Liver Tumors in Children

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Abbreviations

AFP	Alpha Fetoprotein
AMKL	Acute Megakaryoblastic Leukemia
CHIC	Children's Hepatic tumor International Collaboration
COG	Children's Oncology Group
ENCCA	European Network for Cancer Research in Children and Adolescents
FL-HCC	Fibrolamellar hepatocellular carcinoma
FNH	Focal nodular hyperplasia
GCTs	Teratoma (germ cell tumors)
GPOH	German Pediatric Oncology Hematology Study Group
HACE	Hepatic Arterial chemo-Embolization
HB	Hepatoblastoma
HCC	Hepatocellular Carcinoma
HC-NOS	Hepatocellular Neoplasm-Not otherwise specified
HLH	Hemophagocytic Lymphohistiocytosis
IMT	Inflammatory myofibroblastic tumor
JPLT	Japanese Pediatric Liver Tumors Study Group
LCH	Langerhahn's Cell Histiocytosis
LRN	Large regenerative nodules
NOS	Heptocellular tumor Not otherwise specified
NRH	Nodular regenerative hyperplasia
PEI	Percutaneous ethanol injection
PLUTO	Pediatric Liver Unresectable Tumor Observatory
POST-TEXT	POST-Treatment EXTent of tumor
PRETEXT	PRE-Treatment EXTent of tumor
RFA	Radiofrequency ablation
SIOPEL	Liver Tumor Study group of the Societe International Oncologie Pediatriqe
SPLIT	Study of Pediatric Liver Transplantation
TACE	Trans-Arterial chemoembolization
TCLT	Transitional cell liver tumor
TPN	Total Parenteral Nutrition
USL	Undifferentiated sarcoma of the liver
VLBW	Very Low Birth Weight
VOD	Hepatic veno-occlusive disease

Chemotherapy abbreviations see legend for Table 16.9

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Historical Context

As recently as the 1960s, surgical resection of malignant liver tumors in children carried a high perioperative mortality of over 30 %, mostly due to hemorrhage [1]. Increasing knowledge of segmental liver anatomy [2] and more sophisticated perioperative management reduced surgical morbidity, and yet operative mortality remained over 10 % in Exelby's 1974 landmark survey of the American Academy of Pediatrics Surgical Section. In this era, before the introduction of cisplatin based chemotherapy and modern surgical techniques, complete operative excision carried a high risk of morbidity and mortality, but offered the only chance for cure [3]. Maneuvers introduced to minimize bleeding including the Pringle maneuver (clamping of the afferent vascular pedicle), total vascular occlusion (clamping of the aorta and clamping or balloon occlusion of the inferior vena cava), hypothermic and hypotensive anesthesia [4], and preresection ligation of the hepatic inflow and outflow vasculature. A decade later, Price reports in 1982 a series of 11 resections for hepatic neo-

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plasia in children with no operative deaths [5]. The increasing use of preoperative chemotherapy was perhaps even more important than the advances in surgical technique.

Our sophistication with chemotherapy for HB, and adjuvant use of antiangiogenic regimens for HCC continues to evolve. One key advance of chemotherapy has been in a neoadjuvant setting to shrink the tumor and enable complete and safe surgical resection. In addition to the two most common malignant liver tumors in children, Hepatoblastoma (HB) and Hepatocellular Carcinoma (HCC) there are a host of benign tumors and more rare malignant liver tumors which may appear in children. The past three decades have brought significant advances in our epidemiology diagnostic acumen with latest generation radiographic imaging and percutaneous biopsy as well as landmark advances in both chemotherapy and surgical technique [6].

Differential Diagnosis

Most solid hepatic masses in children, contrary to adults, are malignant lesions, however sometimes they represent rare benign diagnoses. The differential diagnosis of liver tumors in children includes epithelial tumors, mixed epithelial and mesenchymal tumors, mesenchymal tumors, germ cell tumors, and metastatic or secondary tumors. Following these broad categories a new consensus classification for pediatric liver tumors was recently developed [7]. This consensus classification is the product of the International Liver Tumors Pathology Symposium sponsored by the Children's Oncology Group (COG) in Los Angeles in March of 2011, and subsequent International Pediatric Liver tumors Biology Symposium sponsored by the Liver Tumor Study group of the Societe International Oncologie Pediatriqe (SIOPEL) and European Network for Cancer Research in Children and Adolescents (ENCCA) in Paris October 2011 (Table 16.1) [8, 9]. More rarely one may encounter metastatic lesions or contiguous invasion from primary pediatric solid tumors such as neuroblastoma, Wilms' tumor, or pancreatoblastoma. Hepatic involvement in hematologic malignancies such as hemophagocytic lymphohistiocytosis (HLH), langerhahn's cell histiocytosis (LCH), and megakaryoblastic leukemia may occasionally mimic a primary hepatic malignancy. A variety of benign tumors can also occur in this age group the most common of which are benign vascular tumors [9] (Fig. 16.1). Other benign tumors include mesenchymal hamartoma, biliary cystadenoma, hepatic adenoma, focal nodular hyperplasia (FNH), macroregenerative nodules, dysplastic nodules, germ cell tumors, and inflammatory myofibroblastic tumors [10]. Non neoplastic masses such as vascular malformations, congenital and acquired cysts, abscess, hematoma, and fatty infiltration of the liver may occasionally be confused with liver tumors (Fig. 16.2). Hepatic hematoma or infarction should be suspected in any child with a history of hepatic trauma or in newborns with sepsis and coagulopathy; especially if there is

