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ARTICLE REVIEW

Hepatoblastoma in children

Hepatoblastoma en niños

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ABSTRACT

Introduction: hepatoblastoma is the most common liver tumor in childhood, its survival currently exceeds 70 %. The main prognostic factor is the clinical stage.
Objective: to describe the clinical-epidemiological factors of childhood hepatoblastoma, the main primary malignant tumor of the liver in children.
Methods: to carry it out, 30 scientific articles on the topic were consulted, obtained from the databases PubMed, Medline, Scielo and Google Scholar, and 27 were used as bibliographies, articles published during the last five years and others predominated due to their relevance.
Development: a hepatoblastoma is a rare tumor that grows from liver cells. It is the most common liver cancer in childhood, occurring during the first 18 months of life (from infants to five years of age), mostly in white, male children born prematurely with low birth weight.
Conclusions: the most important prognostic factor for survival of patients with hepatoblastoma is total surgical resection. Secondly, the presence of metastatic disease at diagnosis, although this factor has been modified by treatment with neoadjuvant chemotherapy. The third factor is histology, where the fetal variety has a better prognosis.

Keywords: Hepatoblastoma; Childhood; Liver Cancer.

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RESUMEN

Introducción: el hepatoblastoma es el tumor hepático más frecuente en la infancia, su sobrevida en la actualidad supera el 70 %. El factor pronóstico principal es la etapa clínica.
Objetivo: describir los factores clínicos y epidemiológicos del hepatoblastoma infantil, principal tumor maligno primario del hígado en niños.
Métodos: para su realización se consultaron 30 artículos científicos sobre el tema, obtenidos de las bases de datos PubMed, Medline, Scielo y Google Académico, y fueron utilizados 27 como bibliografías, predominaron los artículos publicados durante los últimos cinco años y otros por su relevancia.
Desarrollo: un hepatoblastoma es un tumor poco frecuente que crece a partir de las células del hígado. Es el cáncer de hígado más frecuente en la infancia, que se presenta durante los primeros 18 meses de vida (desde lactantes hasta los cinco años de edad), en su mayoría en niños blancos, varones y nacidos prematuramente con bajo peso al nacer.
Conclusiones: el factor pronóstico más importante para la supervivencia de pacientes con hepatoblastoma es la resección quirúrgica total. En segundo lugar, la presencia de enfermedad metastásica al diagnóstico, aunque este factor ha sido modificado por el tratamiento con quimioterapéutico neoadyuvante. El tercer factor es la histología, donde la variedad fetal tiene mejor pronóstico.

Palabras clave: Hepatoblastoma; Infancia; Cáncer Hepático.

INTRODUCTION

The liver is the largest intra-abdominal organ in the human body. Its metabolic function is maintained due to a large arterial flow, its portal venous system, hepatic venous drainage and abundant lymphatic drainage.(1) Liver tumors not only affect adults, but are also seen in pediatric ages, constituting about 0,5 % to 2 % of malignant tumors in this stage of life, and being more common than benign ones, in a ratio of 2:1.2. (1)

Among malignant neoplasms, hepatoblastoma constitutes the most common liver cancer in children under four years of age. It is considered to be a very rare malignant pediatric tumor of embryonal origin from hepatocyte precursor cells.(2)

The annual incidence corresponds to 0,5 to 1,5 cases per million children, predominantly in males and in children under three years of age.(2) In the United States of America, the incidence of hepatoblastoma is reported to be approximately one per million in children under 15 years of age. In Asia and Africa, liver tumors are more frequent and in Japanese children they are the third most common tumor.(2)

In Cuba, the incidence ranges from 0.9 to one case per million children under 15 years of age. under 15 years of age and occurs at ages between 12 and 18 months of life.(3) Its pathogenesis is not well identified.(1)

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From the histological point of view, approximately 56 % of tumors are of the epithelial type, which can be subclassified as pure fetal (31 %) embryonal (19 %), macrotrabecular (39 %) and undifferentiated small cell (anaplastic 3 %) and the remaining 44 % are comprised of tumors containing both mixed components, both epithelial and mesenchymal osteoid or cartilage type. The epithelial type, especially the fetal type, has the best prognosis.[1]

