We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX INDEXED
CLARIVATE ANALYTICS

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Liver Tumors in Infancy and Children

Chunbao Guo and Mingman Zhang

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/51500

1. Introduction

The liver is the third-most-common site for intra-abdominal malignancy in children, following adrenal neuroblastoma and wilms tumor. Although the overall incidence of childhood cancer has been slowly increasing since 1975, cancer in children and adolescents is still rare, the incidence of primary malignant liver tumors per year is 1-1.5 per million children in the United States [1, 2, 3, 4]. This yields a relative low rate for hepatic tumors (1.3% of all pediatric malignancies). Tumors of the liver may be either malignant or benign. Two thirds of liver tumors in children are malignant. Of these malignant tumors, hepatoblastoma (HB) and hepatocellular carcinoma (HCC) are the most common and account for 70 percent of all hepatic neoplasms. Unlike liver tumors in adults, in which the predominant histology is hepatocellular carcinoma, hepatoblastoma accounts for two thirds of liver tumors in children. Other liver malignancies in children include sarcomas, germ cell tumors, as well as rhabdoid tumors. Benign tumors of the liver in children include vascular tumors, hamartomas, adenomas, and focal nodular hyperplasia (FNH). The histology and anatomy of a pediatric liver tumor guides the treatment and prognosis [5, 6, 7, 8].

Recently, dramatic improvements in survival have been achieved for children and adolescents with liver cancer. Children and adolescents with liver cancer should be referred to multidisciplinary team incorporates the skills of the primary care physician, pediatric surgical subspecialists, radiation therapists, pediatric oncologists/hematologists, rehabilitation specialists, pediatric nurse specialists, social workers, and others to ensure that children receive treatment, supportive care, and rehabilitation that will achieve optimal survival and quality of life. Almost all liver masses in children are surgically treated, either primarily or following systemic chemotherapy [9, 10]. The conditions that eventuate in this choice of therapy, when and how to accomplish it, and the medical and surgical consequences for children of transplantation for tumors are described in guidelines for pediatric cancer centers and their role in the treatment of pediatric patients with cancer by the American Acade-

my of Pediatrics [11, 12, 13]. Clinical trials for children and adolescents with cancer are generally designed to compare potentially better therapy with therapy that is currently accepted as standard. Clinical trials are available in many clinical institutes for liver cancer that occur in children and adolescents, and the opportunity to participate in these trials is offered to most patients/families [14].

2. Epidemiology of pediatric hepatic tumors

Benign lesions in children represent 30% of hepatic tumors and are most commonly vascular in origin (eg, hemangiomas, hemangioendotheliomas). Two-thirds of hepatic neoplasms in children are malignant. Liver cancer is also rare malignancy in children and adolescents and account for approximately 1% of all pediatric malignancies. The malignant liver tumor is divided into two major histologic subgroups: hepatoblastoma, affecting around 80% of children, and hepatocellular carcinoma (HCC) [15, 16]. The age of onset of liver cancer in children is related to tumor histology. Hepatoblastoma usually occur before the age of 3 years, and approximately 90% of malignant liver tumors in children aged 4 years and younger are hepatoblastomas. There are 2 distinct groups of HCC patients in childhood: children who develop sporadic HCC without preceding liver disease, and those developing HCC in the context of advanced chronic liver disease (CLD). Sporadic HCC in children has a relatively poor outcome, while the several small series that report on HCC developing in CLD do so in the context of liver transplantation (LT). Some biologic differences may exist between HCCs developing in adults and children. One study reported an high radiological response (49%) in pediatric HCC, higher than adult HCC [17].

The incidence of hepatocellular carcinoma is negligible in children aged 14 years and younger. In china, the incidence of hepatic tumors in children 14 years and younger is 2.6 per 100,000, of which 81 persent are hepatoblastoma. The incidence of hepatoblastoma in the United States increased in the last 25 years, whereas the incidence of hepatocellular carcinoma in the United States has not changed appreciably over time. The cause for the increase in incidence of hepatoblastoma is unknown, but the increasing survival of very low birth weight premature infants, which is known to be associated with hepatoblastoma, may contribute. In Japan, the risk of hepatoblastoma in children who weighed less than 1,000 g at birth are 15 times the risk in normal birth weight children. Other data has confirmed the high incidence of hepatoblastoma in very low birth weight premature infants. In several asian countries, the incidence of hepatocellular carcinoma in children is 10 times more than that in North America. The high incidence appears to be related to the incidence of perinatally acquired hepatitis B, which can be prevented in most cases by vaccination and administration of hepatitis B immune globulin to the newborn [18, 19].

Additional rare malignant liver tumors in children are sarcoma, including its 3 variants rhabdomyosarcoma, embryonal or undifferentiated sarcoma, and angiosarcoma predominantly presenting in early childhood. Also included is the exceedingly uncommon cholangiocarcinoma, which can present at any age, often in the context of chronic biliary

disease.The overall survival rate for children with hepatoblastoma is 70%, but is only 25% for those with hepatocellular carcinoma.

3. Clinical presentation and diagnosis

Most children with liver tumors commonly present insidiously with nonspecific abdominal discomfort, a palpable abdominal mass, feeding difficulties, and abdominal distension. Chronic fatigue secondary to anemia thrombocytopenia, and leukocytosis and lack of appetite are often reported. Jaundice and biochemical derangement are signs of advanced neoplastic change. Children with both HB and HCC may also present with weight loss, fever, and anorexia [20, 21, 22].

Fetal and neonatal presentations include hydramnios, fetal hydrops, congestive heart failure, and respiratory distress. Occasionally, the child may present acutely with vomiting, fever and clinical signs of abdominal irritation, often suggestive of tumor rupture with intraperitoneal spread. Patients with congestive heart failure have been shown to have lower survival rates. Very rarely HB can present with signs of precocious puberty/virilization due to b-HCG secretion by the tumor. Laboratory studies are performed to assess baseline CBC count, electrolyte levels, liver enzyme levels, liver synthetic function, and α-fetoprotein (AFP) levels Serum AFP remains the key clinical marker of malignant neoplastic change, response to the treatment, and relapse. AFP levels are elevated in 50%-70% of children with hepatic neoplasms, and multiple studies confirm that AFP is a valuable surveillance marker in children who have previously undergone hepatic resection for malignancy. However, there are some variants of both HB and HCC that have low or normal AFP. These variants may have distinct histologic features and poorer prognoses [23, 24]. The initial workup for hepatic masses includes radiographic assessment using ultrasonography.

All children with a palpable abdominal mass usually undergo an initial ultrasound to confirm the location and to characterize the consistency as cystic or solid. Cystic or vascular lesions may not require any further imaging. However, definitive characterization of the mass requires a computed tomography (CT) or magnetic resonance imaging (MRI) scan. Calcifications can be seen in a minority of liver tumors. Hypervascularized hepatic lesions with delayed contrast excretion are highly suspicious of a malignant tumor.

Abdominal ultrasonography usually demonstrates a large mass, possibly with some satellite lesions and areas of hemorrhage within the tumor. CT scanning of the abdomen and chest are used for indeterminate or solid lesions to further delineate the location and to assess resectability (Fig. 1) and evaluate for the presence of pulmonary metastasis. MRI angiography is frequently helpful preoperatively to determine resectability because it delineates the vascular anatomy more precisely. Local radiological availability, expertise extent, and multiplicity of the lesions and to detect metastases may facilitate surgical planning and may determine resectability, however, definitive diagnosis can be proven only through biopsy findings [25, 26, 27].
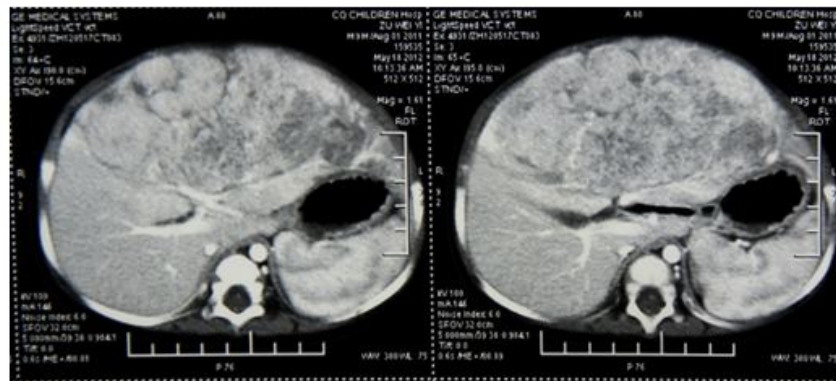
Figure 1. CT scan of a hepatoblastoma amenable to surgical resection.

Any child with a suspected liver tumor should also have AFP and ß-HCG serum assays. The alpha-fetoprotein (AFP) and beta-hCG tumor markers are very helpful in diagnosis and management of liver tumors. Alttough elevation of AFP levels is not diagnostic of hepatic malignancy. AFP is markedly elevated in90% of hepatoblastoma cases and in many cases of hepatocellular carcinoma, and it returns to normal with effective therapy. The level of AFP at diagnosis and rate of decrease in AFP during treatment should be compared to the age-adjusted normal range. Caution should be taken in normal term infants who can have AFP levels in excess of 100,000 ng/ml, however, with a half-life of approximately 1 week, the AFP level normalizes to 10 ng/ml over the first few months of life. Absence of elevated AFP levels at diagnosis occurs in a few percentage of children with hepatoblastoma and appears to be associated with poor prognosis, as well as with the small cell undifferentiated variant of hepatoblastoma. Lack of a significant decrease of AFP levels with treatment may predict a poor response to therapy.