Table 16.1 Pediatric tumors of the liver, international consensus classification [7]

Epithelial tumors
Hepatocellular
Malignant
Hepatoblastoma (epithelial variants)
Pure fetal hepatoblastoma with low mitotic activity
Fetal, pleomorphic *(vs pleomorphic epithelial component)*
Fetal, cholangioblastic variant
Epithelial mixed (fetal, embryonal, small cell)
Small cell component, INI+/–
Hepatocellular carcinoma
Fibrolamellar HCC
Transitional tumors of the liver
Hepatoblastoma with HCC component
Benign
Hepatocellular adenoma (adenomatosis)
Focal nodular hyperplasia
Macroregenerative nodules
Premalignant lesions
Dysplastic nodules (low grade and high grade)
Biliary
Bile duct adenoma (biliary cystadenoma)
Cholangiocarcinoma
Mixed hepatocellular and biliary
Combined hepatocellular-cholangiocarcinoma
Mixed epithelial/mesenchymal or uncertain origin
Hepatoblastoma mixed
Epithelial and mesenchymal
Teratoid hepatoblastoma
Malignant rhabdoid tumor
INI– (documented *INI* mut)
INI+
Nested epithelial stromal tumor
Mesenchymal tumors
Malignant
Embryonal sarcoma
Rhabdomyosarcoma
Epithelial hemangioendothelioma
Angiosarcoma (adult type)
Synovial sarcoma
Other (DSRCT, PNET, NUT carcinoma…)
Benign
Infantile hemangioma
Cavernous hemangioma
Mesenchymal hamartoma
Germ cell tumors
Teratoma
Yolk sac tumor
Metastatic (secondary)
Metastatic
Hepatic involvement hematologic malignancy
Acute myeloid leukemia
Megakaryoblastic leukemia (M7)
Hemophagocystic lymphohistiocytosis (HLH)
Langerhahn's cell histiocytosis (LCH)

