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Hepatoblastoma

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Abstract: Hepatoblastoma is the most common liver cancer in children aged 3 years and younger. The differential diagnosis of this neoplasm is crucial for the proper management. Recent additions to protocols of the International Society of Pediatric Oncology and Children's Oncology Group have been key in tackling this oncological disease. This chapter provides an overview of the etiology, pathogenesis, epidemiology, incidence, symptoms, and therapeutic considerations of hepatoblastoma. The diagnostic measures necessary from a surgical point of view and the essential operational and technical considerations for the various stages of hepatoblastoma are discussed.

Keywords: etiology; diagnosis; hepatoblastoma; risk assessment; therapeutic considerations

INTRODUCTION

Primary liver tumors are a heterogeneous group of epithelial and mesenchymal tumors. They make up between 1 and 2% of all pediatric tumors. They are rare in childhood, and about two-thirds of primary liver tumors are malignant. It has been estimated that about 37% of primary liver tumors are hepatoblastomas (1).

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Hepatoblastoma typically occurs in infants and toddlers. It occurs predominantly in a unifocal manner in the right liver lobe, but it can be multifocal and develop in all liver segments. Well-developed hepatoblastoma may mimic hepatocellular carcinoma. Hematogenous lymph nodal metastases have been reported (2). If hepatoblastoma is completely resectable, the prognosis is favorable, primarily because it responds well to adjuvant chemotherapy. If it cannot be removed completely due to late diagnosis, the prognosis is far less favorable, because hepatoblastoma cells develop resistance to cytostatics after repeated chemotherapy, limiting therapeutic success (3). To optimize the treatment of malignant childhood liver tumors, especially hepatoblastoma, the international cooperative therapy study "Pediatric Hepatic Malignancy International Therapeutic Trial (PHITT)" was initiated in 2015. The scope of the study was to examine the genetic and molecular changes that may enable therapy stratification, as with other embryonic tumors (4, 5). The implementation of this study began at the end of 2017 (https://www.birmingham.ac.uk/research/crctu/trials/phitt/investigators.aspx [accessed on 18 February 2021]).

ETIOLOGY

The etiology of hepatoblastoma, which usually occurs sporadically, has not yet been clarified. Somatic gene mutations in hepatoblasts and other observations suggest tumor development is spontaneous (6). It is believed that premature children with a very low birth weight (<1,500 g) have an increased risk of developing malignant tumors, including hepatoblastoma. This fact, which was first reported in 1997 (7), was confirmed by a worldwide scientific study in 2019. Still, an explanation for this observation - accidental or causal connection - could not be established (8). The fact that relatively common conditions such as pre-eclampsia, fetal distress before or during childbirth, or congenital malformations could play roles as possible tumor inducers could allegedly be statistically determined in some studies, but an explanation for these observations is still missing (9). Regardless of these observations, over the last few decades, various genetic diseases have been found to be risk factors for developing hepatoblastoma. Some of them include familial adenomatous polyposis (10), Beckwith-Wiedemann syndrome (11), and trisomy 18 (Edwards syndrome) (12). A connection between the occurrence of hepatoblastoma with other genetic diseases such as Li-Fraumeni syndrome or Prader-Willi syndrome has been discussed, but the link has not yet been proven satisfactorily (13). Finally, various external and epigenetic influences have been debated as possible causes for neoplastic development. Smoking before and/or during pregnancy is an example of this; opinions on this, however, are equivocal (6, 14).

PATHOGENESIS

Hepatoblastomas develop from degenerate hepatoblasts, which can be differentiated according to the different stages of liver development. Hepatoblastomas are

classified based on the original histological classification of Ishak and Glunz (15). Histologically, hepatoblastoma are broadly classified into two types: epithelial and mixed. Depending on the degree of differentiation, hepatoblastoma cells can be distinguished into two subtypes: embryonic and fetal. In some cases, both cell types are present. Embryonic tumor cells are less differentiated whereas the fetal cells are well-differentiated. Small-cell anaplastic hepatoblastoma is a unique subtype; it mainly infiltrates the bile ducts and is considered prognostically unfavorable (16). In addition to epithelial components, the mixed hepatoblastoma type contains mesenchymal stroma such as osteoid, collagen fibers, and rarely, cartilage and skeletal muscle cells (17). Liver progenitor cells harbor the ability to express of keratin 19 (CK19) and/or the epithelial cell adhesion molecule (EpCAM) (18–21). EpCAM is a transmembrane glycoprotein mediating calcium-independent homotypic cell-cell adhesion in the epithelium. This molecule is also involved in cellular signaling, migration, proliferation, and differentiation. It plays a role in the event-free survival outcome of patients harboring hepatoblastoma (18, 20–23). CK19 expression has been correlated with aggressive behavior in hepatoblastoma [20] and hepatocellular carcinoma (24). Of tremendous importance is that EpCAM expression is independent of previous cisplatin-based chemotherapy and can be utilized as a tumor marker and potential target for immunotherapy (18, 19). Kiruthiga *et al.* found that more than 90% of tumors with strong expression of EpCAM showed viable tumor after chemotherapy (19).