Beta-hCG is a hormone commonly produced by liver tumors and, in excess, can result in precocious puberty. It's levels may also be elevated in children with hepatoblastoma or hepatocellular carcinoma, which may result in isosexual precocity in boys. Extremely high levels of beta-hCG are associated with infantile choriocarcinoma of the liver [28, 29].

Because of the association between familial adenomatous polyposis and hepatoblastoma, obtaining a thorough family history is an important aspect of the management of a child with a liver tumor and his family, with particular attention to any family history of colon cancer or colonic polyps.

A chest CT is an important aspect of the workup because the lung parenchyma is the most common distant site for metastasis. A CBC typically displays mild normocytic and normochromic anemia with thrombocytosis.

Tissue diagnosis of the tumor is essential, although some advocate that in the presence of very high AFP in a young child (6 months to 3 years). The practice in the United States is not to treat without a tissue sample except under the most urgent life-threatening circumstances, such as tumor growth into the right atrium. But this may not be necessary, as avoiding the biopsy theoretically reduces the risks of the tumor seeding. In Europe, The Childhood

Liver Tumor Study Group of the Inter-national Society of Pediatric Oncology (SIOPEL) has developed a preoperative evaluation of the tumor extent (PRETEXT) grading system. The rationale for this recommendation is provided in the section on pathology. Segmental assessment of the extent of the tumor and its relation with the main hepatic vessels is of foremost importance for planning the intensity of chemotherapy and eventual surgery., which could provide a valuable tool for the risk stratification. Formal staging of the tumor should include chest and brain CT and bone scanning [30, 31].

Benign hepatic tumors are usually diagnosed incidentally. Some children may develop the Kasabach-Merritt phenomenon, a triad of coagulopathy, hemolytic anemia and thrombocytopenia due to intralesional pooling of the blood. IHE can have an acute presentation, typically within the first couple of weeks or months of life. Dramatic abdominal distension can lead to major respiratory distress, prompting the need for assisted ventilation and intensive care support. Nowadays some IHEs may be detected on routine antenatal ultrasonography, due to their characteristic vascular multichannel appearance. A proportion of children develop a bizarre secondary hypothyroidism that is thought to be secondary to tumor production of the enzyme iodothyronine deiodinase, which stimulates the conversion of thyroxine to reverse triiodothyronine and of triiodothyronine to 3,3'-diio-dothyronine, leading to a biochemical picture of hypothyroidism, requiring thyroxin supplementation. This phenomenon resolves once the tumor is removed or significantly decreases in size, usually within the first 2 years of life.

3.1. Risk factors

Similar to other embryonal tumors, altered imprinting at the 11–15 locus has been observed in hepatoblastoma. Rearrangements involving the pericentric region of chromosome 1 also appear to be important in hepatoblastoma, with roughly 18% of hepatoblastomas displaying an imbalanced translocation involving this region. Hepatoblastoma is associated with several genetic syndromes and familial cancer predisposition conditions, such as familial adenomatous polyposis and Beckwith-Wiedemann syndrome in addition to several other rare syndromes. Other compelling evidence suggests that acquired aberrations in the ß-catenin/Wnt pathways are important in the pathogenesis of hepatoblastoma. Acquired chromosomal changes in tumors include numerical chromosomal changes, most commonly trisomies of chromosomes 2, 8, and 20. Finally, epigenetic changes in methylation patterns of DNA may be altered in hepatoblastoma.

There is limited but compelling evidence that parental exposures are associated with a higher incidence of liver tumors and, more specifically, hepatoblastoma. Children from parents who have been exposed to metals used in soldering and welding, petroleum, or paints are at a higher risk for hepatoblastoma. Recent reports have also implicated parental smoking as a risk factor for hepatoblastoma [32, 33].

3.2. Beckwith-Wiedemann syndrome

The incidence of hepatoblastoma is increased 1,000 to 10,000-fold in infants and children with Beckwith-Wiedemann syndrome (BWS). BWS can be caused by either genetic mutations and be familial, or much more commonly, by epigenetic changes and be sporadic. Hepatoblastoma is also increased in hemihypertrophy, an overgrowth syndrome caused by the same epigenetic changes in chromosome 11p15.5 that cause many cases of BWS, but in a genetically mosaic fashion. Either mechanism can be associated with an increased incidence of embryonal tumors including Wilms tumor and hepatoblastoma. The gene dosage and ensuing increase in expression of insulin-like growth factor 2 (IGF 2) has been implicated in the macrosomia and embryonal tumors in BWS and hemihypertrophy. When sporadic, the types of embryonal tumors associated with BWS have frequently also undergone somatic changes in the BWS locus and IGF 2. All children with BWS or isolated hemihypertrophy should be screened regularly by ultrasound to detect abdominal malignancies at an early stage. Screening using AFP levels has helped in the early detection of hepatoblastoma in children with BWS or hemihypertrophy. Other somatic overgrowth syndromes, such as Simpson-Golabi-Behmel syndrome, may also be associated with hepatoblastoma.

3.3. Familial adenomatous polyposis

There is an association between hepatoblastoma and familial adenomatous polyposis (FAP); children in families that carry the APC gene are at an 800-fold increased risk for hepatoblastoma. However, hepatoblastoma occurs in less than 1% of FAP family members, so ultrasound and AFP screening for hepatoblastoma in members of families with FAP is controversial. The predisposition to hepatoblastoma may be limited to a specific subset of APC mutations. It has been recommended that all children with hepatoblastoma be examined for congenital hypertrophy of the retinal pigment epithelium, a marker of APC mutation carriers in 70% of polyposis families. In the absence of APC germline mutations, childhood hepatoblastomas do not have somatic mutations in the APC gene; however, they frequently have mutations in the beta-catenin gene, the function of which is closely related to APC.

3.4. Hepatitis B and hepatitis C infection

Hepatocellular carcinoma is associated with hepatitis B and hepatitis C infection, especially in children with perinatally acquired hepatitis B virus [33]. Compared with adults, the incubation period from hepatitis virus infection to the genesis of hepatocellular carcinoma is extremely short in a small subset of children with perinatally acquired virus. Widespread hepatitis B immunization has decreased the incidence of hepatocellular carcinoma in Asia. Mutations in the met/hepatocyte growth factor receptor gene occur in childhood hepatocellular carcinoma, and this could be the mechanism that results in a shortened incubation period.Hepatocellular carcinoma may also arise in very young children with mutations in the bile salt export pump ABCB11, which causes progressive familial hepatic cholestasis. Several specific types of nonviral liver injury and cirrhosis are associated with hepatocellular carcinoma in children including tyrosinemia and biliary cirrhosis.

3.5. Undifferentiated Embryonal Sarcoma of the Liver

Undifferentiated embryonal sarcoma of the liver (UESL) is the third most common liver malignancy in children and adolescents, comprising 9% to 13% of liver tumors. Widespread infiltration throughout the liver and pulmonary metastasis are common, usually between the ages of 5 and 10 years. It could also presents as an abdominal mass, often with pain or malaise. It may appear solid or cystic on imaging, frequently with central necrosis. Distinctive features are characteristic intracellular hyaline globules and marked anaplasia on a mesenchymal background. Many UESL contain diverse elements of mesenchymal cell maturation, such as smooth muscle and fat.

Strong clinical and histological evidence suggest that some UESLs arise from mesenchymal hamartomas of the liver (MHL), which are large benign multicystic masses that present in the first 2 years of life. Many MHLs have a characteristic translocation with a breakpoint at 19q13.4 and several UESLs have the same translocation. In a report of 11 cases of UESL, five arose in association with MHL, and transition zones between the histologies were noted. Some UESLs arising from MHLs may have complex karyotypes not involving 19q13.4.

3.6. Infantile Choriocarcinoma of the Liver

Choriocarcinoma of the liver is a very rare tumor that appears to originate in the placenta and presents with a liver mass in the first few months of life. Infants are often unstable due to hemorrhage from the tumor. Clinical diagnosis may be made without biopsy based on extremely high serum beta-hCG levels and normal AFP levels for age.

3.7. Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EHE) is a rare vascular cancer that occurs in the liver and other organs.

Generally, children with liver masses display normal growth and development unless they show the phenotypes associated with Beckwith-Wiedemann syndrome or the other genetic cancer predisposition syndromes associated with liver tumors.

4. Screening

Hepatic neoplasms develop in a myriad of chronic liver disorders of childhood, often without or with minimal symptoms. Therefore, regular screening with abdominal ultrasound and serum AFP measurement should be in place for all children with CLD at least annually. Therefore, awareness of antecedent conditions that permit screening is essential. Detection of a liver tumor prior to dissemination and/or massive growth is the single most important management tool for all tumor types at all ages. Children with chronic hepatitis B should be also regularly checked, but because communities in which immunization has yet to be provided are typically impoverished and medically underserved, recommendations for screening have not yet been implemented. Some of the conditions with known increased propensity to develop

malignancies such as tyrosinemia type 1 (even on nitizinone treatment) or bile salt export pump (BSEP) deficiency should be assessed every 6 months. However, there is no formal guideline for the frequency and manner of screening at this time [34, 35].

Extraordinary advances in neonatal care in the past 25 years have led to a wholly new population of children, the long-term survivors of birth as early as 22 to 23 weeks of gestation with a weight less than 1000 g. In addition to many other chronic problems, they have extraordinary susceptibility to HB. HB is dramatically more common in expremature babies but arranging effective screening programs could prove to be difficult because of their increasing numbers and fact that their long term care is typically provided outside hepatological clinics. Monitoring much smaller cohorts of children with Beckwith-Wiedemann Syndrome for HB is more feasible, and one study has suggested abdominal ultrasonography and serum AFP every 3 months until 4 years of age.