The most frequent sign is an asymptomatic palpable abdominal mass in the right upper quadrant; abdominal distension, vomiting, anorexia and weight loss have been associated only in advanced stages of the disease.[1]

Jaundice and severe osteopenia occur in 5 % to 10 % of patients and is a condition of advanced disease. Between 20 % and 49 % have pulmonary metastases, which is related to lower long-term survival. It is estimated that this can decrease from 90 % to less than 25 % at five years. The dissemination of hepatoblastoma is by hematogenous route and affects the lung; it has been reported in chemo resistant tumors, the syndrome of spinal cord compression consecutive to epidural extension.[1]

The most frequent laboratory alteration is thrombocytosis, with figures greater than 500 000/mm3 in 80 % of cases, which is related to increased secretion of thrombopoietin. Recently, it has been suggested that thrombocytosis is secondary to intratumoral synthesis of interleukin.[3] Normocytic normochromic anemia may be present. Liver function tests are altered when more than 75 % of the parenchyma is affected, or when the lesion is central and obstructs the biliary tract. Alpha-fetoprotein (AFP) is the most sensitive serum tumor marker. After surgical resection, AFP decreases logarithmically reaching normal values in four to six weeks. A consistent increase in the marker often precedes tumor recurrence, even if it is not identifiable by imaging.

For diagnosis, the International Society of Pediatric Oncology (SIOP) establishes that this can be done with elevated AFP, thrombocytosis with platelet count greater than 500 000/mm3 and a liver-dependent tumor mass, which confers a diagnostic probability of more than 90 % and without reaching liver biopsy, with which it is possible to initiate neoadjuvant treatment.[1]

Treatment consists of surgical management of first intention whenever possible; otherwise, a biopsy will be taken and treatment with neoadjuvant chemotherapy will be initiated.[1]

Regarding the prognostic factor, the most important for survival is total surgical resection. Secondly, the presence of metastatic disease at diagnosis, although this factor has been modified by treatment with neoadjuvant chemotherapy. The third factor is histology, where the fetal variety has a better prognosis.[1]

METHODS

The scientific literature on the development of hepatoblastoma in the pediatric age was reviewed for this study. The databases PubMed, Medline, Scielo and Google Scholar were consulted.

Of the 30 articles selected, 27 were used as bibliographic references, with a predominance of publications published during the last five years and other previous ones according to their relevance. The inclusion criteria for the articles to be selected were: human studies (in pediatric population), published in English or Spanish.

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DEVELOPMENT

Oncological conditions in pediatrics have increased vertiginously in recent years, these present at the beginning with non-specific symptoms and signs that hinder the diagnosis and timely treatment overshadowing the prognosis of these patients. Twenty percent of the solid tumors that occur in childhood are located in the abdomen. Primary neoplasms of the liver in children and adolescents are generally rare, but they can occur.[3]

Hepatoblastoma is a neoplasm of embryonal origin that occurs in infants and young children, almost always in those under five years of age. It is the most frequent malignant liver tumor in childhood and represents 1-2 % of all childhood tumors.

ETIOLOGY

The etiology of hepatoblastoma, which usually occurs sporadically, has not yet been clarified. Somatic genetic mutations in hepatoblasts and other observations suggest that tumor development is spontaneous.[3] Premature infants with very low birth weight (<1,500 g) are thought to be at increased risk of developing malignant tumors, including hepatoblastoma. This fact, first reported in 1997,[4] was confirmed by a worldwide scientific study in 2019. Even so, an explanation for this observation, whether an accidental or causal connection, could not be established.[4] The fact that relatively common conditions such as preeclampsia, fetal distress before or during delivery, or congenital malformations could play a role as possible tumor inducers could be determined statistically in some studies, but an explanation for these elements is still lacking.[5]