EPIDEMIOLOGY

Hepatoblastoma can occur in children of any age but occurs predominantly in children between 6 months and 3 years of age (2, 3, 6, 25). Children over the age of 5 rarely develop hepatoblastoma (26), but hepatoblastoma has been observed in adults (27). There is a male predisposition with a ratio of M:F = 1.6:1.0 (1–3, 25, 28). The probability of hepatoblastoma occurring in an infant or young child varies between 0.5 and 2 cases per million children per year. The explanation for this vast difference could be due to differing age groups and the possibility that the low hepatoblastoma values given in recent individual publications originate from “old” statistics, and therefore no longer accurately depict current incidence rates (29, 30). Regional peculiarities supposedly play a subordinate role (25). For example, in the USA, about 250 children develop hepatoblastoma each year (31), whereas in Germany, only around 20 children per year (32) and in Great Britain only 10–15 children per year (https://www.cancerresearchuk.org/sites/default/files/cs_dt_childhood.pdf) develop such a tumor (33).

SYMPTOMS

Hepatoblastoma can remain asymptomatic for months. Babies born prematurely and newborns with low birth weight should be screened. In affected children, painless swelling in the upper right abdominal area occasionally occurs in the early stages. When sick children begin to suffer from symptoms, it is almost

always when the disease has reached an advanced stage. Overall, the complaints are nonspecific, including nausea, vomiting, weight loss and increasing general weakness, which can delay development. In this context, osteopenia can develop. Children with hepatoblastoma can become conspicuous due to osteopenia, and resultant pathological fractures (34). Very rarely, obstructive jaundice can occur when the tumor occludes the intrahepatic biliary tract (2). Spontaneous tumor rupture with extensive intra- or extra-tumor bleeding is extremely rare (35). Precocious puberty can occur in boys due to the increased formation of human chorionic gonadotropin (β-hCG) caused by hepatoblastoma (36). Further symptoms can occur depending on the site of metastasis. The lungs are most commonly affected, with breathing difficulties, coughing fits, and occasional hemoptysis (2, 3).

DIAGNOSTICS

The diagnosis of hepatoblastoma involves tumor detection and staging. The following diagnostic measures are initially recommended in addition to a clinical examination of the patient. During the clinical examination, the primary focus should be on signs of a genetic diseases (for example, macroglossia and hemihypertrophy, among others, which are characteristic features suggesting Beckwith-Wiedemann syndrome). Most patients affected by this syndrome will require surgery (37).

Laboratory tests

Laboratory diagnostics for hepatoblastoma include a blood count as standard (mild anemia, leukocytosis, and thrombocytosis are possible), a liver function test (SGOT, LDH, AP can be slightly increased) including bilirubin (raised in the case of bile duct obstruction) and the tumor markers ferritin, CEA (carcinoembryonic antigen test) and the NSE (neuron-specific enolase), and, if necessary, urinary catecholamines (to rule out neuroblastoma) and an evaluation of the titer regarding hepatotropic viruses. It is essential to determine the malignancy-associated tumor markers, namely alpha-1-fetoprotein (AFP) and beta-human chorionic gonadotropin (β-HCG). AFP is elevated in 80–90% of patients. The typical AFP values of the respective age group must be observed. Hepatoblastomas with low AFP (<100ng /ml) are considered aggressive and have an abysmal prognosis (38). β-HCG is increased in about 20% of patients. However, this does not seem not to have prognostic significance (39).

Imaging

If a liver tumor is suspected, first contrast-enhanced sonography of the liver is performed. If the tumor shows increased echogenicity on contrast-enhanced sonography and pronounced vascular supply on Doppler ultrasound, possible tumor invasion into one or more hepatic vessels is suspected. This indicates a malignant process; however, these are not confirmatory evidence of malignancy (40). Other imaging options, namely magnetic resonance imaging (MRI) or

computed tomography (CT) of the abdomen with contrast agent, can not only provide evidence of a malignant tumor of the liver, but also allow for the assessment of the extent of malignancy, and even the relationship of the neoplasm to the hepatic vessels and the liver segments. Nevertheless, a reliable diagnosis of hepatoblastoma cannot be achieved with these examinations either (41). But thanks to these techniques, apart from particular indications, angiography or liver scintigraphy can now be used. A lung CT scan to determine or exclude lung metastases and skeletal scintigraphy with 99-technetium phosphonate to realize or exclude possible bone metastases is recommended as a precautionary measure. It remains to be seen whether FDG-PET/CT performed for the initial diagnosis of a possible hepatoblastoma is sensible, especially since only a possible correlation between uptake and tumor-related increased AFP values can be established. It is well known that FDG-PET/CT is vital during treatment or as part of the follow-up of a malignant tumor. For example, for hepatoblastoma, the detection of metabolically active metastases indicates an unfavorable prognosis (42).