There are several conditions for which screening of children for primary liver cancer is recommended by virtue of the attendant risk. Hepatitis B virus can cause HCC as early as age 4 following perinatal transmission from infected carrier mothers. Vaccination and perinatal administration of hepatitis B immunoglobulin have already reduced the incidence dramatically. A relative risk for such prematures versus term babies of 16- to 52-fold is recognized around the world. HB occurs at the same age as HB in term babies or later. Screening of infants with hemihypertrophy or hemiaplasia, as part of the Beckwith-Wiedemann over-growth syndrome, has been carried out for many years via ultrasound to detect intraabdominal malignancies. These include Wilms' tumor and adreno cortical carcinoma, in addition to the less common HB, which has a relative risk of 2280. HB is not the only proliferative lesion of the Beckwith-Wiedemann syndrome liver, as hemangioendothelioma and mesenchymal hamartoma have also been observed, either con-currently or sequentially [37, 38].

In familial adenomatous polyposis (FAP), the first manifestation of an autosomal dominant mutation in a family may be HB in a baby, with the colonic polyps detected only afterwards in a parent. The relative risk for children in such cohorts is 800-fold, but many examples are due to new germ-line mutations at 5q21,22 or only in the tumor.

A series from the Children's Oncology Group focused primarily on known FAP families but raised the issue of de novo cases or the potential for infants of parents too young to be aware of the symptoms of FAP themselves.

The largest report of sporadic cases looked at 50 patients and found 5 germline antigen-presenting cell (APC) mutations. This led the authors to recommend routine screening for APC mutations in all cases of sporadic HB, including both a screen for APC deletion or duplication and sequencing through the gene itself. In the only prospective screening study to date, 20 children with confirmed or suspected FAP were followed for 10 years by ultrasonography, and no tumors were detected. In FAP, other forms of hepatocellular neoplasia are also observed, including adenoma and HCC, as well as biliary adenomas.

The timelines of the development of these various cancers in distinct tissues are not linked, and therefore, surveillance for these cancers needs to continue throughout the patient's life

[39]. Chronic cholestatic syndromes may be the substrate for liver cancers, with HB, cholangiocarcinoma, and in the Alagille syndrome of a paucity of intrahepatic bile ducts due to Jagged 1 or NOTCH mutations. Also, we have observed HB in three 2-year olds with congenital hepatic fibrosis and autosomal recessive polycystic disease. HB and HCC have been seen in the explants of infants with cirrhosis due to biliary atresia as early as 1 year. On the basis of the growth rate of HCC and with the aim of detecting tumors when they are 3 cm in diameter, the American Association for the Study of Liver Disease and the European Association for the Study of the Liver recommend screening ultrasound examinations at 6-month intervals, and some institutions shorten this interval to 3 months when the patient is on a transplant waiting list. These organizations have also published diagnostic criteria for liver nodules detected during the screening process.

HCC can be diagnosed noninvasively by computed tomography (CT) or magnetic resonance imaging (MRI) if a lesion 2cm in diameter within a cirrhotic liver demonstrates rapid contrast enhancement during the arterial phase and washout on the delayed venous phase. These guidelines were developed for cirrhotic adults, and there are no validated evidence-based guidelines for screening for tumors in children and adolescents with chronic liver disease.

According to adult data, ultrasound is insensitive for the diagnosis of HCC in the cirrhotic liver and should not be used for the detection of focal liver lesions in this setting. MRI is more sensitive than multidetector 3-phase CT for the diagnosis of regenerative and dysplastic nodules and is comparable to CT for the detection of HCC. There is a lower false-positive rate with MRI. Interval growth is probably the best indicator of malignancy, and there is a definite need for the establishment of protocols for follow-up imaging in centers that care for children with diffuse liver disease.

In the case of hereditary tyrosinemia type 1 due to fumaryl acetoacetate hydrolase deficiency, prompt medical management, by blocking an enzyme upstream in the tyrosine catabolic pathway, can avert the injury that otherwise leads to HCC more often than any other metabolic defect. However, a low risk of developing HCC remains even with adequate medical management, so these children require life-long surveillance. Therefore, for the conditions listed, periodic abdominal ultrasonography and serum alpha fetoprotein measurements, at 3-month intervals in the case of Beck-with-Wiedemann syndrome and similarly for the first 3 years of life for others and then every 6 months thereafter, are advocated [40, 41]. In addition, recognition of the rare sequential occurrences of mesenchymal hamartoma and sarcoma and of hemangioendothelioma with angiosarcoma indicates the need for surveillance ultrasonography whenever a complete resection or transplant has not taken place [42, 43].

5. Staging

The process used to find out if cancer has spread within the liver or to other parts of the body is called staging. The staging system would be useful in determining treatment plans and offers good prognostic value for overall and disease-free survival out-

come. Historically, north Americans have staged liver tumors similar to other solid tumors, with surgical resectability and the presence of metastases as the primary criteria. The European staging system considers only the pretreatment extent of disease, and was developed by the Childhood Liver Tumor Strategy Group. After childhood liver cancer has been diagnosed, tests are done to find out if cancer cells have spread within the liver or to other parts of the body. The PRETEXT staging system divides the liver into four sectors, and the number of segments involved by tumor indicates stage. A lettering system further indicates extrahepatic involvement.The information gathered from the staging process determines the stage of the disease [44, 45].

The following tests and procedures may be used in the staging process: -CT scan (CAT scan): This procedure is also called computed tomography, computerized tomography, or computerized axial tomography. The pictures are made by a computer linked to an x-ray machine. A procedure that makes a series of detailed pictures of areas inside the body, taken from different angles. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly.

-MRI (magnetic resonance imaging): Also called nuclear magnetic resonance imaging (NMRI), a procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures of areas inside the body.

-Ultrasound exam: A procedure in which high-energy sound waves (ultrasound) are bounced off internal tissues or organs and make echoes. The echoes form a picture of body tissues called a sonogram. The picture can be printed to be looked at later.

-Surgery: An operation will be done to look at or remove the tumor. Tissues removed during surgery will be checked by a pathologist.

There are 2 staging systems for childhood liver cancer.

-Presurgical (before surgery) staging: This staging system is called PRETEXT, based on imaging procedures such as MRI or CT, where the tumor has shown within the four parts (sections) of the liver.

The liver is divided into 4 vertical sections.

In PRETEXT stage 1(Fig. 2A), the cancer is found in one section of the liver. Three sections of the liver that are next to each other do not have cancer in them.

In PRETEXT stage 2 (Fig. 2B), cancer is found in one or two sections of the liver. Two sections of the liver that are next to each other do not have cancer in them.

In PRETEXT stage 3(Fig. 2C), the cancer is found in three sections of the liver and one section does not have cancer. OR, cancer is found in two sections of the liver and two sections that are not next to each other do not have cancer in them.
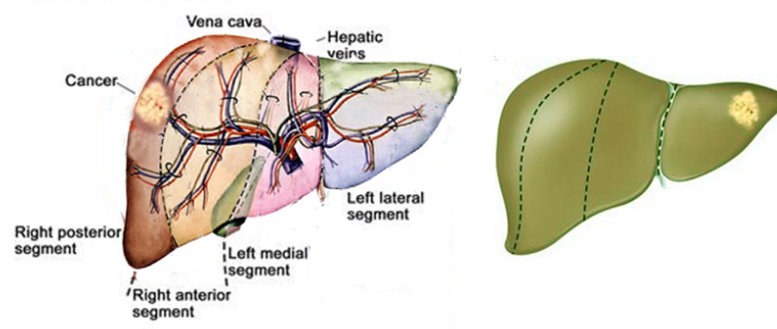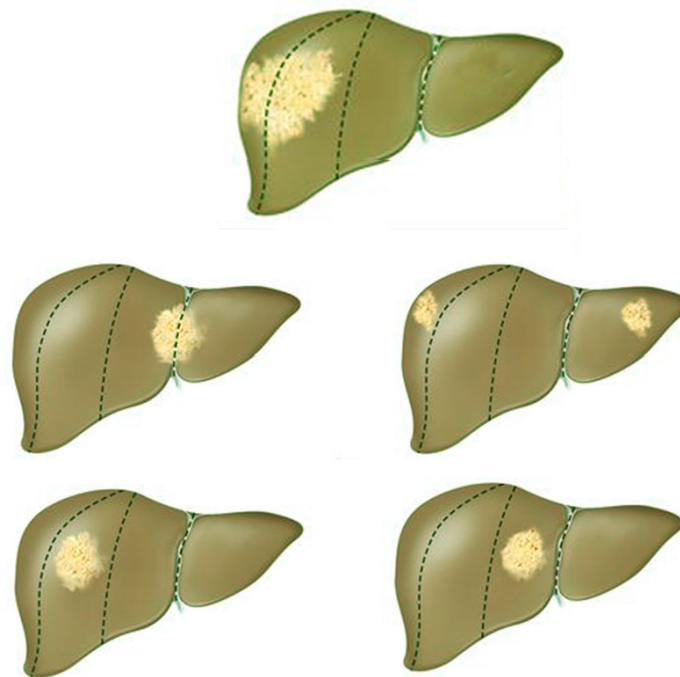
Figure 2.

Figure 3.

Postsurgical (after surgery) staging: The stage is based on the amount of tumor that remains after the patient has had surgery to look at or remove the tumor.

Stage I

In stage I, all of the cancer was removed by surgery in the liver.

Stage II

In stage II, a small amount of cancer remains in the liver, but it can be seen only with a microscope, or the tumor cells may have spilled into the abdomen before surgery or during surgery.

Stage III

In stage III:

In stage III, the tumor cannot be removed by surgery; orcancer that can be seen without a microscope remains after surgery; or the cancer has spread to nearby lymph nodes.

Stage IV

In stage IV, the cancer has spread to other parts of the body. Cancer invades the surrounding normal tissue. Cancer invades the lymph system and travels through the lymph vessels to other places in the body. Cancer invades the veins and capillaries and travels through the blood to other places in the body.

