

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

Important prognostic factors are the localisation and the extent of the tumour at diagnosis and, thus, its operability (*see chapter regarding stages of disease below*). Complete removal of the tumour and of potential metastases has a big impact on the patient's prognosis, and therefore the exact evaluation of the stage of the disease is crucial for valid risk assessment and treatment planning. Since most patients receive a chemotherapy prior to surgery to shrink the tumour, the response to this preoperative therapy has an effect on prognosis, too.

Additional relevant prognostic factors include the patient's age at diagnosis, the level of certain laboratory parameters (alpha-1-fetoprotein, AFP), and the histological characteristics of the tumour. All these factors are included in treatment planning in order to achieve the best outcome possible for each patient.

6.1. Staging of hepatoblastoma based on the extent of the disease (PRETEXT grouping system)

Assessment of the stage of the disease is based on the so-called PRETEXT grouping system ("PRETEXT" means "pre-treatment extension") of the hepatoblastoma study group of the International Society of Pediatric Oncology (SIOPEL). This system considers – using diagnostic imaging – the tumour extent within the liver prior to surgery (preoperatively): depending on how many of the four (surgically relevant) liver sections of a liver lobe are affected, four stages of disease are defined (I-IV).

Assessment of tumour extent also takes under consideration whether the large liver vessels, such as the portal vein (P) or liver veins (V), are affected by the hepatoblastoma or whether the tumour has grown beyond liver tissue (E, for extrahepatic growth), whether there is multifocal extent (F), tumour rupture (R) or lymph node involvement (L) at the time of diagnosis, or whether there even are distant metastases (M), respectively. Such findings are known as additional risk factors and documented with the assigned capital letters.

6.2. Staging of hepatoblastoma based on risk groups

The previously assessed extent of the disease as well as additional prognostic factors result in therapeutical consequences, for example with regard to decision-making of tumour removal (resection) versus transplant or how intensive chemotherapy should be, respectively. In order to provide optimal individual therapy, patients are assigned to risk or treatment groups with different treatment plans. The higher the patient's risk of relapse, the more intensive will usually be his treatment.

Good to know: The international therapy optimising trial PHITT, which is currently open for recruitment of all patients with newly diagnosed hepatoblastoma, differentiates between a total of four risk groups.

7. Treatment

Treatment of children and adolescents with a liver tumour should take place in a children's hospital with a paediatric oncology program. Only in such a childhood cancer centre, highly experienced and qualified staff (doctors, nurses and many more) is guaranteed, since they are specialized and focus 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 and treat their patients according to treatment plans (protocols) that are continuously optimised.

The **goal of the treatment** is to achieve higher cure rates while avoiding side effects as much as possible.

7.1. Treatment methods

Treatment of children and adolescents with hepatoblastoma includes **surgery**, the goal of which is to remove the tumour, and almost always **chemotherapy**. For some patients, **liver transplantation** may be an option. According to current knowledge, radiotherapy is not effective in hepatoblastoma treatment. The individual treatment choice is based particularly on the type, site and extent (thus, operability) of the tumour as well as on other prognostic factors (*see chapter „Treatment planning“*). The overall treatment duration takes about nine to twelve months.

Treatment of a patient with hepatoblastoma is mainly based on two columns: chemotherapy and surgical tumour removal. Gross complete tumour resection is the most important factor for the patient’s probability of survival.

In rare situations of a small single tumour (for example PRETEXT stage I or even II), surgery is an immediate option to remove the tumour. However, in most patients, hepatoblastoma is already too large for successful surgery at the time of diagnosis or presents with lung metastases, respectively. For these patients, chemotherapy prior to surgery serves to shrink the tumour volume for subsequent removal. Since most hepatoblastomas respond well to chemotherapy, this strategy has proven successful in up to 90 % of patients.

Following preoperative chemotherapy, response to treatment and surgical options are reassessed. In case the tumour has not responded sufficiently to chemotherapy, additional cycles of chemotherapy can be an option. Following surgical removal, chemotherapy will be continued (postoperative chemotherapy) with the goal to eliminate potentially remaining tumour cells, thereby minimizing the risk of relapse.

7.1.1. Chemotherapy

Chemotherapy uses drugs (so-called cytostatic agents) that can kill fast-dividing cells, such as cancer cells, or inhibit their growth, respectively. In order to optimize treatment efficacy, multiple agents are being used in different combinations and given in blocks. Usually, chemotherapy involves two major phases: preoperative induction chemotherapy and postoperative chemotherapy (consolidation).

The most important cytostatic agent is cisplatin, which can also be given in combination with other medications (such as carboplatin, doxorubicin, vincristine, 5-fluorouracil and etoposide). The intensity of chemotherapy (total dose, number of treatment cycles) is based on the risk group the patient has been assigned to due to the individual extent of the disease. The more progressed the disease is, the more intense will treatment be.