Regardless of these observations, several genetic diseases have been found in recent decades to be risk factors for developing hepatoblastoma. Some of these are familial adenomatous polyposis,[6] Beckwith-Wiedemann syndrome,[7] and trisomy 18 (Edwards syndrome).[8] A connection between the occurrence of hepatoblastoma and other genetic diseases such as Li-Fraumeni syndrome or Prader-Willi syndrome has been discussed, but the relationship has not yet been satisfactorily demonstrated.[8] Finally, various external and epigenetic influences have been discussed as possible causes of neoplastic development. Smoking before and/or during pregnancy is one such example; however, opinions are equivocal.[3]

PATHOGENESIS

Hepatoblastomas develop from degenerated hepatoblasts, which can be differentiated according to different stages of liver development. Hepatoblastomas are classified according to the original histological classification by Ishak and Glunz.[9] Histologically, hepatoblastomas are broadly classified into two types: epithelial and mixed. Depending on the degree of differentiation, hepatoblastoma cells can be distinguished into two subtypes: embryonal and fetal. In some cases, both cell types are present. Embryonal tumor cells are less differentiated, whereas fetal cells are well differentiated. Anaplastic small cell anaplastic hepatoblastoma is a unique subtype; it mainly infiltrates the bile ducts and is considered to have a poor prognosis. In addition to epithelial components, the mixed hepatoblastoma type contains mesenchymal stroma such as osteoid, collagen fibers and, rarely, cartilage and skeletal muscle cells.[9]

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Hepatic progenitor cells harbor the ability to express keratin 19 (CK19) and/or epithelial cell adhesion molecule (EpCAM). EpCAM is a transmembrane glycoprotein that mediates homotypic calcium-independent cell-cell adhesion in the epithelium. This molecule is also involved in cell signaling, migration, proliferation and differentiation, playing a role in the event-free survival outcome of patients with hepatoblastoma. CK19 expression has been correlated with aggressive behavior in hepatoblastoma and hepatocellular carcinoma. Of enormous importance is that EpCAM expression is independent of prior cisplatin-based chemotherapy and can be used as a tumor marker and potential target for immunotherapy. Authors such as Kiruthiga found that more than 90% of tumors with strong EpCAM expression showed viable tumor after chemotherapy.[10]

EPIDEMIOLOGY

Hepatoblastoma can occur in children of any age, but predominantly occurs in children between six months and three years of age. Children older than five years rarely develop hepatoblastoma, but hepatoblastoma has been observed in adults. [11] There is a male predisposition with an M: F ratio = 1,6:1.0. The probability of hepatoblastoma occurring in an infant or young child varies between 0,5 and two cases per million children per year. The explanation for this large difference could be due to the different age groups and the possibility that the low values for hepatoblastoma reported in recent individual publications are from "old" statistics and therefore no longer accurately represent current incidence rates. Regional peculiarities supposedly play a secondary role. For example, in the USA about 250 children a year develop hepatoblastoma, while in Germany only about 20 children a year and in Great Britain only 10-15 children a year.[11]

SYMPTOMS

Hepatoblastoma can remain asymptomatic for months. Prematurely born infants and low birth weight newborns should be screened. In affected children, painless swelling in the right upper abdominal area occasionally occurs in the early stages. When sick children begin to experience symptoms, it is almost always when the disease has reached an advanced stage. In general, the complaints are nonspecific, such as nausea, vomiting, weight loss and increased general weakness, which may delay progression. In this context, osteopenia may develop. Children with hepatoblastoma may become conspicuous due to osteopenia and resultant pathologic fractures.[11]

Very rarely, obstructive jaundice may occur when the tumor occludes the intrahepatic biliary tract. Spontaneous tumor rupture with extensive intra- or extratumoral hemorrhage is extremely rare. In males, precocious puberty may occur due to increased human chorionic gonadotropin (β-hCG) caused by hepatoblastoma. Depending on the location of the metastasis, other symptoms may appear. The lungs are the most affected, with respiratory difficulties, coughing attacks and occasional hemoptysis.[12]