The metastasis is described as when cancer cells break away from the primary (original) tumor and travel through the lymph or blood to other places in the body, another (secondary) tumor may form [46]. The secondary (metastatic) tumor is the same type of cancer as the primary tumor. For example, if breast cancer spreads to the bones, the cancer cells in the bones are actually breast cancer cells. The disease is metastatic breast cancer, not bone cancer.
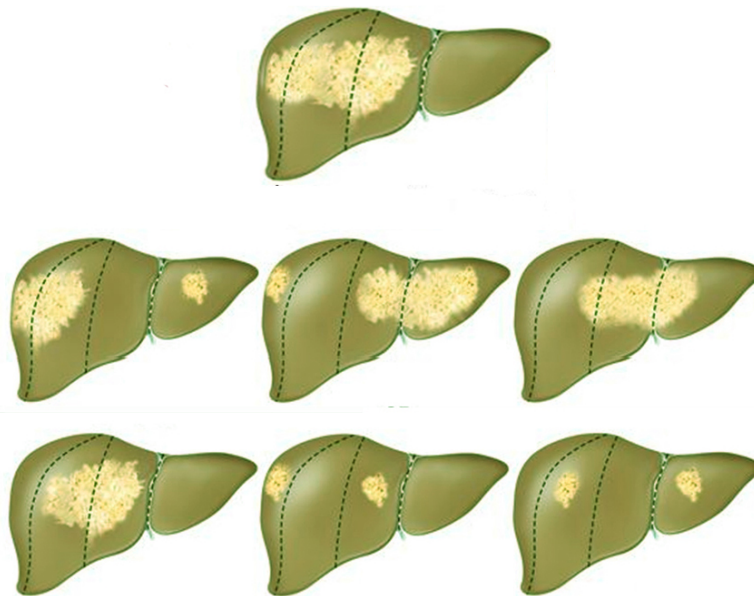
Figure 4.

In PRETEXT stage 4(Fig. 2D), cancer is found in all four sections of the liver.
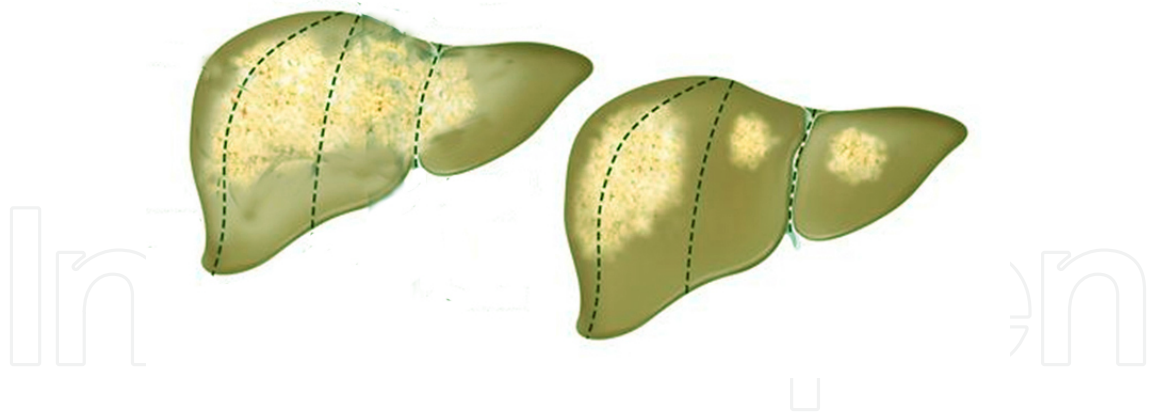
Figure 5.

6. Management

The key to successful treatment of malignant liver tumors in children is surgical removal, either by tumor resection/partial hepatectomy or Live Transplantation. Historically, complete surgical resection of the primary tumor has been required to cure malignant liver tumors in children. Complete surgical resection of the primary tumor continues to be the goal of definitive surgical procedures, but surgical resection is often combined with other treatment modalities (e.g., chemotherapy) to achieve this goal. SIOPEL recommends initial chemotherapy, while the American guidelines from COG require primary resection if possible, followed by chemotherapy, unless the tumor is pure fetal type HB stage 1, when the chemotherapy is not given. Both strategies have been successful in increasing the 5-year survival rates in HB to approximately 80% due to effective chemotherapy (cisplatinum in combination with doxorubicin or vincristine). Moreover, the timing and nature of surgical interventions are better defined for HB, and they are well-placed within the management protocols. For HCC, however, complete surgical excision or transplantation are essential for cure, and chemotherapy is not effective. On the whole, treatment planning by a multidisciplinary team of cancer specialists with experience treating tumors of childhood is required to determine and implement optimum treatment [47, 48].

The most important step in the management of benign tumors in children is confirmation of their genuine benign nature. Multiphase contrast CT imaging and, less frequently, direct angiography are required for the radiological diagnosis. Some of the benign tumors, including IHE, mesenchymal hamartoma, and FNH, would have characteristic radiological features, not always requiring a tissue diagnosis.

Many of the improvements in survival in childhood cancer have been made using new therapies that have attempted to improve on the best available, accepted therapy. Clinical trials in pediatrics are designed to compare potentially better therapy with therapy that is currently accepted as standard.Because of the relative rarity of cancer in children, all children with liver cancer should be considered for entry into a clinical trial. This comparison

may be done in a randomized study of two treatment arms or by evaluating a single new treatment, comparing the results with those previously obtained with standard therapy [49].

6.1. Surgical approaches

The timing of the surgical approach is critical. For this reason, surgeons with experience in pediatric liver resection and transplantation should be involved early in the decision-making process for determining optimal timing and extent of resection.There are three ways in which surgery is used to treat primary pediatric liver cancer, including initial surgical resection (alone or followed by chemotherapy), delayed surgical resection (chemotherapy followed by surgery) and orthotopic liver transplantation [50].
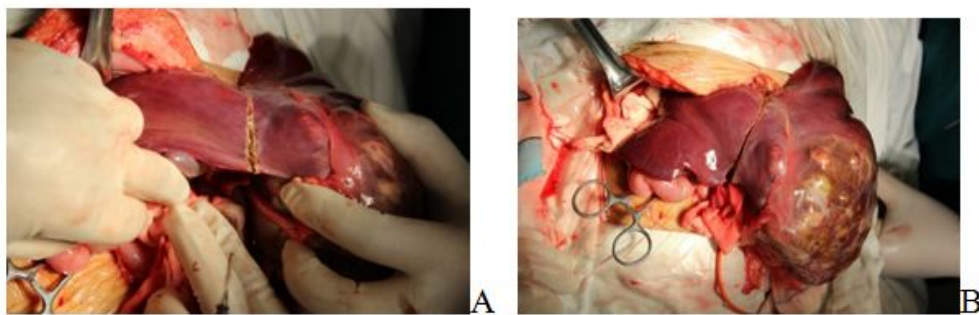

Figure 6. The lesion to resect is marked out.

Figure 7. Electrocautery is useful for dissecting through the liver capsule and parenchyma.

Resection is typically performed through a bilateral subcostal incision, and, occasionally, a right thoracoabdominal approach is necessary for large lesions arising high in the right lobe. Surgical resection has seen applications of newer technology. Intraoperative ultrasonography has been widely applied to determine the exact location of the tumor relative to the vessels. Once deemed resectable, the resection is marked out (Fig. 3, 4), and various tools may

then be used to perform the resection; electrocautery, bipolar devices such as LigaSure, and argon beam coagulation for hemostasis have been used.

The most frequently performed procedure is a right hepatectomy (60%) because hepatoblastomas (HBs) occur 3 times more often in the right lobe than in the left. The hilar plate is divided, exposing the bifurcation of the hepatic artery and portal vein. These structures are ligated (Fig. 5).
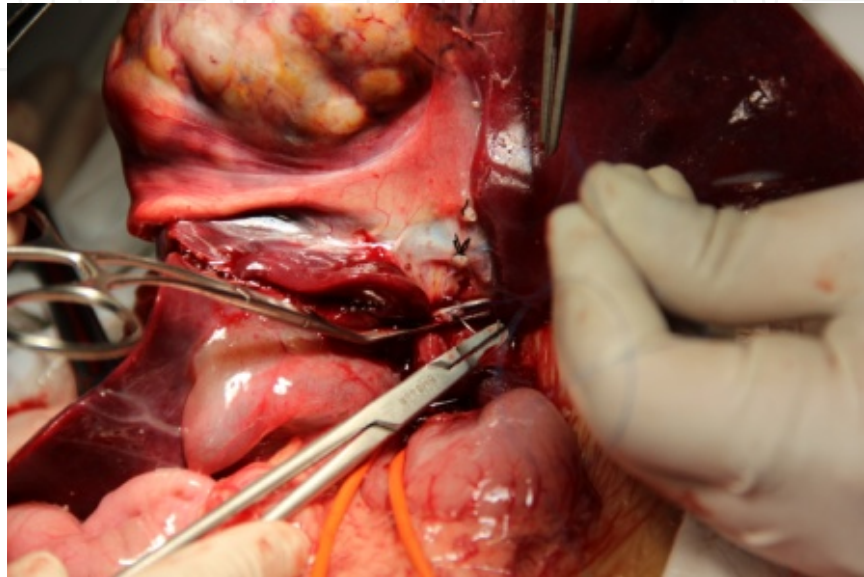

Figure 8. Suture and ligation may be useful in sealing blood vessels and hepatic ducts.

In an extended right hepatectomy, the middle hepatic vein is ligated and segment 4 is resected. The right hepatic vein is identified and ligated before any division of the hepatic parenchyma. At completion, only segments 2 and 3 and the caudate lobe remain.