Histology

To confirm the diagnosis of hepatoblastoma, histological examination of the tumor biopsy is the gold standard. In most suspected cases, the biopsy material can be removed using a percutaneous punch (approximately 3–6 liver cores). If the tumor is difficult to access percutaneously or is heavily vascularized, a biopsy is indicated either laparoscopically or via laparotomy. Fine-needle aspiration of a possible hepatoblastoma for the aspirate's cytological examination is not regarded by most oncologists as sufficient for a reliable diagnosis, even if there have been isolated experiences to the contrary (43). This also applies to a percutaneous punch biopsy by an interventional radiologist (44). The biopsy material should be examined both conventionally histologically (as a paraffin preparation) and immunohistochemically. The diagnosis of hepatoblastoma should always be confirmed by a reference pathologist, that is, a pathologist with experience working for either the Children's Oncology Group (COG) or the International Society of Pediatric Oncology (SIOP) or the United Kingdom Children Cancer Study Group (UKCCSG). According to the guidelines of the (German) Society for Pediatric Oncology and Hematology (GPOH), children between the ages of 6 months and 3 years of age who have a liver tumor suspected of being hepatoblastoma by imaging and an AFP value of over 1,000 ng/ml or an AFP value that is at least three times higher than the age norm, biopsy confirming the diagnosis of hepatoblastoma is not necessary, especially since in these cases the incriminated liver tumor is always hepatoblastoma (3). However, this view is not generally approved; on the contrary, most oncologists require a tumor biopsy to confirm the diagnosis (19) (Figure 1).

In the case of resected specimens, size, the exterior (solid/cystic), and tumor necrosis are noted (19). Histology is key in reporting hepatoblastoma, and the report should include the histological subtype, mitotic activity in 10 high power fields (HPF) (low mitotic activity when ≤5/10 HPF and high mitotic activity when >5/10 HPF, presence of extramedullary hematopoiesis, and intratumoral fatty change [steatosis]). Six major subtypes are recognized, including: pure fetal epithelial, mixed embryonal and fetal epithelial, macro trabecular, small cell