DIAGNOSIS

Diagnosis of hepatoblastoma involves detection and staging of the tumor. In addition to clinical examination of the patient, the following diagnostic measures are recommended initially. During the clinical examination, the primary focus should be on signs of genetic disease (e.g., macroglossia and hemihypertrophy, among others, which are characteristic features suggestive

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of Beckwith-Wiedemann syndrome). Most patients affected by this syndrome will require surgery.[12]

Laboratory tests

Laboratory diagnostics for hepatoblastoma include a complete blood count as standard (mild anemia, leukocytosis and thrombocytosis are possible), a liver function test: gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP) may be slightly increased) including bilirubin (elevated in case of bile duct obstruction) and the tumor markers ferritin, CEA (carcinoembryonic antigen test) and NSE (neuronal specific enolase) and, if necessary, urinary catecholamines (to rule out neuroblastoma) and an evaluation of hepatotropic virus titers.

It is essential to determine tumor markers associated with malignancy, namely alpha-1-fetoprotein (AFP) and beta-human chorionic gonadotropin (β-HCG). AFP is elevated in 80-90 % of patients. AFP values typical of the corresponding age group should be observed. Hepatoblastomas with low AFP (<100ng /ml) are considered aggressive and have an abysmal prognosis. The β-HCG is increased in approximately 20 % of patients. However, this does not appear to have prognostic significance.[12]

If a liver tumor is suspected, contrast-enhanced liver ultrasound is first performed. If the tumor shows increased echogenicity on contrast-enhanced ultrasound and pronounced vascular irrigation on Doppler ultrasound, possible tumor invasion into one or more hepatic vessels is suspected. This indicates a malignant process; however, they are not confirmatory evidence of malignancy.[12] Other imaging options, namely magnetic resonance imaging (MRI) or computed tomography (CT) of the abdomen with contrast, can not only demonstrate the presence of a malignant tumor in the liver, but also allow assessment of the degree of malignancy and even the relationship of the neoplasm to the hepatic vessels and hepatic segments. However, even with these scans it is not possible to reach a reliable diagnosis of hepatoblastoma.[12]

But thanks to these techniques, apart from particular indications, angiography or liver scintigraphy can now be used. As a precautionary measure, a pulmonary CT scan is recommended to determine or exclude pulmonary metastases and a skeletal scan with 99-tequnetium phosphonate to realize or exclude possible bone metastases. It remains to be seen whether FDG-PET/CT performed for the initial diagnosis of possible hepatoblastoma is sensible, especially since only a possible correlation between uptake and increased tumor-related 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, in the case of hepatoblastoma, the detection of metabolically active metastases indicates an unfavorable prognosis.[12]

Histology

To confirm the diagnosis of hepatoblastoma, histologic examination of the tumor biopsy is the gold standard. In most suspicious cases, biopsy material can be removed by percutaneous punch (approximately 3-6 liver cores). If the tumor is difficult to access percutaneously or is highly vascularized, biopsy by laparoscopy or laparotomy is indicated. Fine needle aspiration of a possible hepatoblastoma for cytologic examination of the aspirate is not considered by most oncologists to be sufficient for a reliable diagnosis, although there have been isolated experiences to the contrary.[13]

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This also applies to a percutaneous punch biopsy performed by an interventional radiologist. The biopsy material should be examined both conventionally histologically (as a kerosene preparation) and immunohistochemically. The diagnosis of hepatoblastoma should always be confirmed by a referral pathologist, i.e. a pathologist with expertise in the Children's Oncology Group (COG), the International Society of Pediatric Oncology (SIOP) or the UK Childhood Cancer Study Group (UKCCSG).

According to the guidelines of the German Society of Pediatric Oncology and Hematology (GPOH), children between six months and three years of age with a liver tumor suspected of hepatoblastoma by imaging and an AFP value above 1. 000 ng/ml, a biopsy confirming the diagnosis of hepatoblastoma is not necessary, especially since in these cases the incriminated liver tumor is always a hepatoblastoma.[12] However, this opinion is not generally approved; on the contrary, most oncologists require a tumor biopsy to confirm the diagnosis.