Left hepatic lobectomy begins the same way right hepatectomy, with division of the left hepatic artery and left branch of the portal vein. The left and middle hepatic veins are identified after dissection through the sinus venosus. The liver is then transected after vascular isolation of the resected segments. An extended left hepatectomy includes removal of all or most of segments 5 and 8. Unresectability is usually determined by involvement of hilar structures or all hepatic veins, multicentricity, and invasion of inferior vena cava (IVC) or portal vein. Centrally located tumors are, by definition, more likely unresectable.

Laparoscopic and robotic resections of both benign and malignant liver tumors have been described. Their role in standard practice is still being defined.

If preoperative chemotherapy is to be administered, it is very important to consult frequently with the surgical team concerning the timing of resection, as prolonged chemotherapy can lead to unnecessary delays and in rare cases, tumor progression. If the tumor can be completely excised by an experienced surgical team, less postoperative chemotherapy may be needed.

In PRETEXT stage 3 or 4 disease patients with involvement of major liver vessels, early involvement with an experienced pediatric liver surgeon is especially important, patients with. Although initially thought to be a contraindication to resection, experienced liver surgeons could also perform aggressive approaches avoiding transplantation for vascular involvement patients. Accomplishing a complete resection is imperative since rescue transplant of incompletely resected patients has an inferior outcome compared to patients who are transplanted as the primary surgical therapy.

Surgical resection of distant disease has also contributed to the cure of children with hepatoblastoma and is often performed at the same time as resection of the primary tumor. Resection of pulmonary metastases is recommended when the number of metastases is limited. When possible, resection of areas of locally invasive disease, such as in the diaphragm, and of isolated brain metastasis is recommended. Second resection of positive margins and/or radiation therapy may not be necessary in patients with incompletely resected hepatoblastoma whose residual tumor is microscopic and who receive subsequent chemotherapy.

Major intraoperative complications include hemorrhage, air embolism, tumor embolus, and bile duct injury. Only 20% of the liver is necessary to maintain hepatic function; thus, postoperative insufficiency is rare. Postoperative complications include hemorrhage, bile leak, abscess formation, pulmonary complications, and wound problems. Postoperative care consists of adequate fluid replacement, intravenous albumin supplementation, vitamin K, and clotting factors for the first 3-4 days. The liver function test results generally normalize within the first 2 weeks, and hepatic insufficiency is reasonably rare. Postoperative monitoring consists of frequent ultrasonography, chest radiography, and serial α-fetoprotein (AFP) level measurements, generally at 3-month to 6-month intervals.

Tumor rupture at presentation, resulting in major hemorrhage that can be controlled by transcatheter arterial embolization or partial resection to stabilize the patient, does not preclude a favorable outcome when followed by chemotherapy and definitive surgery. The decision as to which surgical approach to use depends on many factors including: PRETEXT stage, size of the primary tumor, presence of multifocal hepatic disease, AFP levels, Vascular involvement, preoperative chemotherapy as well as orthotopic liver transplantation criteria.

In North American clinical trials, the Children's Oncology Group (COG) has recommended that surgery be performed initially if a complete resection can be accomplished. COG is investigating the use of PRETEXT stage at diagnosis and after chemotherapy to determine the optimal surgical approach and its timing. In European clinical trials, only patients with PRETEXT stage 1 receive resection surgery and all other patients are biopsied [51, 52, 53].

It is difficult to compare the North American and European approaches. Somewhat comparable results for children with PRETEXT stage 1 and 2 tumors were obtained in two international studies. The 5-year survival of PRETEXT stage 1 and 2 patients(chemotherapy prior to attempted surgical resection of the primary liver tumor) is 90% to 100% on the European studies and seems to be similar to that of children treated on North American studies where surgery was performed before chemotherapy. In comparison, a survey of children with liver tumors who were treated prior to the consistent use of combination chemotherapy found that 45 of 78 patients (57%) with hepatoblastoma who had com-

plete excision of the tumor survived while no children with positive margins or gross disease following resection survived.

6.2. Orthotopic liver transplantation

Orthotopic liver transplantation was first described in 1968 by Starzl. Liver transplantation has recently been associated with significant success in the treatment of children with unresectable hepatic tumors. The criteria currently used to evaluate adult transplant candidates may not be applicable for pediatric patients. The main indication for transplantation is nonmetastatic, unresectable lesions. Extrahepatic disease and lymph node involvement did not prove to be contraindications. Hepatoblastoma (HB) now constitutes an indication for 3% of all pediatric liver transplantations, whereas the role of liver transplantation for HCC is more controversial. In hepatocellular carcinoma, vascular invasion, distant metastases, lymph node involvement, tumor size, and male gender were significant risk factors for recurrence. Because of the poor prognosis in patients with hepatocellular carcinoma, liver transplant should be considered for disorders such as tyrosinemia and familial intrahepatic cholestasis early in the course, prior to the development of liver failure and malignancy. Because no good medical therapy for pediatric HCC has been identified, liver transplantation should be carefully evaluated as front-line therapy. Additionally, successful transplantation has been used benign lesions such as diffuse hepatic hemangiomas. In addition, liver transplantation may be an option in children with unresectable primary tumors, without metastatic disease, after neoadjuvant chemotherapy and pulmonary metastasectomy, if necessary. It has been suggested that adjuvant chemotherapy following transplant may decrease the risk of tumor recurrence. Generally, preoperative and postoperative chemotherapy are recommended, in addition to postoperative immunosuppression [54, 55, 56].

Transplantation may also be used in selected cases of tumor recurrence but is much less successful when used for salvage therapy. There are discrepant results on the outcomes for patients with lung metastases at diagnosis who undergo orthotopic liver transplantation following complete resolution of lung disease in response to pretransplant chemotherapy. Some studies have reported favorable outcomes for this group of patients, while others have noted high rates of hepatoblastoma recurrence. All of these studies are limited by small patient numbers; further study is needed to better define outcomes for this subset of patients [57, 58].

A review of the world experience has documented a posttransplant survival rate of 70% to 80% for children with hepatoblastomas. Intravenous invasion, positive lymph nodes, and contiguous spread did not have a significant adverse effect on outcome.

The primary cause of death for both HB and HCC was metastatic disease. Generally, the 5-year survival rate for patients transplanted for HB is 70%.

A study of the United Network for Organ Sharing (UNOS) database reported 135 patients undergoing 135 transplants for HB and 43 transplants for HCC with 1-year, 5-year, and 10-year survival of 79%, 69%, and 66% for HB, respectively, and 86%, 63%, and 58% for HCC, respectively [59, 60]. Liver transplantation for hepatic hemangioma has been studied in 59

patients in Europe with 1-year, 5-year, and 10-year patient survival rates of 93%, 83%, and 72%, respectively.

The availability of donor organs has increased with the use of split-liver grafting and other "technical variant" techniques, along with living-related liver transplant techniques. Prognosis in terms of graft and patient survival appear to be the same between full-size liver and technical variant liver transplants; however, morbidity following transplant appears to be higher in those patients who receive technical variant grafts [61, 62, 63, 64].

Early failure of liver transplant (< 30 d) is usually due to vascular complications or primary nonfunction. Late failure is usually more a result of infection, posttransplant lymphoproliferative disease, chronic rejection, biliary complications, or recurrence of malignant disease. These failures may warrant retransplantation. The predictors of success after retransplantation remain unknown. The United Network for Organ Sharing (UNOS) Standard Transplant and Research Files registry reported all children younger than 18 years listed for a liver transplant in the United that the 5-year survival rates of 69% for hepatoblastoma and 63% for hepatocellular carcinoma and the 10-year survival rates were similar to the 5-year rates. Application of the Milan criteria for UNOS selection of recipients of deceased donor livers is controversial. However, living donor liver transplants are more common with children and the outcome is similar [65, 66, 67, 68, 69].

6.3. Chemotherapy

In recent years, virtually all children with hepatoblastoma have been treated with chemotherapy, which may reduce the incidence of surgical complications at the time of resection, and in some centers, even children with resectable hepatoblastoma are treated with preoperative chemotherapy. For PRETEXT stage 1 hepatoblastoma, it was resected and treated with doxorubicin and cisplatin chemotherapy. The pre-resection neoadjuvant chemotherapy (doxorubicin and cisplatin) was given to all children with PRETEXT stage 2, 3, or 4 hepatoblastoma with or without metastases. The chemotherapy was well tolerated. This strategy resulted in an OS of 75% at 5 years after diagnosis. Identical overall results were seen in a follow-up international study. Following chemotherapy, and excluding those who received liver transplant (less than 5% of patients), complete resection was obtained in 87% of children. In contrast, an American Intergroup protocol for treatment of children with hepatoblastoma, encouraged resection at the time of diagnosis for all tumors amenable to resection without undue risk. The protocol did not treat children with stage I tumors of purely fetal histology with preoperative or postoperative chemotherapy unless they developed progressive disease. Further study will be needed to determine whether presurgical chemotherapy is preferable to resection followed by chemotherapy for children with PRETEXT stage 2, 3, and 4 hepatoblastoma [70, 71].

Routine assessment of hearing, renal, and cardiac function is standard during treatment for pediatric malignancies. Post-chemotherapy neutropenia rarely represents additional concerns during the surgical treatment. Platinum compounds (cisplatin and carboplatin), which have been a backbone of the successful treatment for pediatric liver tumors, are also quite ototoxic. Around 40% of children develop significant hearing loss, which typically affects

high-register tones, and could be delayed. Chronic dose-related nephrotoxicity remains a significant long-term issue for both chemotherapy for malignant liver tumors and calcineurin inhibitor-based immunosuppression. Therefore, early use of calcineurin inhibitor-sparing agents, such as mycophenolate mofetil or sirolimus, is recommended for children after LT for liver tumors. Nevertheless, it is prudent not to give chemotherapy 2 weeks before or after resection or LT.