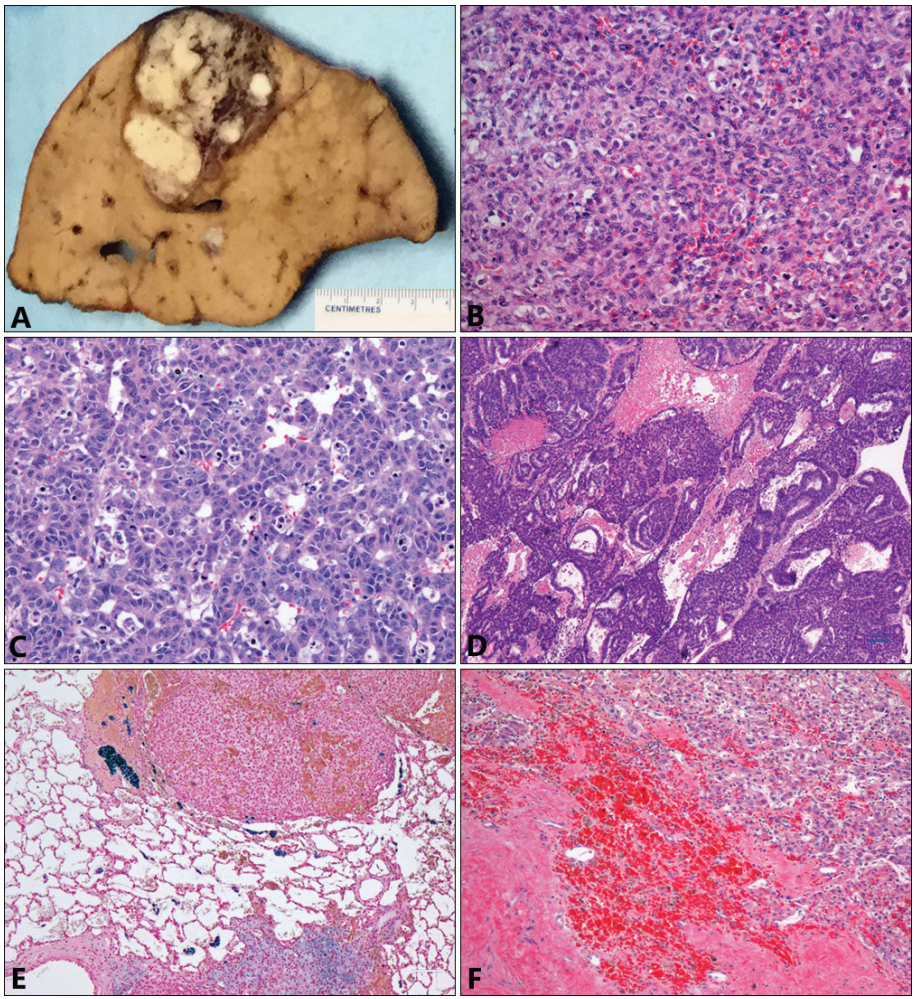

Figure 1. Histology of hepatoblastoma. A. Slice following partial resection of the liver showing a hepatoblastoma with grey cut surface and small areas of hemorrhages. **B.** Microphotograph showing hepatoblastoma with pure fetal histology and minimal mitotic activity (hematoxylin and eosin staining, x200 original magnification). **C**. Microphotograph showing hepatoblastoma of embryonal type (hematoxylin and eosin staining, x200 original magnification). **D**. Microphotograph showing a teratoid hepatoblastoma with ribbons and nephroblastoma-like tubules and acini (hematoxylin and eosin staining, x50 original magnification, scale bar: 100 micrometers). **E**. Microphotograph showing lung metastasis of a hepatoblastoma with two nodules depicting hemosiderin accumulation (blue) both inside and at the edges of the tumor clusters. The lung tissue in the middle of the microphotograph shows the characteristic alveolar pattern. Perls' Prussian Blue (PPB) has its name from the 19th century German pathologist Max Perls, who introduced this technique in histopathology to stain iron in the ferric state (e.g., ferritin and hemosiderin (Perls' Prussian Blue, x50 original magnification, scale bar: 100 micrometers). **F**. Microphotograph showing a hepatoblastoma post chemotherapy exhibiting some cell maturation (right) and some hemorrhage (center). Some fibrosis is encountered on the left side of the microphotograph (hematoxylin and eosin staining, x200 original magnification).

undifferentiated (SCUD), and mixed epithelial and mesenchymal (MEM) with or without teratoid features. Hepatoblastoma should be assigned a category depending on the prevalent epithelial subtype (≥60%) demonstrated. In the case of a hepatoblastoma with 60:40 ratios of two or more components, the tumor should be classified as a mixed subtype. In the post-chemotherapy pathology report, the percentage of the viable tumor should be included. This rate should be graded as 0% as no viable tumor, <25% as "low viable tumor", 25%–50% as "moderate viable tumor", and ≥50% as "substantial viable tumor" following an extensive examination of the pathology specimen. Maturation, cytopathic effects of chemotherapy and microvascular invasion (MVI) should be documented. The assessment should also involve the radicality, and the distance of the neoplasm to the surgical resection margin should be measured microscopically and categorized as ≤0.5 cm, 0.6–1 cm, and >1 cm (19).

THERAPEUTIC CONSIDERATIONS

The current therapeutic approach involves three treatment options: (i) pre- and/or post-operative chemotherapy, (ii) tumorectomy with possible partial liver resection, and (iii) liver transplantation (29). The use of chemotherapies, including platinum compounds for neoadjuvant and adjuvant treatment of hepatoblastomas resulted in a significant improvement in outcome. It has been shown that the results concerning patient survival are relatively similar between the three treatment options, even though the appropriate regimens of the various pediatric oncological groups around the world are not identical (5). Regardless of this fact, surgical treatment of hepatoblastoma is of great importance. The aim of the surgical procedure, which aims to be curative, is complete tumor resection. Thanks to neoadjuvant chemotherapy and various improvements in surgical techniques and equipment (vascular exclusion, ultrasound knife, etc.), this goal has been achieved more and more frequently in recent years; unfortunately, in about 10% of PRETEXT ("PRETreatment EXTension of disease") IV children, despite aggressive neoadjuvant chemotherapy, hepatoblastoma is not completely resectable. Orthotopic liver transplant must be considered in this setting (45).

Staging

According to the generally accepted view, precise clinical staging is a prerequisite for accurate risk stratification and adequate therapy planning. The so-called PRETEXT system of the liver tumor study group of the International Society for Pediatric Oncology (SIOPEL) is used internationally for this purpose. The PRETEXT system categorizes tumors according to their extent in pre-therapeutic imaging and has high prognostic relevance (46). Hepatoblastomas are divided into four different PRETEXT groups (I-IV), depending on how many of the liver's four surgical sectors are affected (Table 1).