For resected specimens, size, exterior (solid/cystic), and tumor necrosis are noted.[10] Histology is key in the reporting of hepatoblastoma, and the report should include histologic 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 main subtypes are recognized, including: pure fetal epithelial, mixed embryonal and fetal epithelial, macrotrabecular, small cell undifferentiated (SCUD), and mixed epithelial and mesenchymal (MEM) with or without teratoid features. Hepatoblastoma should be assigned a category based on the prevalent epithelial subtype (≥60%) demonstrated.

In the case of a hepatoblastoma with a 60:40 ratio of two or more components, the tumor should be classified as a mixed subtype. The percentage of viable tumor should be included in the post-chemotherapy pathology report. This percentage should be classified as 0% as no viable tumor, <25% as "low viable tumor," 25%-50% as "moderate viable tumor," and ≥50% as "substantial viable tumor" after thorough examination of the pathologic specimen. Maturation, cytopathic effects of chemotherapy and microvascular invasion (MVI) should be documented. Evaluation should also include radicality, and the distance of the neoplasm to the surgical resection margin should be measured microscopically and classified as ≤0.5 cm, 0.6-1 cm and >1 cm.[10]

THERAPEUTIC CONSIDERATIONS

The current therapeutic approach includes three treatment options: (I) pre- and/or postoperative chemotherapy, (II) lumpectomy with possible partial liver resection, and (III) liver transplantation. [14] The use of chemotherapies, including platinum compounds, for neoadjuvant and adjuvant treatment of hepatoblastoma has resulted in significantly improved outcomes. Patient survival outcomes have been shown to be relatively similar among the three treatment options, although the appropriate regimens of the various pediatric oncology groups around the world are not identical.[14] Regardless of this fact, surgical treatment of hepatoblastoma is of great importance.

The goal of surgical intervention, which is intended to be curative, is complete resection of the tumor. Thanks to neoadjuvant chemotherapy and various improvements in surgical techniques and equipment (vascular exclusion, ultrasound scalpel, etc.), this goal has been achieved more and more frequently in recent years; unfortunately, in approximately 10% of PRETEXT ("PRETreatment EXTension of disease") IV children, despite aggressive neoadjuvant chemotherapy, the hepatoblastoma is not completely resectable. In this case, orthotopic liver transplantation should be considered.[14]

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Treatment of pulmonary metastases.
About 20 % of children with hepatoblastoma have pulmonary metastases at the time of tumor diagnosis. Up to 50 % of these patients can achieve remission with neoadjuvant chemotherapy. However, if pulmonary metastases occur during this treatment, the prognosis for these children is poor.[15] After completion of neoadjuvant chemotherapy, persistent pulmonary metastases should be surgically removed. The only contraindication is deterioration of lung function. Opinions differ as to when this procedure should be performed.[15]

Most authors recommend performing this intervention before the start of postoperative adjuvant chemotherapy and approximately two weeks after resection of the primary tumor, especially since the affected children will have recovered from the abdominal intervention by then.[15] There is also no unanimous opinion regarding the surgical procedure. Surgical treatment of metastases can be performed thoracoscopically or by thoracotomy, depending on the extent of the findings.

Many authors advocate thoracotomy, mainly because this procedure makes it possible to identify foci that cannot be identified from the morphology of the image or that are located deep in the parenchyma. Thoracotomy (VATS technique) is also used successfully in children. Both techniques allow finding pulmonary metastases. The use of ICG is recommended, but only superficial tumor nodules (up to a depth of one centimeter) can be adequately visualized.[16]

If there are pulmonary metastases on both sides, there is no unanimous approach. Some centers approach the most severely affected lung first and the next day the less severely affected lung. Other centers operate on both lungs on the same day, by sternotomy. Still other centers perform the operations with a longer time interval.[17] The procedural differences are due to the lack of evidence-based guidelines dictating the appropriate surgical treatment for pulmonary metastases from hepatoblastoma.[17]