In rare cases, intensive platinum- and doxorubicin-based multidrug chemotherapy can induce complete regressions in approximately 50% of patients, with subsequent 3-year event-free survival of 56% for pulmonary metastases and eliminated multinodular tumor foci in the liver. Chemotherapy has been much more successful in the treatment of hepatoblastoma than in hepatocellular carcinoma.

6.4. Other Treatment Approaches

Other treatment approaches such as transarterial chemoembolization, have been used for patients with postsurgically-staged stage III hepatoblastoma. Transarterial chemoembolization has been used in a few children to successfully shrink tumor size to permit resection.Cryosurgery, intratumoral injection of alcohol, and radiofrequency ablation can successfully treat small (<5 cm) tumors in adults with cirrhotic livers. Some local approaches such as cryosurgery, radiofrequency ablation, and transarterial chemoembolization that suppress hepatocellular carcinoma tumor progression are used as bridging therapy in adults to delay tumor growth while on a waiting list for cadaveric liver transplant [72].

7. Medical issues related to current chemotherapy

It is no surprise that most of the toxicity data stem from HB treatment survivors, while information from the HCC setting is lacking.

7.1. Recurrent hepatic tumors

The prognosis for a patient with recurrent or progressive hepatoblastoma depends on many factors, including the site of recurrence, prior treatment, and individual patient considerations. If possible, isolated metastases should be resected completely in patients whose primary tumor is controlled. For example, in patients with stage I hepatoblastoma at initial diagnosis, aggressive surgical treatment of isolated pulmonary metastases that develop in the course of the disease may make extended disease-free survival possible. Liver transplant should be considered for patients with isolated recurrence in the liver. Combined vincristine/irinotecan has been used with some success. Some patients treated with cisplatin/vincristine/fluorouracil could be salvaged with doxorubicin-containing regimens, but patients treated with doxorubicin/cisplatin could not be salvaged with vincristine/fluorouracil. Treatment in a clinical trial should be considered if all of the recurrent disease cannot be surgically removed. Phase I and phase II clinical trials may be appropriate and should be considered [73, 74].

The prognosis for a patient with recurrent or progressive hepatocellular carcinoma is poor. Chemoembolization or liver transplant should be considered for those with isolated recurrence in the liver. Phase I and phase II clinical trials may be appropriate and should be considered [75, 76].

8. Summary and future issues

Management of pediatric liver tumors has significantly improved over the last 2 decades. The principal reasons are that efficient chemotherapy and established medico-surgical treatment algorithms for HB have now integrated LT as a very valuable complementary treatment option. The management options for HCC are less effective and not well defined, broadly mirroring the therapeutic guidelines in adults except for a more cautionary approach to neoadjuvant and loco-regional methods. In the pediatric context the main clinical aims are to reduce chemotherapy toxicity (predominantly ototoxicity and nephrotoxicity) in children treated for HB and to investigate additional modes of treatment for HCC.

Improved understanding of HB and HCC biology may improve risk stratification a presentation and direct the treatment at specific molecular targets in the future. Management of less common benign and malignant tumors should benefit from establishing international collaborative pediatric networks such as the Pediatric Liver Unresectable Tumor Observatory (PLUTO).

Author details

Chunbao Guo[*] and Mingman Zhang[*]

*Address all correspondence to:

*Address all correspondence to:

Dept. of hepatobiliary Surgery, Children's Hospital, Chongqing Medical University, ChongqingP.R. China, P.R. China

References

[1] Smith, N. L., Altekruse, S. F., Ries, L. A., Melbert, D. L., O'Leary, M., Smith, F. O., & Reaman, G. H. (2010). Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol.*, 28(15), 2625-34.

[2] Guidelines for the pediatric cancer center and role of such centers in diagnosis and treatment. (1997). *American Academy of Pediatrics Section Statement Section on Hematology/Oncology. Pediatrics*, 99(1), 139-41.

[3] Eheman, C., Henley, S. J., Ballard-Barbash, R., Jacobs, E. J., Schymura, Noone. A. M., Pan, L., Anderson, Fulton. J. E., Kohler, J. A., Ward, E., Plescia, M., Ries, L. A., & Edwards, B. K. (2012). Annual Report to the Nation on the status of cancer, 1975-2008, featuring cancers associated with excess weight and lack of sufficient physical activity. *Cancer.*, 118(9), 2338-66.

[4] Darbari, A., Sabin, K. M., Shapiro, C. N., & Schwarz, K. B. (2003). Epidemiology of primary hepatic malignancies in U.S. children. *Hepatology*, 38(3), 560-6.

[5] Czauderna, P., Otte, J. B., Aronson, D. C., Gauthier, F., Mackinlay, G., Roebuck, D., Plaschkes, J., & Perilongo, G. (2005). Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). Guidelines for surgical treatment of hepatoblastoma in the modern era--recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). *Eur J Cancer*, 41(7), 1031-6.

[6] Exelby, P. R., Filler, R. M., & Grosfeld, J. L. (1975). Liver tumors in children in the particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatrics Surgical Section Survey--1974. *J Pediatr Surg.*, 10(3), 329-37.

[7] Katzenstein, H. M., Krailo, Malogolowkin. M. H., Ortega, J. A., Liu-Mares, W., Douglass, E. C., Feusner, J. H., Reynolds, M., Quinn, J. J., Newman, K., Finegold, Haas. J. E., Sensel, M. G., Castleberry, R. P., & Bowman, L. C. (2002). Hepatocellular carcinoma in children and adolescents: results from the Pediatric Oncology Group and the Children's Cancer Group intergroup study. *J Clin Oncol.*, 20(12), 2789-97.

[8] Czauderna, P., Mackinlay, G., Perilongo, G., Brown, J., Shafford, E., Aronson, D., Pritchard, J., Chapchap, P., Keeling, J., Plaschkes, J., & Otte, J. B. (2002). Liver Tumors Study Group of the International Society of Pediatric Oncology. Hepatocellular carcinoma in children: results of the first prospective study of the International Society of Pediatric Oncology group. *J Clin Oncol.*, 20(12), 2798-804.

[9] Ortega, J. A., Douglass, E. C., Feusner, J. H., Reynolds, M., Quinn, J. J., King, D. R., Liu-Mares, W., & Sensel, M. G. (2000). Randomized comparison of cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: A report from the Children's Cancer Group and the Pediatric Oncology Group. *J Clin Oncol.*, 18(14), 2665-75.

[10] Katzenstein, H. M., Krailo, Malogolowkin. M. H., Ortega, J. A., Liu-Mares, W., Douglass, E. C., Feusner, J. H., Reynolds, M., Quinn, J. J., Newman, K., Sensel, M. G., Castleberry, R. P., & Bowman, L. C. (2002). Hepatocellular carcinoma in children and adolescents: results from the Pediatric Oncology Group and the Children's Cancer Group intergroup study. *J Clin Oncol.*, 20(12), 2789-97.

[11] Andres, A. M., Hernandez, F., Lopez-Santamaría, M., Gámez, M., Murcia, J., Leal, N., López, Gutierrez. J. C., Frauca, E., Sastre, A., & Tovar, J. A. (2007). Surgery of liver tumors in children in the last 15 years. *Eur J Pediatr Surg.*, 17(6), 387-92.

[12] D'Antiga, L., Vallortigara, F., Cillo, U., Talenti, E., Rugge, M., Zancan, L., Dall'Igna, P., De Salvo, G. L., & Perilongo, G. (2007). Features predicting unresectability in hepatoblastoma. *Cancer.*, 110(5), 1050-8.

[13] Hemming, A. W., Reed, A. I., Fujita, S., Zendejas, I., Howard, R. J., & Kim, R. D. (2008). Role for extending hepatic resection using an aggressive approach to liver surgery. *J Am Coll Surg.*, 206(5), 870-5.

[14] Czauderna, P., Mackinlay, G., Perilongo, G., Brown, J., Shafford, E., Aronson, D., Pritchard, J., Chapchap, P., Keeling, J., Plaschkes, J., Otte, J. B., Liver, Tumors., Study, Group., of, the., International, Society., & of, Pediatric. (2002). Hepatocellular carcinoma in children: results of the first prospective study of the International Society of Pediatric Oncology group. *J Clin Oncol.*, 20(12), 2798-804.

[15] Otte, J. B., Pritchard, J., Aronson, D. C., Brown, J., Czauderna, P., Maibach, R., Perilongo, G., Shafford, E., Plaschkes, J., International, Society., of, Pediatric., & Oncology, . S. I. O. P. (2004). Liver transplantation for hepatoblastoma: results from the International Society of Pediatric Oncology (SIOP) study SIOPEL-1 and review of the world experience. *Pediatr Blood Cancer.*, 42(1), 74-83.

[16] Austin, M. T., Leys, C. M., Feurer, I. D., Lovvorn, H. N., O'Neill, J. A., Pinson, C. W., & Pietsch, J. B. (2006). Liver transplantation for childhood hepatic malignancy: a review of the United Network for Organ Sharing (UNOS) database. *J Pediatr Surg.*, 41(1), 182-6.

[17] Czauderna, P., Otte, J. B., Aronson, D. C., Gauthier, F., Mackinlay, G., Roebuck, D., Plaschkes, J., & Perilongo, G. (2005). Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL).Guidelines for surgical treatment of hepatoblastoma in the modern era--recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). *Eur J Cancer.*, 41(7), 1031-6.

[18] Tsukuma, H., Hiyama, T., Tanaka, S., Nakao, M., Yabuuchi, T., Kitamura, T., Nakanishi, K., Fujimoto, I., Inoue, A., Yamazaki, H., et al. (1993). Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med.*, 328(25), 1797-801.