Also, other characteristics of the extent of the tumor are recorded in capital letters: C, infiltration of the caudate lobe; V, invasion of the hepatic veins; P, invasion of the portal vein; F, multifocality; E, extrahepatic tumor extension; N, lymph node involvement; and M, hematogenous metastasis. To describe the extent of the

TABLE 1 PRETEXT classification

PRETEXT	Definition
I	Three contiguous hepatic sections are free of tumor
II	One or two sections have tumor involvement, but two adjoining sections are tumor-free
III	Two or three sections have tumor involvement, but no two adjoining sections are tumor-free
IV	All four sections showing tumor involvement

TABLE 2 Children's Cancer Study Group Staging

Stage	Definition
I	Hepatoblastoma completely resected
II	Evidence of microscopic residual neoplastic disease only
III	Evidence of gross residual neoplastic disease or positive lymph nodes or "tumor spillage"
IV	Evidence of metastatic disease

Source: https://www.childrensoncologygroup.org/index.php/newly-diagnosed-with-hepatoblastoma-or-hepatocellular-carcinoma-[accessed on 04 February 2021]

tumor after two cycles of neoadjuvant chemotherapy, the same system is then used for the new staging as the so-called POSTTEXT system ("post-treatment extension") (47). It should be noted that the PRETEXT system is accused of being an almost "overly precise" stage assessment, which is why stages III and IV should be checked particularly carefully, taking into account the PHITT criteria (48). An additional classification about the risk assessment of hepatoblastoma was proposed by the Children's Hepatic Tumors International Collaboration - Hepatoblastoma Stratification (CHIC-HS), taking into account the PHITT consideration. This proposal, which is based on the PRETEXT system and includes the patient's age and AFP level, classifies hepatoblastomas into groups as very low-, low-, medium-, and high-risk (4). Alternatively, hepatoblastomas can be classified according to the Children's Cancer Study Group of the Children's Oncology Group (Table 2). Hepatoblastomas are not staged using the American Joint Committee on Cancer criteria (49).

Risk assessment and therapy planning

As noted above, tumor diagnosis involves two aspects: accurate determination of hepatoblastoma followed by staging. Staging is essential for appropriate therapeutic procedure. In this context, essential criteria are to treat a localized hepatoblastoma to a minimum and an extensive hepatoblastoma as intensively

as possible (50, 51). Of the imaging methods, sonography is initially of great importance. Apart from verifying the tumor, its extent can also be assessed (50, 51). Also, the vascular supply of the hepatoblastoma can be visualized utilizing color-coded Doppler sonography, or, in the case of focal liver lesions, employing contrast-enhanced ultrasound (CEUS) (40, 52). Furthermore, existing thrombus in the vena hepatica, the portal vein, or the vena cava inferior can be established (48). To be able to examine hepatoblastoma more closely, the method of choice is MRI (CT should be avoided because of radiation exposure) (13, 29). Gadolinium-containing contrast media have proven to be particularly beneficial for the diagnosis of liver tumors using MRI examinations, in particular gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid (Gd-EOB-DTPA), because it not only provides a clear distinction between healthy and malignant liver tissue, in the biliary tract and the hepatic vessels, but also detects satellite tumors or a multifocal hepatoblastoma (53). In addition, an invasion of the blood vessels can be detected employing MR angiography for confirmation. With this method, vascular anomalies can be seen as an incidental finding (54). As already mentioned, approximately 20% of children with hepatoblastoma have lung metastases, which is why many oncologists require a multidetector CT (MDCT) of the lungs when initially investigating suspicion of hepatoblastoma (44). Abdominal CT, despite radiation exposure, can be beneficial (55). Because a CT can be done much faster (short sedation or ON duration) than an MRI and provides similarly useful information, even though it is supposedly less accurate. Also, variations in the liver segments can be verified, which is certainly not insignificant from a surgical and technical perspective (56).

Time of surgical procedure

Primary resection of hepatoblastoma is rarely possible in children. According to the PHITT study, a prerequisite for simple lobectomy is a small solitary hepatoblastoma (PRETEXT I and possibly II) with a well-differentiated fetal histological structure, corresponding to a “very low-risk tumor”, that does not show any differentiated fetal tissue. Neoadjuvant therapy (for example, two cycles) is often necessary to reach tumor clearance (57). According to the new classification, the parameters are listed for very low, low, intermediate, and high-risk tumors. Induction chemotherapy is carried out within these groups or their subgroups. By incorporating PRETEXT stages, age, and AFP level in the stratification of neoadjuvant chemotherapy regimen patient-specific decision can be made (58). Hepatoblastomas positively respond to individualized neoadjuvant chemotherapy with a significant reduction in size in 90% of cases. To monitor effect, imaging examination of the patient is carried out following the cytostatic treatment (usually after two cycles) (29). If it turns out that a simple lobectomy can safely remove a hepatoblastoma, tumor resection is scheduled. If this is not possible, the child will receive two more chemotherapy blocks. This makes up to 50% of children with PRETEXT stage IV operable (59). After completing block 4, they are prepared for a possible liver transplant (60).