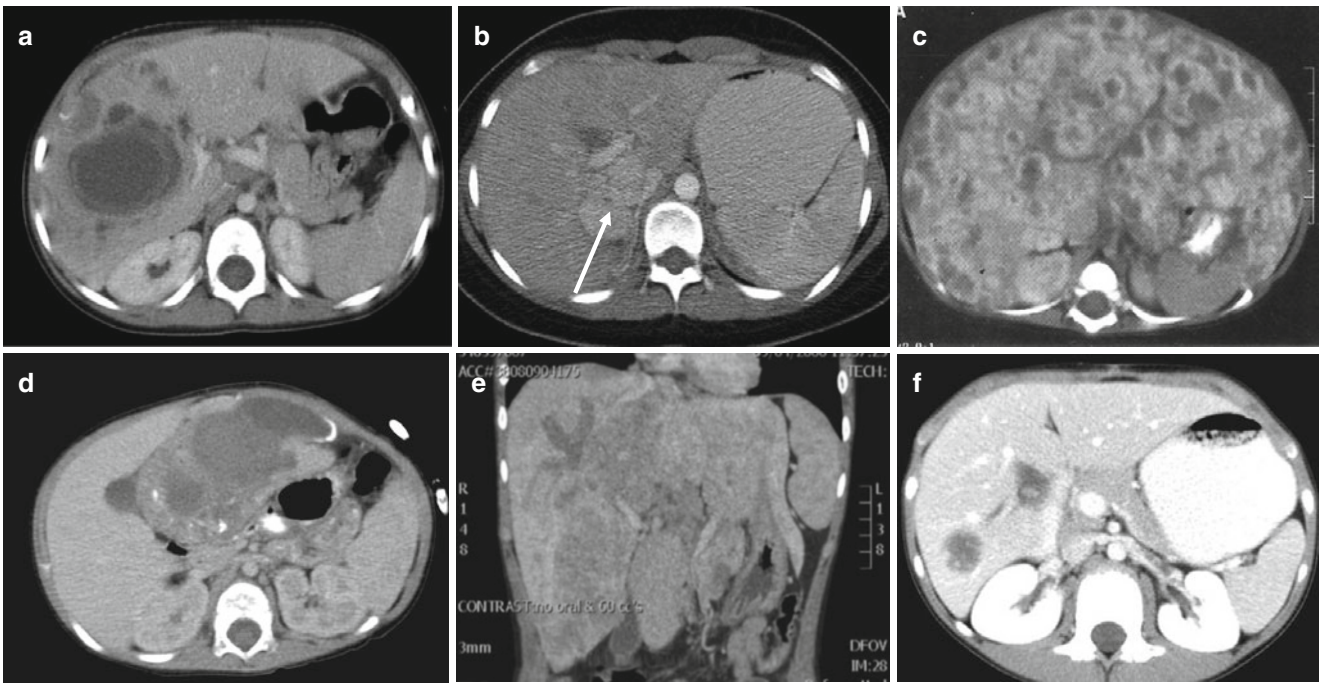

Fig. 16.1 Radiographic appearance of the most common hepatic benign and malignant neoplastic masses of the liver in children. (**a**) Mesenchymal hamartoma a complex multicystic mass with solid septae; (**b**) Focal nodular hyperplasia with arrow pointing to classic stellate central scar; (**c**) Diffuse infantile hepatic hemangioma with multiple nodules showing peripheral contrast enhancement; (**d**) PRETEXT II Hepatoblastoma; (**e**) PRETEXT IV + P hepatocellular carcinoma with involvement of main portal vein; (**f**) Metastatic tumor, two nodules of metastatic colorectal carcinoma in right anterior and posterior sections

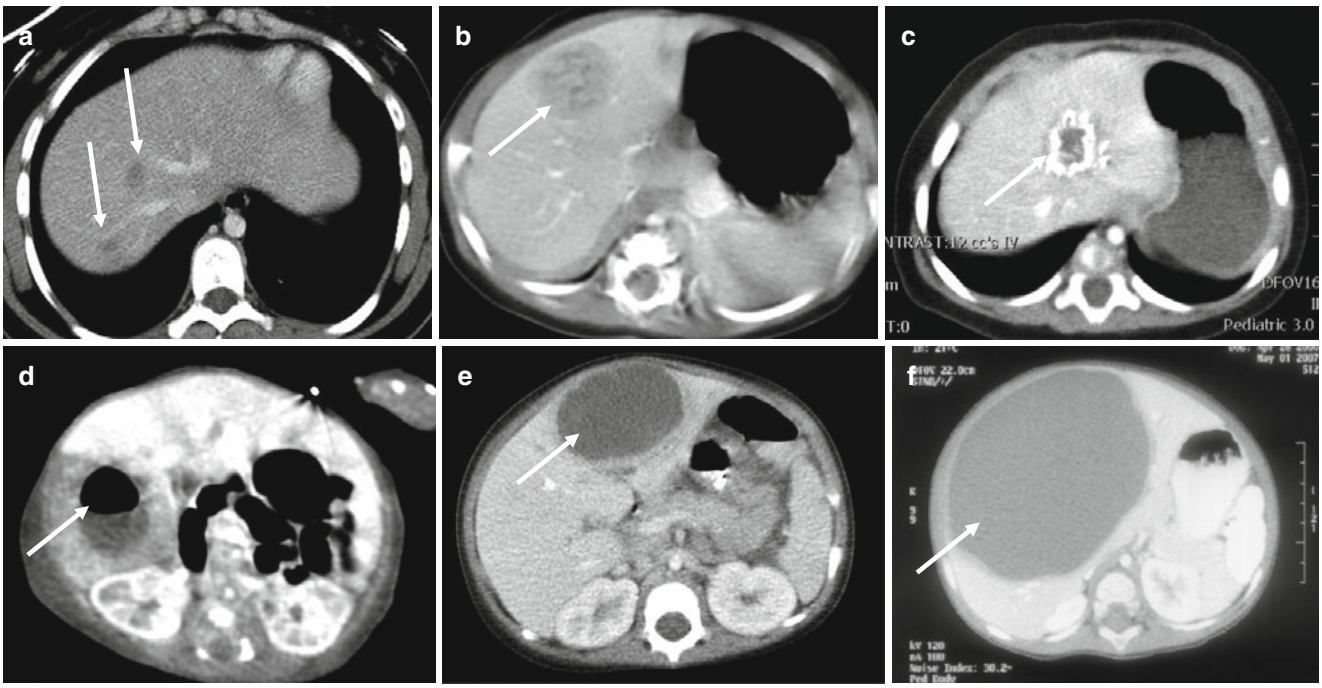

Fig. 16.2 Differential diagnosis: Radiographic appearance of non-neoplastic masses and cysts. (**a**) Multiple small bacterial abscess in a child with chronic granulomatous disease; (**b**) Inspissated bile lake in a child with biliary atresia and cholangitis; (**c**) organizing hematoma in a newborn with sepsis and coagulopathy; (**d**) infarction of right lobe liver and hepatic abscess (with air fluid level) in a premature baby with necrotizing enterocolitis; (**e**) acquired cyst is an amoebic abscess in a toddler with fever; (**f**) congenital cyst is a ciliated foregut cyst in an infant with abdominal distension and feeding difficulties

Table 16.2 Differential diagnosis based upon age at diagnosis [11, 12]

Age group	Malignant	Benign
Infant/toddler	Hepatoblastoma 43 % Rhabdoid tumor 1 % Malignant germ cell 1 %	Hemangioma/vascular 14 % Mesenchymal hamartoma 6 % Teratoma 1 %
School age/adolescent	Hepatocellular (transitional or HC-NOS tumors) 23 % Sarcomas 7 %	Focal nodular hyperplasia 3 % Hepatic adenoma 1 %

a history of perinatal birth trauma, thrombocytopenia, or hemodynamic collapse requiring cardiopulmonary resuscitation. Congenital liver cysts are rare and represent a spectrum ranging from large simple cysts, intrahepatic choledochal cyst, and ciliated hepatic foregut cyst. Acquired cysts might be bacterial, hydatid, or amoebic abscess.