Any remaining pulmonary metastases pose a major problem when liver transplantation is the only option. This is because lung metastases that do not respond to neoadjuvant chemotherapy and those that cannot be surgically addressed are contraindications to liver transplantation. In other words, lung metastases that persist after neoadjuvant therapy should be surgically removed if possible and resection should always be performed before liver transplantation.[17] In exceptional cases, for example, when a living donor is not available, it can also be performed soon after transplantation. In such a case, a liver transplant may be preferred to resection of pulmonary metastases, as this procedure may represent the child's only chance of survival.[17]

Timing of surgery

Primary resection of hepatoblastoma is rarely possible in children. According to the Paediatric Hepatic International Tumour Trial (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", showing no differentiated fetal tissue. Neoadjuvant therapy (e.g. two cycles) is usually necessary to achieve tumor disappearance.[15] According to the new classification, parameters are listed for very low, low, intermediate and high risk tumors. Induction chemotherapy is performed within these groups or their subgroups. The incorporation of PRETEXT stages, age and AFP level in the stratification of the neoadjuvant chemotherapy regimen allows patient-specific decisions to be made.[3]

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Hepatoblastomas respond positively to individualized neoadjuvant chemotherapy, with a significant reduction in size in 90 % of cases. To monitor the effect, an imaging examination of the patient is performed after cytostatic treatment (usually after two cycles). If it turns out that a simple lobectomy can safely remove a hepatoblastoma, the tumor is scheduled for resection. If this is not possible, the child will receive two more blocks of chemotherapy. This makes up to 50 % of children with PRETEXT stage IV operable. After completing block four, they are prepared for a possible liver transplant.[3]

After further imaging examination of the treatment outcome, two options are possible: if there is improvement, a complex or extended liver resection can be chosen in selected cases, assuming that the hepatoblastoma can be removed.[3] Otherwise, only a liver transplantation can be planned.

The prolongation of preoperative chemotherapy is due to the resistance that often occurs to cytostatic drugs. Radiotherapy is not indicated because of insufficient tumor sensitivity. In the PHITT study it is not clearly defined whether patients benefit more from an extended resection or liver transplantation, as there are insufficient data.[18] The decision to perform a wide liver resection is difficult, because this procedure is not always feasible. In these cases, a salvage liver transplantation must be performed. Rupture of a hepatoblastic socket constitutes a therapeutic challenge. It is not discussed here because only a few cases have been published. It should be noted that there are several therapeutic proposals with satisfactory results in this regard.[3]

Surgical approach

In the conventional surgical approach, a slightly bowed transverse upper abdominal laparotomy is usually chosen, which can be extended in the linea alba in a T-shape up to the xiphoid if necessary. The liver is completely mobilized and the hepatoduodenal ligament and inferior vena cava are located. They are placed below and above the liver. Once the associated supply and drainage vessels have been removed, the incriminated hepatic segment is resected, partly bluntly and partly with an ultrasound scalpel or LigaSureTM. All cross vessels are ligated. It should be noted that anatomical resections such as segmental resection, lobectomy or extended lobectomy (trisegmental resection) are preferable to atypical ("wedge") resections or enucleations, as they usually allow more radical resections and fewer complications. If the distance to the tumor is sufficiently large, resection can be done without bleeding with careful mattress sutures.

There are various debates as to whether the liver should be clamped during such an operation. It has been suggested that some surgical techniques are also critical for postoperative liver function. Avoiding clamping the liver for resection has the advantage that postoperative function regenerates more rapidly.[19] In difficult cases, preoperative imaging of the arteries supplying the tumor is recommended to better assess tumor supply. As a primary therapeutic consideration, it is possible in this setting to deliver chemotherapy-loaded particles directly into the tumor. As a result, tumor blood flow can be greatly reduced and tumor tissue destruction can be achieved. However, this procedure can lead to serious complications.[19]