After another imaging examination of the treatment result, two options are possible: if there is an improvement, one can opt for a complex or extended liver resection in selected cases on the assumption that the hepatoblastoma can be removed (61). If this is not the case, all that remains is a planned liver transplant.

An extension of the preoperative chemotherapy is because of the often-occurring resistance to cytostatic drugs. Radiation therapy is not indicated due to insufficient tumor sensitivity (56, 57). Whether the patients benefit more from an extended resection or from a liver transplant is not clearly defined in the PHITT study, as there is not enough data on this (62). The decision to have an extensive liver resection is difficult, because this procedure is not always feasible. A rescue liver transplant should be carried out in such a setting (5). A ruptured hepatoblastoma is a therapeutic challenge. It is not discussed here because of only a few published cases. It should be noted that there are various therapy proposals with satisfactory results in this regard (63).

Surgical approach

In the conventional surgical approach, a slightly arched, transverse upper abdominal laparotomy is usually chosen, which can be extended in the linea alba in a T-shape to the xiphoid if necessary. The liver is fully mobilized, the hepatoduodenal ligament and the inferior vena cava located. They are looped under and above the liver. After the associated supplying and draining vessels have been removed, the incriminated liver segment is resected, partly blunt, partly with an ultrasound knife or LigaSure™. All crossing vessels are ligated. It should be noted that anatomical resections such as segment resection, lobectomy or extended lobectomy (tri-segment resection) are to be preferred to atypical ("wedge") resections or enucleations, as they usually allow more radical resections and fewer complications. If the distance to the tumor is large enough, a bleeding-free resection can be made possible with thorough mattress sutures. There are various discussions about whether the liver should be pinched out during such an operation. It has been suggested that some surgical techniques are also critical for postoperative liver function (64). Avoiding clamping the liver for resection has the advantage that postoperative function regenerates faster (64). In difficult cases, preoperative imaging of the arteries supplying the tumor is recommended to evaluate the tumor supply better. As a primary therapeutic consideration, it is possible in this context to apply particles loaded with a chemotherapeutic directly into the tumor (65, 66). As a result, the tumor blood flow can be vastly reduced, and tumor tissue destruction can be achieved. However, this procedure can lead to severe complications (67). It is possible to remove up to 80% of the liver tissue through the operation since the liver can regenerate from the remaining tissue. Because the liver plays a vital role in producing various proteins that are important for the body, multiple disorders can temporarily occur after the operation due to tissue loss, for example, blood clotting disorders, disorders of blood sugar regulation, or a lack of plasma proteins. In the last few years, liver surgery has seen an incredible boom, including in children. On one hand this is because of surgical-technical innovations (for example, minimally invasive partial liver resection) and on the other hand, because of advances in imaging technologies such as image-guided three-dimensional reconstructions, intraoperative ultrasound (IOUS), and indocyanine green (ICG) angiography to detect metastasis (68).

A laparoscopic partial liver resection, even of larger sections, is now a widespread method in adults, especially since various technical aids (for example, B-mode and Doppler ultrasonography) have been developed for this. According to the literature, hepatoblastomas can be removed in children in a minimally

invasive manner, but the problem is the abdominal cavity's size (65, 66). Although neoadjuvant chemotherapy makes most hepatoblastomas significantly smaller and thus safely operable, there are no clear international guidelines for laparoscopic approach (69). A method that has been known for a long time and is also suitable for making hepatoblastoma visible is the three-dimensional tumor reconstruction based on CT data (68, 69). It is crucial because it enables the tumor and relevant surrounding anatomical structures to be displayed selectively, thanks to new software and a virtual operation simulation. The three-dimensional reconstruction provides information about the neoplasm, its topography, whether a blood vessel has been infiltrated, and the extent of the infiltration (70, 71).