Age at presentation and level of alpha fetoprotein (AFP) are frequent keys to differential diagnosis [11, 12] (Table 16.2). HB is most common in very young children; more than 80 % of children with HB are under the age of 3 at diagnosis [13]. More rare malignant liver tumors in infants and toddlers are teratoma, rhabdoid tumor, and biliary rhabdomyosarcoma [9]. Benign tumors in infants and toddlers may be infantile hepatic hemangioma or mesenchymal hamartoma. In older children and adolescents the main malignant liver tumors are HCC and undifferentiated sarcoma of the liver. HCC in this age group is comprised of an heterogeneous group of tumors, including tumors with features of both HB and HCC, *de novo* HCC tumors, HCC developing on an underlying metabolic or cirrhotic liver disease, and fibrolamellar carcinomas [14, 15]. Tumors in older children with features of both HB and HCC were previously, and somewhat imprecisely, dubbed "transitional cell liver tumors (or TCLT)." The new international consensus classification designates these tumors as [7]. The median age at diagnosis for HCC is about 12 years, but HCC has been described in children as young as 5 [16, 17].

High AFP favors a malignant diagnosis of HB. AFP is sometimes, but not always, elevated in HCC, and is less specific. Other conditions are sometimes associated with an elevated AFP level and this may lead to errors in diagnosis in the absence of a biopsy. Elevated AFP may be associated with other tumor types including germ cell tumors and benign liver tumors such as mesenchymal hamartoma [18] and infantile hemangioma [19]. Other conditions such as viral hepatits or tyrosinemia may be associated with a high AFP [20]. In these situations the AFP level is usually not as high as in HB. Alternatively high AFP is a nonspecific finding in infants as the high fetal AFP levels gradually decline to postnatal levels by 6–8 months of age. Consequently in children younger than 1 year it may be difficult to distinguish physiologic elevation of AFP from AFP secreted by a malignant tumor. Moreover, AFP is often secreted at very high levels in the regenerating liver and/or after ischemic liver injury. A spontaneous decline in the AFP level without any treatment is a good argument in favor of physiologic, not neoplastic, origin. Low AFP is seen in some children with HCC, and other malignant liver tumors like rhabdoid and sarcomas, and benign tumors. Beware that a false low AFP level may sometimes be seen in HB due to lab error. This lab error called the "Hook effect" is a problem that can occur in the presence of extremely high AFP overwhelming the assay technique and generating an erroneously low result [21].

Regardless of the AFP level, unless the tumor has unequivocal radiographic characteristics of a benign tumor, such as an infantile hemangioma, biopsy is recommended. Ultrasound guided or CT guided percutaneous biopsy by co-axial technique is the most common approach to tumor biopsy, except in situations where a larger amount of tissue is desired for biologic study and genetic testing. In patients with high AFP level the main aim is to distinguish between HB, transitional liver tumor, and HCC. In patients with normal AFP the main aim is to distinguish benign tumors, from rhabdoid tumor, fibrolamellar HCC, sarcomas, and metastatic tumors.

Malignant Tumors

Hepatoblastoma (HB)

Epidemiology, Biology, Genetics

The incidence of hepatoblastoma (HB) throughout the world is fairly constant at 0.5 ± 1.5 cases per million children and the male: female ratio of HB is 2:1 [6]. HB is the cause of 80 % of all malignant liver neoplasms in children and accounts for 91 % of the malignant tumors in children younger than 5 years [22]. Epidemiological studies in the United States describe an incidence of 0.7 cases per one million per year [6, 22]. HB rates have increased from 0.6 to 1.2 per million in the past two decades [23]. An increase in the incidence of malignant tumors in the United States has been described between 1973 and 1977 and between 1993 and 1997. HB rates increased (from 0.6 to 1.2 cases per one million population), suggesting that the improved survival rates of extremely premature babies (birth weight <1500 g) has led to a new population of children having increased susceptibility to HB.