[19] González-Peralta, R. P., Langham, M. R., Jr Andres, J. M., Mohan, P., Colombani, P. M., Alford, M. K., & Schwarz, K. B. (2009). Hepatocellular carcinoma in 2 young adolescents with chronic hepatitis C. *J Pediatr Gastroenterol Nutr.*, 48(5), 630-5.

[20] Ni, Y. H., Chang, M. H., Hsu, H. Y., Hsu, H. C., Chen, C. C., Chen, W. J., & Lee, C. Y. (1991). Hepatocellular carcinoma in childhood. Clinical manifestations and prognosis. *Cancer*, 68(8), 1737-41.

[21] Stocker JT.Hepatic tumors in children. Clin Liver Dis. (2001). , 5(1), 259-81.

[22] De Ioris, M., Brugieres, L., Zimmermann, A., Keeling, J., Brock, P., Maibach, R., Pritchard, J., Shafford, L., Zsiros, J., Czaudzerna, P., & Perilongo, G. (2008). Hepatoblastoma with a low serum alpha-fetoprotein level at diagnosis: the SIOPEL group experience. *Eur J Cancer.*, 44(4), 545-50.

[23] Meyers, R. L., Rowland, J. R., Krailo, M., Chen, Z., Katzenstein, H. M., & Malogolowkin, M. H. (2009). Predictive power of pretreatment prognostic factors in children with hepatoblastoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer*, 53(6), 1016-22.

[24] Schneider, D. T., Calaminus, G., & Göbel, U. (2001). Diagnostic value of alpha 1-fetoprotein and beta-human chorionic gonadotropin in infancy and childhood. *Pediatr Hematol Oncol.*, 18(1), 11-26.

[25] Nicol, K., Savell, V., Moore, J., Teot, L., Spunt, S. L., Qualman, S., Children's, Oncology., Group, Soft., & Tissue, Sarcoma. (2007). Distinguishing undifferentiated embryonal sarcoma of the liver from biliary tract rhabdomyosarcoma: a Children's Oncology Group study. *Pediatr Dev Pathol.*, 10(2), 89-97.

[26] Katzenstein, H. M., Steelman, C. K., Wulkan, M. L., Gow, K. W., Bridge, J. A., Kenney, Thompson. K., de Chadarévian, J. P., & Abramowsky, C. R. (2011). Undifferentiated embryonal sarcoma of the liver is associated with mesenchymal hamartoma and multiple chromosomal abnormalities: a review of eleven cases. *Pediatr Dev Pathol.*, 14(2), 111-6.

[27] Stringer, M. D., & Alizai, N. K. (2005). Mesenchymal hamartoma of the liver: a systematic review. *J Pediatr Surg.*, 40(11), 1681-90.

[28] Malogolowkin, M. H., Stanley, P., Steele, D. A., & Ortega, J. A. (2000). Feasibility and toxicity of chemoembolization for children with liver tumors. *J Clin Oncol.*, 18(6), 1279-84.

[29] Zsíros, J., Maibach, R., Shafford, E., Brugieres, L., Brock, P., Czauderna, P., Roebuck, D., Childs, M., Zimmermann, A., Laithier, V., Otte, J. B., de Camargo, B., Mac, Kinlay. G., Scopinaro, M., Aronson, D., Plaschkes, J., & Perilongo, G. (2010). Successful treatment of childhood high-risk hepatoblastoma with dose-intensive multiagent chemotherapy and surgery: final results of the SIOPEL-3HR study. *J Clin Oncol.*, 28(15), 2584-90.

[30] Clericuzio, C. L., Chen, E., Mc Neil, D. E., O'Connor, T., Zackai, E. H., Medne, L., Tomlinson, G., & De Baun, M. (2003). Serum alpha-fetoprotein screening for hepatoblastoma in children with Beckwith-Wiedemann syndrome or isolated hemihyperplasia. *J Pediatr.*, 143(2), 270-2.

[31] Malogolowkin, M. H., Stanley, P., Steele, D. A., & Ortega, J. A. (2000). Feasibility and toxicity of chemoembolization for children with liver tumors. *J Clin Oncol.*, 18(6), 1279-84.

[32] Tanimura, M., Matsui, I., Abe, J., Ikeda, H., Kobayashi, N., Ohira, M., Yokoyama, M., & Kaneko, M. (1998). Increased risk of hepatoblastoma among immature children with a lower birth weight. *Cancer Res.*, 58(14), 3032-5.

[33] Mc Laughlin, C. C., Baptiste, M. S., Schymura, M. J., Nasca, P. C., & Zdeb, M. S. (2006). Maternal and infant birth characteristics and hepatoblastoma. *Am J Epidemiol.*, 163(9), 818-28.

[34] Chang, M. H., Chen, T. H., Hsu, H. M., Wu, T. C., Kong, M. S., Liang, D. C., Ni, Y. H., Chen, C. J., & Chen, D. S. (2005). Taiwan Childhood HCC Study Group. Prevention of hepatocellular carcinoma by universal vaccination against hepatitis B virus: the effect and problems. *Clin Cancer Res.*, 11(21), 7953-7.

[35] Zsíros, J., Maibach, R., Shafford, E., Brugieres, L., Brock, P., Czauderna, P., Roebuck, D., Childs, M., Zimmermann, A., Laithier, V., Otte, J. B., de Camargo, B., Mac, Kinlay. G., Scopinaro, M., Aronson, D., Plaschkes, J., & Perilongo, G. (2010). Successful treatment of childhood high-risk hepatoblastoma with dose-intensive multiagent chemotherapy and surgery: final results of the SIOPEL-3HR study. *J Clin Oncol.*, 28(15), 2584-90.

[36] Schnater, J. M., Aronson, D. C., Plaschkes, J., Perilongo, G., Brown, J., Otte, J. B., Brugieres, L., Czauderna, P., Mac, Kinlay. G., & Vos, A. (2002). Surgical view of the treatment of patients with hepatoblastoma: results from the first prospective trial of the International Society of Pediatric Oncology Liver Tumor Study Group. *Cancer*, 94(4), 1111-20.

[37] Yoon, J. M., Burns, R. C., Malogolowkin, M. H., & Mascarenhas, L. (2007). Treatment of infantile choriocarcinoma of the liver. *Pediatr Blood Cancer.*, 49(1), 99-102.

[38] Brown, J., Perilongo, G., Shafford, E., Keeling, J., Pritchard, J., Brock, P., Dicks-Mireaux, C., Phillips, A., Vos, A., & Plaschkes, J. (2000). Pretreatment prognostic factors for children with hepatoblastoma-- results from the International Society of Paediatric Oncology (SIOP) study SIOPEL 1. *Eur J Cancer*, 36(11), 1418-25.

[39] Perilongo, G., Shafford, E., Maibach, R., Aronson, D., Brugières, L., Brock, P., Childs, M., Czauderna, P., Mac, Kinlay. G., Otte, J. B., Pritchard, J., Rondelli, R., Scopinaro, M., Staalman, C., Plaschkes, J., International, Society., of, Paediatric., & Oncology-S, I. O. P. E. L. . (2004). Risk-adapted treatment for childhood hepatoblastoma. final report of the second study of the International Society of Paediatric Oncology--SIOPEL 2. *Eur J Cancer.*, 40(3), 411-21.

[40] DeBaun, M.R., & Tucker, M.A. (1998). Risk of cancer during the first four years of life in children from The Beckwith-Wiedemann Syndrome Registry. *J Pediatr.*, 132, (3 Pt 1):398-400.

[41] Sparago, A., Russo, S., Cerrato, F., Ferraiuolo, S., Castorina, P., Selicorni, A., Schwienbacher, C., Negrini, M., Ferrero, G. B., Silengo, M. C., Anichini, C., Larizza, L., & Riccio, A. (2007). Mechanisms causing imprinting defects in familial Beckwith-Wiedemann syndrome with Wilms' tumour. *Hum Mol Genet*, 16(3), 254-64.

[42] Algar, E. M., St, Heaps. L., Darmanian, A., Dagar, V., Prawitt, D., Peters, G. B., & Collins, F. (2007). Paternally inherited submicroscopic duplication at 1115 implicates insulin-like growth factor II in overgrowth and Wilms' tumorigenesis. *Cancer Res.*

[43] Steenman, M., Westerveld, A., & Mannens, M. (2000). Genetics of Beckwith-Wiedemann syndrome-associated tumors: common genetic pathways. *Genes Chromosomes Cancer.*, 28(1), 1-13.

[44] Roebuck, D. J., Olsen, Ø., & Pariente, D. (2006). Radiological staging in children with hepatoblastoma. *Pediatr Radiol.*, 36(3), 176-82.

[45] Tiao, G. M., Bobey, N., Allen, S., Nieves, N., Alonso, M., Bucuvalas, J., Wells, R., & Ryckman, F. (2005). The current management of hepatoblastoma: a combination of chemotherapy, conventional resection, and liver transplantation. *J Pediatr.*, 146(2), 204-11.

[46] Atri, P., Paredes, J. L., Di Cicco, L. A., Sindhi, R., Soltys, K. A., Mazariegos, G. V., & Kane, T. D. (2010). Review of outcomes of primary liver cancers in children: our institutional experience with resection and transplantation. *Surgery*, 148(4), 778-82.

[47] Otte, J. B., Pritchard, J., Aronson, D. C., Brown, J., Czauderna, P., Maibach, R., Perilongo, G., Shafford, E., & Plaschkes, J. (2004). International Society of Pediatric Oncology (SIOP). Liver transplantation for hepatoblastoma: results from the International Society of Pediatric Oncology (SIOP) study SIOPEL-1 and review of the world experience. *Pediatr Blood Cancer*, 42(1), 74-83.