With IOUS, up to 20% of the patients could have morphologically different results compared to the preoperative MRI examination results, which make it necessary to change the surgical procedure in individual cases. These changes in results mainly concern the relationship between hepatoblastomas and hepatic veins, which is problematic, concerning imaging (72). Apart from the IOUS, an operating microscope and fluorescent dyes, which accumulate in the tumor and make it visible under the operating microscope with special filters, are usually used for tumor and tumor border imaging. ICG has achieved particular importance for this. It is a fluorescent, colored, water-soluble compound suitable for various human medical examinations. It has a high binding affinity for all plasma proteins. ICG absorbs and fluoresces in the visible and near-infrared light spectrum (73). ICG allows the monitoring of liver perfusion. Healthy liver tissue excretes the preparation via the bile within a few hours. In contrast, ICG is retained in the tumor tissue (29) and therefore ideal for detecting metastases. ICG is usually administered intravenously 48–72 hours preoperatively to achieve its visualization in the liver. This procedure is also used in hepatoblastoma patients as it allows the resection margins to be assessed clearly and enable the identification of residual tumors (74). An essential criterion in the surgical removal of hepatoblastoma is, as in all operations, the avoidance of complications (secondary bleeding and biliary leaks [bilioma formation or occurrence of bilious peritonitis]). During this phase, growth factors that are increasingly formed in connection with the surgical trauma can develop a tumor-promoting effect (75). Postoperative chemotherapy usually consists of 1–2 courses after liver resection, and twice after liver transplantation. There are new considerations for reducing ototoxic preparations as much as possible (76).

Liver transplantation

Liver transplantation is provided for cases of hepatoblastomas that are nonresectable: (i) multifocal hepatoblastomas across all four sectors (PRETEXT IV), since chemotherapy is unlikely to completely eradicate all intrahepatic metastases; (ii) Central PRETEXT IV hepatoblastomas with vascular invasion, in which the neoadjuvant chemotherapy cannot downstage the tumor to a PRETEXT III; (iii) Hepatoblastomas (PRETEXT III), which tightly surround or enclose large vessels (vena cava inferior, hepatic veins), and (iv) hepatoblastomas that do not respond to chemotherapy. Also, critical tumor resections may be performed using the heart-lung machine or *ex-situ* resection. In some settings, liver transplantation may produce better long-term results than resection alone from an oncological point of view (77, 78). If tumor resection cannot be carried out, a so-called

"rescue" transplant can be performed, but the prognosis is worse than a primary liver transplant (79). Otte *et al*. found that orthotopic (split) liver transplant to treat hepatoblastomas achieved a 6-year survival rate of 82% in 106 patients, whereas of the 41 patients who underwent "rescue" liver transplantation, it was only 30% (80). It should be noted that the prognosis of children who have had a hepatectomy with orthotopic liver transplantation for hepatoblastoma is as good as that of children who had conventional resection of smaller tumors (81). However, it must be noted that liver transplantation is not free from comorbidities and requires lifelong immunosuppression, which in turn implies side effects. Against a transplant, it is argued that microscopic residues after a tumorectomy do not reduce the survival rate of those affected (79). It is expected that the PHITT study will provide further information (82). Opinions differ on the importance of post-transplant chemotherapy. Otte *et al*. compared the relevant results in 147 patients in 2004: 65 received post-transplant chemotherapy, 82 did not. The survival rates of 77% versus 70% were not statistically significant (80). This means that post-transplant chemotherapy's benefit must be weighed against the toxic risks of the treatment, even though a transplanted liver can withstand adjuvant chemotherapy (79).

For a liver transplant to treat hepatoblastoma, a living donation is best, from example from a parent. Until the first year of life, due to the immaturity of the immune system and immunosuppression, such a transplant can be manageable without risk for the affected child and during the second year of life with a manageable risk, unlike, for example, blood group compatibility (83). After four weeks, patients with liver transplants can be switched from tacrolimus to sirolimus after completion of chemotherapy, or due to the wound healing disorders associated with these drugs.

Treatment of lung metastases

About 20% of children with hepatoblastoma have lung metastases at the time of tumor diagnosis. Up to 50% of these patients can achieve remission with neoadjuvant chemotherapy (29, 84). However, if lung metastases occur during this treatment, the prognosis for these children is poor (85). After completion of neoadjuvant chemotherapy, pulmonary metastases that persist must be surgically removed (86). The only contraindication is impaired lung function. Opinions differ as to when this intervention should take place (85, 86). The majority of authors recommend performing this intervention before the start of postoperative adjuvant chemotherapy and approximately 2 weeks after resection of the primary tumor, mostly because the affected children will have recovered from the abdominal procedure by this time (84, 85, 87). There is also no unanimous opinion with regards to the surgical procedure. Surgical treatment of the metastases can be carried out thoracoscopically or by means of thoracotomy, depending on the extent of the findings. Many authors advocate a thoracotomy, especially since this procedure allows identifying foci that cannot be identified from image morphology or that lie deep in the parenchyma (29). A thoracoscopic procedure (VATS technique) is also used successfully in children. Both techniques will find lung metastases. The use of ICG is recommended, but only superficial tumor nodules (up to a depth of 1 centimeter) can be adequately visualized (88, 89).