The etiology of HB is largely unknown. It is considered to be an embryonic tumor that probably arises from hepatoblasts present in the liver during embryonal life [24]. HB is well-

Table 16.3 Constitutional genetic syndromes associated with pediatric liver tumors [21, 25, 28–34]

Disease tumor type	Gene (chromosome locus)
Familial adenomatous polyposis	*APC (5q21.22) p57KIP2, others*
Beckwith-Wiedemann syndrome	*(11p15.5)*
Li-Fraumeni syndrome	*TP53, others (17p13)*
Trisomy 18	*18*
Glycogen storage disease type I	Glucose-6-phosphatase
Hereditary tyrosinemia	Fumarylaceto-acetate hydrolase
Alagille syndrome	*JAG1*
PFIC (familial cholestatic syndromes)	*FIC1, BSEP*
Neurofibromatosis	*NF-1*
Ataxia–telangiectasia	*ATM*
Fanconi anemia	*FAA, FAC, others*
Tuberous sclerosis	*TSC1, TSC2*

known to be associated with several constitutional genetic syndromes and malformations including Beckwith-Wiedemann syndrome, familial intrahepatic cholestasis, renal or adrenal agenesis, fetal alcohol syndrome, and Prader-Willi syndrome [21, 25] (Table 16.3). Beckwith-Wiedemann syndrome, which shows a loss of heterozygosity at the p57(KIP2) sites located at the chromosomal locus 11p15.5 [26, 27], is characterized by an overgrowth syndrome, an umbilical defect (either an umbilical hernia or omphalocele) and macroglossia Cases of HB have also been associated with hemihypertrophy, total parenteral nutrition (TPN) related cholestasis, and Type 1 glycogen storage disease [28]. Environmental factors including maternal use of oral contraceptives, exposure to metals and smoking may play a role in the occurrence of HB [29, 30]. Familial case reports of HB with FAP are striking and suggest a role in the pathogenesis of HB for chromosomes 5 and 11 [31]. Additional screening for cases in FAP kindred families is recommended by testing for germline mutations in the APC tumor suppressor gene [31, 32]. Germline APC mutations are not commonly seen in children with sporadic HB [33, 34]. Recurring translocations involving 1q12-21 have been described [35].

It is apparent that very low birth weight (VLBW), generally defined as <1500 g, is a potent risk factor for HB which is independently associated with congenital abnormalities [21, 23]. Since these babies have many problems associated with prematurity that require various treatments including total parenteral nutrition, phototherapy, and administration of numerous drugs, some component of these treatments for prematurity appears to be carcinogenic of hepatoblasts. The odds ratio (OR) of the occurrence of HB was 17.18 for babies weighing less than 1500 g compared to an OR of 1.56 for those weighing more than 2500 g with a 95 % confidence interval [23]. Preterm and very low birthweight babies may be exposed to potential newborn intensive care risk factors such as light, oxygen, irradiation, plastics, medications, and total parenteral nutrition [36].

Of several distinct developmentally regulated pathways known to be active in HB, such as IGF2/H19 [37–39], Notch [40], hypermethylation of RASSF1A [41], 4q deletion [42], and Wnt/β-catenin [43, 44]. The Wnt/β-catenin pathway that is most closely implicated in its origin [45]. Nuclear and cytoplasmic accumulations of β-catenin whose oncogenic mutations are associated with chromosomal instability and abnormalities of the Wnt/β-catenin signaling pathway, are seen in patients with HB and may contribute to tumorigenesis [44]. Such aberrant Wnt signaling is a hallmark of HB [46]. Several previous studies of sporadic HB have identified mutations or deletions clustered in exon 3 of *CTNNB1*, the gene for β-catenin [46–48]. Wnt ligand binding site coding at exon 3 is required for β-catenin degradation by serine/threonine phosphorylation of β-catenin using the APC/Axin/GSK3β protein complex. Therefore, mutation or absence of this site leads to β-catenin cytoplasmic accumulation. Accumulated β-catenin binds TCF/LEF transcription factors, translocates to the nucleus and activates the expression of many target genes, including those involved in cell proliferation (e.g. c-myc and cyclin D1), anti-apoptosis (e.g. survivin), invasion (e.g. matrix metalloproteinases) and angiogenesis (e.g. VEGF) [43, 45]. Since the Wnt signaling pathway plays an important role in embryonic development, this pathway appears to have an important role in the tumorigenesis of HB. A significant increase in the risk of HB has been noted in families with familial adenomatous polyposis and Gardner's syndrome [35], which is related to APC gene mutations, which is one of destabilized proteins of β-catenin. Survivors of HB who have this particular syndrome are at risk for developing familial adenomatous polyposis at a young age.

Activation of telomerase, which maintain telomere length and is required for cell immortalization, was reported as the prognostic factor of HB [49, 50]. Recently, TERT (telomerase reverse transcriptase), a catalytic component of human telomerase, was identified as one of cofactors of β-catenin to

bind TCF/LEF transcription factors. Therefore, telomerase activation might activate the expression of many target genes of Wnt signals. Interestingly, expression levels of Wnt signal target genes were more elevated TERT activated tumors in the comparison with others regardless β-catenin mutations, suggesting that TERT may be one of the strong activators of LEF/TCF factors. TERT promoter contains MYC binding sites. The highly malignant HB shows significantly high expression of *MYC* and *MYC*-related genes [51]. Since MYC will be activated as one of Wnt signal target genes, TERT expression might be activated by MYC, suggesting that vicious cycle may exist in HB and contributes to develop the highly malignant HB [48]. Recently, Hedgehog signaling and IGF/PI3K/AKT signaling, whose aberrations have been reported previously, were identified as the simulating pathway of Wnt signaling. Therefore, high activation of Wnt signaling by complicated pathways might be strongly correlated with the malignancy of HB.