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It is possible to remove up to 80 % of the liver tissue by the operation, as the liver can regenerate from the remaining tissue. Since the liver plays a vital role in the production of various proteins important for the body, multiple disorders may temporarily occur after the operation due to the loss of tissue, e.g. blood clotting disorders, blood sugar regulation disorders or lack of plasma proteins. In recent years, liver surgery has experienced an incredible boom, even in children. This is due, on the one hand, to surgical-technical innovations (e.g. minimally invasive partial liver resection) and, on the other hand, to advances in imaging technologies, such as image-guided three-dimensional reconstructions, intraoperative ultrasound (IOUS) and indocyanine green (ICG) angiography for detecting metastases.[19]

Laparoscopic partial liver resection, even of larger sections, is now a widespread method in adults, especially since various technical aids (e.g., B-mode and Doppler ultrasound) have been developed for this purpose. According to the literature, hepatoblastomas can be removed minimally invasively in children but the problem is the size of the abdominal cavity. Although neoadjuvant chemotherapy makes most hepatoblastomas significantly smaller and therefore safely operable, there are no clear international guidelines for the laparoscopic approach.[20]

A long-known and also suitable method to make hepatoblastoma visible is three-dimensional reconstruction of the tumor based on CT data. It is crucial because it allows to selectively visualize the tumor and relevant surrounding anatomical structures, thanks to new software and a virtual operation simulation. Three-dimensional reconstruction provides information about the neoplasm, its topography, whether any blood vessels have been infiltrated and the extent of infiltration.[20]

With IOUS, up to 20 % of patients may present morphologically different results compared to the results of the preoperative MRI examination, making 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, as far as imaging is concerned.[19] In addition to IOUS, an operating microscope and fluorescent dye, which accumulate in the tumor and make it visible under the surgical microscope with special filters, are often used for imaging of the tumor and its edges. For this purpose, ICG has attained special importance. It is a fluorescent, colored, water-soluble compound suitable for various medical examinations in humans.

It has a high affinity for all plasma proteins. ICG absorbs and emits fluorescence in the visible and near-infrared light spectrum.[19] ICG allows monitoring of hepatic perfusion. Healthy liver tissue excretes the preparation via bile within a few hours. In contrast, ICG is retained in tumor tissue and is therefore ideal for detecting metastases. ICG is usually administered intravenously 48-72 hours before surgery to achieve visualization in the liver. This procedure is also used in patients with hepatoblastoma, as it allows clear assessment of the resection margins and identification of residual tumors.[20]

An essential criterion in the surgical removal of hepatoblastoma is, as in all operations, to avoid complications (secondary hemorrhages and biliary leakage [formation of bilioma or occurrence of biliary peritonitis]). During this phase, growth factors that are increasingly formed in relation to surgical trauma may develop a tumor-promoting effect.[20] Postoperative chemotherapy usually consists of 1-2 cycles after liver resection, and two after liver transplantation. There are new considerations to minimize ototoxic preparations.[21]

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Liver transplantation

Liver transplantation is planned for cases of unresectable hepatoblastoma: (I) Multifocal hepatoblastomas in all four sectors (PRETEXT IV), as chemotherapy is unlikely to completely eradicate all intrahepatic metastases; (II) PRETEXT IV central hepatoblastomas with vascular invasion, in which neoadjuvant chemotherapy cannot shrink the tumor to a PRETEXT III; (III) hepatoblastomas (PRETEXT III), which closely surround or enclose large vessels (inferior vena cava, hepatic veins); and (IV) hepatoblastomas that do not respond to chemotherapy. In addition, critical tumor resections can 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 oncologic standpoint.[22]

If tumor resection cannot be performed, a "salvage" transplant can be performed, but the prognosis is worse than that of a primary liver transplant. Otte et al. found that orthotopic (split) liver transplantation to treat hepatoblastomas achieved a 6-year survival rate of 82 % in 106 patients, whereas in the 41 patients who underwent "salvage" liver transplantation, it was only 30 %.[23]