If lung metastases are present on both sides, there is no unanimous approach. Some centers address the more severely affected lung first, and the less affected lung the next day. Other centers operate on both lungs on the same day, using sternotomy. Still, other centers carry out the interventions at a longer time interval (84, 90). The procedural differences are due to the lack of evidence-based guidelines that dictate the appropriate surgical treatment for pulmonary hepatoblastoma metastases (82, 84).

Any remaining lung metastases pose a significant problem when a liver transplant is the only option. This is because pulmonary metastases that do not respond to neoadjuvant chemotherapy and those that cannot be approached surgically are contraindications for liver transplantation (79, 91). In other words, lung metastases that persist after neoadjuvant therapy should be surgically removed if possible and the resection should always be performed before the liver transplant (29, 91). In exceptional cases, for example, when no living donor is available, this can also be done shortly after the transplant. In such a case, a liver transplant may be preferred to resection lung metastases, as this procedure may represent the child's only chance of survival (79).

FOLLOW-UP CARE

All children with a treated malignant liver tumor require a follow-up period of at least 5 years after remission. Regular, initially monthly, later 3-monthly, and then 6-monthly check-ups including liver sonography, chest X-ray, and if necessary, CT and/or MRI (in the event of an increase in AFP) and laboratory values to rule out tumor recurrence and to assess the long-term effects of therapy are necessary. In this context, AFP is of great importance as a tumor marker and thus as an indirect indicator of therapeutic effectiveness. Normalization of the AFP values can be expected during the neoadjuvant chemotherapy, and after the removal of hepatoblastoma. If the AFP values do not normalize, a residual tumor can be assumed. If they have been regular and then rise, the tumor is likely relapsed (92, 93); however, some observations show that relapse does not have to be accompanied by an increase in AFP (94). Chemotherapy-induced changes to cardiac and renal functions, changes in blood parameters, and hearing should be monitored. Attention must also be paid to the development of a second malignancy.

Treatment of relapses

According to the literature, about 12% of hepatoblastoma patients who have achieved a complete remission are likely to relapse in the liver and/or lungs. To achieve remission, chemotherapy (95) and surgical removal of the local recurrence or the newly occurring lung metastases is necessary (96). Matsunaga *et al.* stated in 2003 that, of the 90 patients (without metastases) in whom the hepatoblastoma had been fully resected, four had a liver recurrence and eight had lung metastases. Except for one case with multiple lung metastases, all achieved remission via medicinal or surgical treatment (97). In liver transplant patients it is less favorable if additional metastases had initially existed. For example, in 2014, Yamada *et al*. reported that about 30% of such the cases relapse (98).

A second operation on the liver is often difficult and a complete resection of the recurrence is not possible. According to the literature, only a palliative procedure is possible in about a third of the cases (98, 99). This means that before relaparotomy is indicated, it should be mostly clear whether surgical removal of a hepatoblastoma recurrence in the liver is possible or whether a liver transplant should be considered (29). Based on this, an extensive liver resection should be attempted before a liver transplant, but if it turns out intraoperatively that this is not possible, only a rescue liver transplant is the option; however, as already mentioned, it should be noted that the prognosis in this case is poor, although opinions differ (86).

Pulmonary relapses are a big problem (96). They can occur as part of liver recurrences but can also occur in isolation. To give the affected children a realistic chance of survival, these metastases should also be surgically removed under chemotherapy (97). Meyers *et al.* reported that of the 13 thoracotomies, only four were long-term survivors (87). Shi *et al.* succeeded in removing the lung metastases in 8 out of 10 patients; the operated children had a mean survival rate of around 18 months at the time of publication (100). Passmore *et al.* pointed out that repeated thoracotomies can be useful in lung metastases (101). The role of other techniques for example radiofrequency ablation of metastases is not yet fully established (102, 103).

CONCLUSION

Hepatoblastoma typically occurs in infants and toddlers and its etiology has not yet been clarified. Hepatoblastoma is a challenging diagnosis for clinicians and pathologists. About 20% of children with hepatoblastoma have lung metastases at the time of tumor diagnosis. Several histological patterns have been associated with different prognosis. The current therapeutic approach involves chemotherapy, tumorectomy with possible partial liver dissection, and liver transplantation. Chemotherapy-induced changes to vital functions should be monitored. About 12% of hepatoblastoma patients who have achieved a complete remission are likely to relapse. Regular, follow-up is necessary to monitor long-term effects of therapy.

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