Pathology

Guidelines for the optimal gross and histologic work-up of HB have been formulated in a College of American Pathologists protocol [52]. A detailed gross description should include information about what Couinaud segments are involved, number and size of tumor nodules, multifocality, macroscopic vascular involvement including detailed analysis of portal vein, hepatic vein, and or retrohepatic vena cava involvement. For the evaluation of surgical resection margins and the assessment of microscopic residual disease, it is recommended that surgeons and pathologists work closely together using colored sutures and/or inking to identify critical margin areas especially as they relate to the vascular and biliary trees. Untreated HB is solitary in about 80 % of patients, multifocal in about 20 %, and located in the right lobe in about 60 %. The color of the cut surface is often variegated as a result of necrosis and hemorrhage. Pure fetal HB will have the tan color of normal liver. Tumors which have been pretreated with chemotherapy are usually firm, well-delineated with whitish fibrotic areas and calcifications.

An internationally agreed upon pathologic classification of the histologic subtypes of hepatoblastoma has recently been [7] (Table 16.4). Subtypes are rarely homogeneous and about 85 % of all HB contain at least some fetal and embryonal components [53, 55]. In pure fetal histology (PFH) also referred to as "well differentiated fetal" there is very little mitotic activity and the tumors appear to carry a very favor-

Table 16.4 International consensus classification histologic subtypes hepatoblastoma [7]

Epithelial	Subtype/definition	Mixed	Subtype/definition
Fetal	**Well-differentiated** Uniform (10–20 μm diameter), round nuclei, cords with minimal mitotic activity, EMH[a]	Stromal derivatives	Spindle cells ("blastema"), osteoid, skeletal muscle, cartilage
	Crowded or mitotically active (>2 per 10 400× microscopic fields); conspicuous nucleoli (usually less glycogen)	Teratoid	Mixed, plus primitive endoderm; neural derivatives, melanin, squamous and glandular elements
	Pleomorphic, poorly differentiated Moderate anisonucleosis, high N/C, nucleoli		
	Anaplastic Marked nuclear enlargement and pleomorphism, hyperchromasia, abnormal mitoses		
Embryonal	10–15 μm diameter, high N/C, angular, primitive tubules, EMH		
Macrotrabecular	Epithelial HB (fetal or embryonal) growing in clusters of >5 cells between sinusoids		
Small cell undifferentiated (SCU)	(5–10 μm diameter) no architectural pattern, minimal pale amphophilic cytoplasm, round to oval nuclei with fine chromatin and inconspicuous nucleoli, +/– mitoses; +/– INI[b]		
Cholangioblastic	Bile ducts, usually at periphery of epithelial islands, can predominate		

[a]*EMH* extramedullary hematopoiesis

[b]Pure small cell undifferentiated needs to be differentiated from malignant rhabdoid tumors (discohesive, eccentric irregular nuclei, prominent nucleoli, abundant cytoplasmic filaments including cytokeratin and vimentin, negative nuclear INI)

able prognosis. Other subtypes of fetal HB include "crowded"/mitotically active, pleomorphic/poorly differentiated, and anaplastic as defined in Table 16.4. The embryonal pattern almost always occurs in combination with fetal components and areas of tumor with transition from fetal to embryonal cells are common. In contrast to fetal tumors, with predominantly embryonal tumors bile production and extramedullary hematopoiesis are rare. Macrotrabecules are 10–20 or more cells thick and the cells in the macrotrabecular part may be fetal, embryonal, or indistinguishable from those of adult type HCC and the cell type of predominance is sometimes used to further subclassify this type [56]. Originally termed "anaplastic", Haas et al [57] proposed the term small cell undifferentiated (SCU) subtype in 1989. Sometimes found in only a few small foci within the tumor, this subtype may portend a poor prognosis. Clearly the prognosis is poor when SCU A subis the dominant histologic phenotype. The impact of an isolated focus of SCU histology upon prognosis is not yet clear, and it is being studied in the current COG trial AHEP-0731. Some SCU HB displays rhabdoid features and shares lack of INI1 expression with malignant rhabdoid tumors [58]. A large proportion of HB (about 45 % when examined after chemotherapy) reveal a mixed epithelial and mesenchymal phenotype. The mixed phenotype can be further subdivided into those where stromal derivatives vs teratoid features are dominant. Osteoid-like bone formation more commonly present after chemotherapy is felt by some to be induced by exposure to chemotherapy [54].