[48] Douglass, E. C., Reynolds, M., Finegold, M., Cantor, A. B., & Glicksman, A. (1993). Cisplatin, vincristine, and fluorouracil therapy for hepatoblastoma: a Pediatric Oncology Group study. *J Clin Oncol.*, 11(1), 96-9.

[49] Pritchard, J., Brown, J., Shafford, E., Perilongo, G., Brock, P., Dicks-Mireaux, C., Keeling, J., Phillips, A., Vos, A., & Plaschkes, J. (2000). Cisplatin, doxorubicin, and delayed surgery for childhood hepatoblastoma: a successful approach--results of the first prospective study of the International Society of Pediatric Oncology. *J Clin Oncol.*, 18(22), 3819-28.

[50] Perilongo, G., Shafford, E., Maibach, R., Aronson, D., Brugières, L., Brock, P., Childs, M., Czauderna, P., Mac, Kinlay. G., Otte, J. B., Pritchard, J., Rondelli, R., Scopinaro, M., Staalman, C., & Plaschkes, J. (2004). International Society of Paediatric Oncology-SIOPEL 2.Risk-adapted treatment for childhood hepatoblastoma. final report of the second study of the International Society of Paediatric Oncology--SIOPEL 2. *Eur J Cancer*, 40(3), 411-21.

[51] Feusner, J. H., Krailo, M. D., Haas, J. E., Campbell, J. R., Lloyd, D. A., & Ablin, A. R. (1993). Treatment of pulmonary metastases of initial stage I hepatoblastoma in childhood. *Report from the Childrens Cancer Group. Cancer*, 71(3), 859-64.

[52] Perilongo, G., Brown, J., Shafford, E., Brock, P., De Camargo, B., Keeling, J. W., Vos, A., Philips, A., Pritchard, J., & Plaschkes, J. (2000). Hepatoblastoma presenting with

lung metastases: treatment results of the first cooperative, prospective study of the International Society of Paediatric Oncology on childhood liver tumors. *Cancer*, 89(8), 1845-53.

[53] Malogolowkin, M. H., Katzenstein, H. M., Krailo, M., Chen, Z., Quinn, J. J., Reynolds, M., & Ortega, J. A. (2008). Redefining the role of doxorubicin for the treatment of children with hepatoblastoma. *J Clin Oncol.*, 26(14), 2379-83.

[54] Lubienski, A. Hepatocellular carcinoma: interventional bridging to liver transplantation. *Transplantation*, 2005. 80(1 Suppl):S113-9.

[55] Otte, J. B., Pritchard, J., Aronson, D. C., Brown, J., Czauderna, P., Maibach, R., Perilongo, G., Shafford, E., Plaschkes, J., International, Society., of, Pediatric., & Oncology, . S. I. O. P. (2004). Liver transplantation for hepatoblastoma: results from the International Society of Pediatric Oncology (SIOP) study SIOPEL-1 and review of the world experience. *Pediatr Blood Cancer*, 42(1), 74-83.

[56] Reyes, Carr. B., Dvorchik, I., Kocoshis, S., Jaffe, R., Gerber, D., Mazariegos, G. V., Bueno, J., & Selby, R. (2000). Liver transplantation and chemotherapy for hepatoblastoma and hepatocellular cancer in childhood and adolescence. *J Pediatr.*, 136(6), 795-804.

[57] Austin, M. T., Leys, C. M., Feurer, I. D., Lovvorn, H. N., O'Neill, J. A., Pinson, C. W., & Pietsch, J. B. (2006). Liver transplantation for childhood hepatic malignancy: a review of the United Network for Organ Sharing (UNOS) database. *J Pediatr Surg.*, 41(1), 182-6.

[58] Beaunoyer, M., Vanatta, J. M., Ogihara, M., Strichartz, D., Dahl, G., Berquist, W. E., Castillo, R. O., Cox, K. L., & Esquivel, C. O. (2007). Outcomes of transplantation in children with primary hepatic malignancy. *Pediatr Transplant.*, 11(6), 655-60.

[59] Guiteau, J. J., Cotton, R. T., Karpen, S. J., O'Mahony, C. A., & Goss, J. A. (2010). Pediatric liver transplantation for primary malignant liver tumors with a focus on hepatic epithelioid hemangioendothelioma: the UNOS experience. *Pediatr Transplant.*, 14(3), 326-31.

[60] Suh, M. Y., Wang, K., Gutweiler, J. R., Misra, M. V., Krawczuk, L. E., Jenkins, R. L., & Lillehei, C. W. (2008). Safety of minimal immunosuppression in liver transplantation for hepatoblastoma. *J Pediatr Surg.*, 43(6), 1148-52.

[61] Browne, M., Sher, D., Grant, D., Deluca, E., Alonso, E., Whitington, P. F., & Superina, R. A. (2008). Survival after liver transplantation for hepatoblastoma: a 2-center experience. *J Pediatr Surg.*, 43(11), 1973-81.

[62] Faraj, W., Dar, F., Marangoni, G., Bartlett, A., Melendez, H. V., Hadzic, D., Dhawan, A., Mieli-Vergani, G., Rela, M., & Heaton, N. (2008). Liver transplantation for hepatoblastoma. *Liver Transpl.*, 14(11), 1614-9.

[63] Austin, M. T., Leys, C. M., Feurer, I. D., Lovvorn, H. N., 3rd O'Neill, J. A., Pinson, C. W., & Pietsch, J. B. (2006). Liver transplantation for childhood hepatic malignancy: a

review of the United Network for Organ Sharing (UNOS) database. *J Pediatr Surg.*, 41(1), 182-6.

[64] Heaton, N., Faraj, W., Melendez, H. V., Jassem, W., Muiesan, P., Mieli-Vergani, G., Dhawan, A., & Rela, M. (2008). Living related liver transplantation in children. *Br J Surg.*, 95(7), 919-24.

[65] Reyes, Carr. B., Dvorchik, I., Kocoshis, S., Jaffe, R., Gerber, D., Mazariegos, G. V., Bueno, J., & Selby, R. (2000). Liver transplantation and chemotherapy for hepatoblastoma and hepatocellular cancer in childhood and adolescence. *J Pediatr.*, 136(6), 795-804.

[66] Sevmis, S., Karakayali, H., Ozçay, F., Canan, O., Bilezikci, B., Torgay, A., & Haberal, M. (2008). Liver transplantation for hepatocellular carcinoma in children. *Pediatr Transplant.*, 12(1), 52-6.

[67] Madanur, Battula. N., Davenport, M., Dhawan, A., & Rela, M. (2007). Staged resection for a ruptured hepatoblastoma: a 6-year follow-up. *Pediatr Surg Int.*, 23(6), 609-11.

[68] Schnater, J. M., Aronson, D. C., Plaschkes, J., Perilongo, G., Brown, J., Otte, J. B., Brugieres, L., Czauderna, P., Mac, Kinlay. G., & Vos, A. (2002). Surgical view of the treatment of patients with hepatoblastoma: results from the first prospective trial of the International Society of Pediatric Oncology Liver Tumor Study Group. *Cancer*, 94(4), 1111-20.

[69] Otte, J.B. (2008). Should the selection of children with hepatocellular carcinoma be based on Milan criteria? *Pediatr Transplant.*, 12(1), 1-3.

[70] Douglass, E. C., Reynolds, M., Finegold, M., Cantor, A. B., & Glicksman, A. (1993). Cisplatin, vincristine, and fluorouracil therapy for hepatoblastoma: a Pediatric Oncology Group study. *J Clin Oncol.*, 11(1), 96-9.

[71] Ortega, J. A., Douglass, E. C., Feusner, J. H., Reynolds, M., Quinn, J. J., Finegold, Haas. J. E., King, D. R., Liu-Mares, W., Sensel, M. G., & Krailo, M.D. (2000). Randomized comparison of cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: A report from the Children's Cancer Group and the Pediatric Oncology Group. *J Clin Oncol.*, 18(14), 2665-75.

[72] Habrand, J. L., Nehme, D., Kalifa, C., Gauthier, F., Gruner, M., Sarrazin, D., & Terrier-Lacombe, Lemerle. J. (1992). Is there a place for radiation therapy in the management of hepatoblastomas and hepatocellular carcinomas in children? *Int J Radiat Oncol Biol Phys.*, 23(3), 525-31.

[73] Feusner, J. H., Krailo, M. D., Haas, J. E., Campbell, J. R., Lloyd, D. A., & Ablin, A. R. (1993). Treatment of pulmonary metastases of initial stage I hepatoblastoma in childhood. *Report from the Childrens Cancer Group. Cancer*, 71(3), 859-64.

[74] Perilongo, G., Brown, J., Shafford, E., Brock, P., De Camargo, B., Keeling, J. W., Vos, A., Philips, A., Pritchard, J., & Plaschkes, J. (2000). Hepatoblastoma presenting with lung metastases: treatment results of the first cooperative, prospective study of the International Society of Paediatric Oncology on childhood liver tumors. *Cancer.*, 89(8), 1845-53.

[75] Robertson, P. L., Muraszko, K. M., & Axtell, R. A. (1997). Hepatoblastoma metastatic to brain: prolonged survival after multiple surgical resections of a solitary brain lesion. *J Pediatr Hematol Oncol.*, 19(2), 168-71.

[76] Perilongo, G., Maibach, R., Shafford, E., Brugieres, L., Brock, P., Morland, B., de Camargo, B., Zsiros, J., Roebuck, D., Zimmermann, A., Aronson, D., Childs, M., Widing, E., Laithier, V., Plaschkes, J., Pritchard, J., Scopinaro, M., Mac, Kinlay. G., & Czauderna, P. (2009). Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. *N Engl J Med.*, 361(17), 1662-70.