It should be noted that the prognosis of children undergoing hepatectomy with orthotopic liver transplantation for hepatoblastoma is as good as that of children undergoing conventional resection of smaller tumors. However, it should be kept in mind that liver transplantation is not without comorbidities and requires lifelong immunosuppression, which in turn entails side effects. Against transplantation it is argued that microscopic residuals after lumpectomy do not reduce the survival rate of those affected.[23]

Opinions differ on the importance of post-transplant chemotherapy. Authors such as Otte compared relevant outcomes in 147 patients in 2004: 65 received post-transplant chemotherapy and 82 did not. The survival rates of 77 % vs. 70 % were not statistically significant. This means that the benefit of post-transplant chemotherapy must be weighed against the toxic risks of treatment, even if a transplanted liver can withstand adjuvant chemotherapy.[23]

For a liver transplant to treat hepatoblastoma, a living donation, for example from a parent, is best. Up to the first year of life, due to the immaturity of the immune system and immunosuppression, such a transplant can be managed without risk for the affected child and during the second year of life with a manageable risk, unlike, for example, blood group matching.[23]

FOLLOW-UP CARE

All children with a treated malignant liver tumor require a follow-up period of at least five years after remission. Periodic check-ups are necessary, initially monthly, later quarterly and then semi-annually, including liver ultrasound, chest X-ray and, if necessary, CT and/or MRI (in case of increased AFP) and laboratory values to rule out tumor recurrence and to assess the long-term effects of treatment.

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In this context, AFP is of great importance as a tumor marker and, therefore, as an indirect indicator of therapeutic efficacy. Normalization of AFP values can be expected during neoadjuvant chemotherapy and after removal of the hepatoblastoma. If AFP values do not normalize, the existence of a residual tumor can be assumed. If they have regularized and then increase, it is likely that the tumor has relapsed; however, some observations show that relapse need not be accompanied by an increase in AFP.[24] Chemotherapy-induced alterations in cardiac and renal function, changes in blood parameters and hearing should be monitored. Attention should also be paid to the development of a second malignancy.

Treatment of relapses

According to the literature, about 12 % of patients with hepatoblastoma who have achieved complete remission are prone to relapse in the liver and/or lungs. To achieve remission, chemotherapy and surgical removal of local recurrence or new-onset pulmonary metastases are necessary.[25] Authors such as Matsunaga stated in 2003 that, of the 90 patients (without metastases) in whom hepatoblastoma had been completely resected, four had liver recurrence and eight had pulmonary metastases. Except for one case with multiple pulmonary metastases, all achieved remission by pharmacological or surgical treatment.[26] In patients with liver transplantation, it is less favorable if additional metastases were initially present. For example, in 2014, Yamada reported that about 30 % of these cases relapse.[27]

A second liver intervention is often difficult and a complete resection of the recurrence is not possible. According to the literature, a palliative procedure is only possible in about one third of cases.[27] This means that, before a relaparotomy is indicated, it should be clear in most cases whether surgical removal of a hepatoblastoma recurrence in the liver is possible or whether liver transplantation should be considered. Based on this, extensive liver resection should be attempted prior to liver transplantation, but if it turns out intraoperatively that this is not possible, the only option is a salvage liver transplant; however, as mentioned above, it should be noted that the prognosis in this case is poor, although opinions differ.

Pulmonary recurrences are a major problem. They can occur as part of liver recurrences, but also in isolation. To give affected children a realistic chance of survival, these metastases must also be surgically removed with chemotherapy.[26] The role of other techniques, e.g. radiofrequency ablation of metastases, is not yet fully established.[27]

CONCLUSIONS

In conclusion, the most important prognostic factor for the survival of patients with hepatoblastoma is total surgical resection. Secondly, the presence of metastatic disease at diagnosis, although this factor has been modified by treatment with neoadjuvant chemotherapy. The third factor is histology, where the fetal variety has a better prognosis.

Conflict of interest
The authors declare that there is no conflict of interest.

Authors' contribution
All authors participated in conceptualization, formal analysis, project management, writing - original draft, writing - revision, editing and approval of the final manuscript.

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