Imaging, Staging, PRETEXT, Risk Group Stratification

Radiographic Imaging

Appropriate, high quality radiographic imaging remains an essential diagnostic and preoperative step in the treatment of all liver tumors, particularly malignant ones. However it is usually difficult to establish the true nature of a lesion based on imaging alone. Radiographically hepatocellular carcinoma (HCC) in otherwise normal (non-cirrhotic) liver of the pediatric patient is difficult to distinguish from hepatoblastoma. Both tumors are typically large (unless HCC is detected by screening in a cirrhotic patient). While HCC is more commonly multifocal, HB may be multifocal as well. In both diagnoses there may be calcification, venous invasion, and lung metastases. Other forms of metastases (for example to bone) are rare in hepatoblastoma and favor a diagnosis of HCC or rhabdoid. Identification of a central fibrous "scar" suggests fibrolamellar carcinoma or focal nodular hyperplasia (FNH) [59, 60].

Usually, the first method used in imaging of liver masses is abdominal ultrasound (US) which will localize the tumor within the liver and offer some clues regarding its possible character. The typical sonographic appearance of HB and HCC is of a large, heterogeneous (usually predominantly hyperechoic), and vascular mass. The use of US contrast agents in children is currently experimental, but the results in adults suggest that they may be helpful for identifying and characterizing hypervascular liver lesions [61]. In the immediate preoperative assessment of patients with vascular involvement, Doppler US is particularly valuable in helping to differentiate between overt vascular invasion and thrombus versus vessel compression by mass effect. In such cases it is very helpful, when the surgeon is present at the US examination time.

The gold standards of hepatic imaging are the triphasic contrast-enhanced abdominal computed tomography (CT) and the MR with hepatocyte specific contrast agents such as diffusion weighted sequences and delayed hepatobiliary phase imaging with hepocyte specific contrast agents gadoxetate disodium or gabobenate dimeglumine. With contrast CT, the three phases correspond to arterial phase and venous phase and delayed phase imaging. The arterial phase shows the hepatic arterial supply to the liver and may be useful for the detection of small hypervascular lesions, for example small HCC or metastatic lesions [62]. Images in the venous phase usually maximize the margins of primary tumors and are best for assessment of portal and hepatic venous involvement; the hepatic veins usually opacify with contrast almost simultaneously with the portal veins. If for some reason only one scan is to be performed, it should be done in the portal venous phase [63]. In addition, in every case of a suspicion of a malignant lesion, high resolution spiral chest CT should be performed in order to visualize potential lung metastases. With the new generation of CT scanners there is a slight risk of overdiagnosis of very small lesions (below 0.5–1 cm) which in fact may rather represent benign lesions rather than true metastatic foci and even, if they are neoplastic in origin, their clinical significance may be controversial [64, 65]. One should also keep in mind relatively frequent occurrence of lung atelectases in basal lung segments in children undergoing CT under general anesthesia.

An alternative and excellent imaging technique for liver tumors is magnetic resonance (MRI) with hepatocyte specific contrast administration. MRI is prone to motion artifact in small children and its accessibility may be limited due to costs resulting from the need for prolonged general anesthesia with special equipment being capable to work under strong magnetic field. The appearance of HB on both CT and MRI is generally a sharply circumscribed mass that is slightly hypoattenuating relative to the adjacent liver parenchyma on unenhanced and contrast-enhanced images [66]. Calcifications are seen quite frequently. On MRI, HB is homogeneously slightly hypointense on T1-weighted images and hyperintense on T2-weighted images relative to adjacent liver parenchyma [66]. Mixed tumors demonstrate more