7.1.2. Surgical tumour removal

Gross total tumour resection as well as the removal of distant metastases, if present, are crucial for the patient's probability of survival. Hence, even for large hepatoblastomas, extended removal (including sufficient surrounding safety margin within normal tissue) is attempted. This is eventually achieved by using special techniques, for example by occluding both efferent and afferent blood vessels. Frequently, complete liver segments or even a complete liver lobe are removed. The latter is also known as lobectomy. Also, distant metastases diagnosed by imaging require removal after chemotherapy.

7.1.3. Liver transplantation

For patients for whom surgical tumour removal carries too high a risk, the option of a liver transplant can be evaluated. This may affect patients who, for example, have been diagnosed with a multifocal hepatoblastoma involving all four sectors (PRETEXT IV). In those situations, it is rather unlikely, that all metastases can be surgically removed. Also, patients with stage PRETEXT IV and blood vessel involvement, whose tumour stage does not decrease to stage III upon chemotherapy, maybe considered for a liver transplant.

7.1.4. Further treatment methods

If the tumour does not respond to chemotherapy, or for any other reasons that do not allow tumour removal or liver transplant to be an option, other treatment strategies need to be considered. The most promising approach is the so-called chemoembolisation. This involves the injection of certain agents bound to carry substances in the afferent blood vessels, thereby occluding (embolising) them. Aim of this local chemotherapy is to shrink the tumour volume by destroying tumour cells. For some patients, this makes subsequent surgical removal possible or bridge the time until liver transplant. This approach, however, can be associated with complications and hence, thorough assessment of the individual benefit-risk-ratio is crucial.

Other strategies as used in adults with liver tumours (such as laser therapy, cryoablation, radiofrequency ablation) are currently only considered for children and adolescents in palliative treatment settings.

8. Therapy optimising trials and registries

In Germany, the majority of the children and adolescents with neuroblastoma in receive therapy according to the treatment plans of therapy optimising trials or registries. Therapy optimising trials are standardised and controlled clinical trials that aim at steadily developing and improving treatment concepts for sick patients based on the current scientific knowledge.

Patients who cannot participate in any study, for example because none is available or open for them at that time or since they do not meet the required inclusion criteria, respectively, are often included in a so-called registry. Such a registry primarily serves to acquire disease- and treatment-associated data, which are supposed to help structuring the knowledge about the disease and its management, thereby continuously optimizing treatment. Furthermore, the registry centre supports the doctors at site with (non-commital) treatment recommendations based on the most recent data on best treatment options, in order to provide the patient with optimal therapy even without the framework of a clinical study.

The following trials and registries for treatment of children and adolescents with hepatoblastoma are currently active in Germany (with international participation):

- **Trial PHITT:** Since September 2018, children, adolescents and young adults (under 30 years of age) with a newly diagnosed hepatoblastoma or hepatocellular carcinoma can be recruited into the **P**aediatric **H**epatic **I**nternational **T**umour **T**rial (PHITT). All large study groups are participating in this trial worldwide; numerous childrens‘ hospitals and treatment centres all over Germany and other European as well as non-European countries participate in this trial. The German trial centre is located at the Ludwig-Maximilians-University Munich (Dr. von Hauner Children’s Hospital), with Prof. Dr. med. Irene Schmid as the national coordinating investigator.

- **GPOH Lebertumorregister** (liver tumour registry of the Germany Society for Paediatric Oncology and Haematology): Registry for children, adolescents and young adults (aged 0-20 years) who are diagnosed with a malignant or benign liver tumour in Germany. The registry was opened in 2011 after cessation of the therapy optimizing trial HB99 and has been serving particularly for data acquisition since, with the aim to improve the understanding of the disease, thereby optimising future treatment options. The study group has also been involved in the development of the PHITT study (*see above*). Prinicipal investigator is Prof. Dr. med. Irene Schmid (Dr. von Hauner Childrens‘ Hospital, Ludwig-Maximilians-University München, Munich, Germany). Patients who are not eligible to be treated as per PHITT study can be registered within the registry also in the future. The study centre will provide treatment recommendations.

9. Prognosis

The probability of survival for children and adolescents with hepatoblastoma depend on the extent of the disease, the response to chemotherapy and the possible extent of tumour removal. Total gross tumour resection is crucial for a favourable prognosis.

Over the past 10 to 20 years, the options of chemotherapy could be significantly optimised, so that improved cure rates for patients with hepatoblastoma are increasingly achieved. According to the German Childhood Cancer Registry, a total of about 85 % of all hepatoblastoma patients achieve cure (10-year survival). Individual prognosis, however, depends primarily on the stage of the disease at the time of diagnosis and, thus, on the risk group the patient has been assigned to:

Patients in risk groups “very low” and “low” have the most favourable prognosis. Since their disease usually responds very well to chemotherapy, the probability of a total tumour resection is over 90 %, with correspondingly high survival rates (5-year-survival rate of 90 %). Patients with “medium risk” have a 5-year-survival rate of about 70 to 80 %, whereas patients with “high risk” have shown a 5-year-survival rate of 50 to 60 and thus a less favourable prognosis. The liver tumour experts are hoping for an increase in cure rates due to the PHITT-study.

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

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