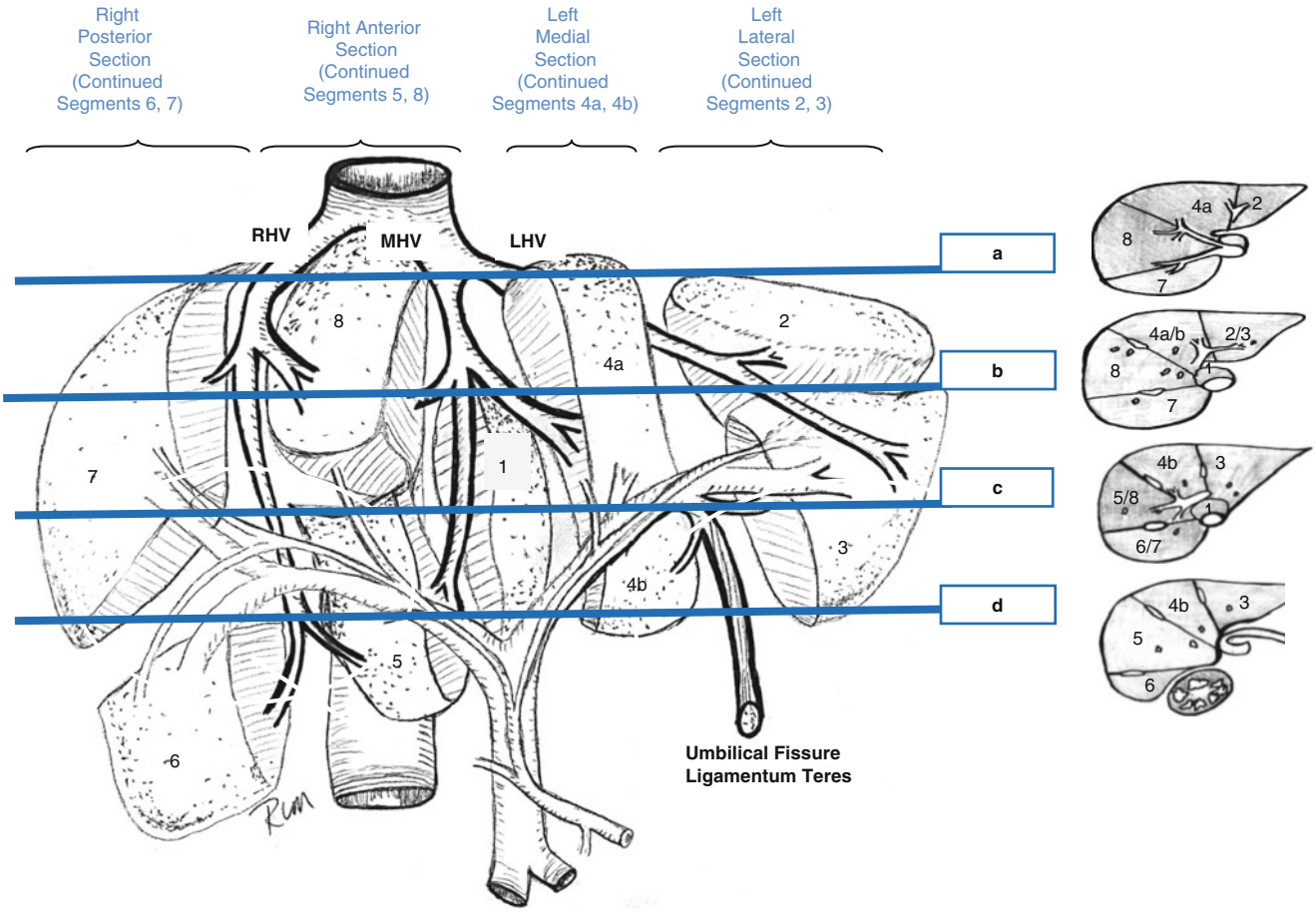

Fig. 16.3 Segmental anatomy of the liver. (**a**) Axial view at the level of the hepatic venous confluence with the suprahepatic venacava; (**b**) Axial view at the level of the left portal vein; (**c**) Axial view at the level of the right portal vein; (**d**) Axial view at the level of the mail portal vein. Numbers 1–8 denote continued segments

heterogeneous signal intensity characteristics [66]. HCCs are heterogeneous (but predominantly hypointense) on T1-weighted images, and mildly hyperintense in comparison with normal liver on T2-weighted images [67]. Contrast-enhanced T1-weighted HCC images show a similar pattern to CT, with early arterial enhancement and reduced signal intensity in the portal venous phase [68]. Recently there has been a whole generation of new, more selective contrast agents used with MRI. In adults, the use of newer contrast agents such as ferucarbotran [69] and mangafodipir [70] may increase the sensitivity of NMR for the detection of HCC, but the results are inconsistent [71]. Experience with the MR contrast agent gadalinium gababinate dimegluonone gd-EOB-DTPA Premovistan Europe Sovist in SUA was recently reported in pediatric HB [72]. The full potential of gd-EOB-DTPA is in evaluation study to date. However, this has clearly shown anatomic differentiation of benign versus malignant tumors with a clarity that is unobtainable with standard contrast agents [73]. There are case reports using positron emission tomography (PET-scan) in detection of recurrent HB, especially when standard imaging (US, CT, MRI) is negative and AFP rises, however false negative and false positive results have been reported [74]. PET-CT is more commonly used nowadays in adult HCC diagnosis, prognostication and staging, however pediatric experience with this modality is very limited.

PRETEXT Group and PRETEXT Annotation Factors

Starting with SIOPEL 1, the cardinal feature of all SIOPEL liver tumor trials has been the use of preoperative neoadjuvant chemotherapy. Such approach required introduction of the preoperative tumor staging system which was called PRETEXT (PRE-Treatment EXTent of tumor). PRETEXT is based upon the segmental anatomy of the liver It has been described in detail in several publications [75–77] (Fig. 16.3). In short it describes the number of contiguous uninvolved liver sections, as well as presence of extrahepatic disease or vascular involvement coded by additional letters (V, P, E, M, C) (Fig. 16.4) (Table 16.5). In addition to risk stratification, PRETEXT has been used to determine tumor resectability and to assess tumor response to neoadjuvant chemotherapy [78, 79]. PRETEXT system applied prior to surgical resec-

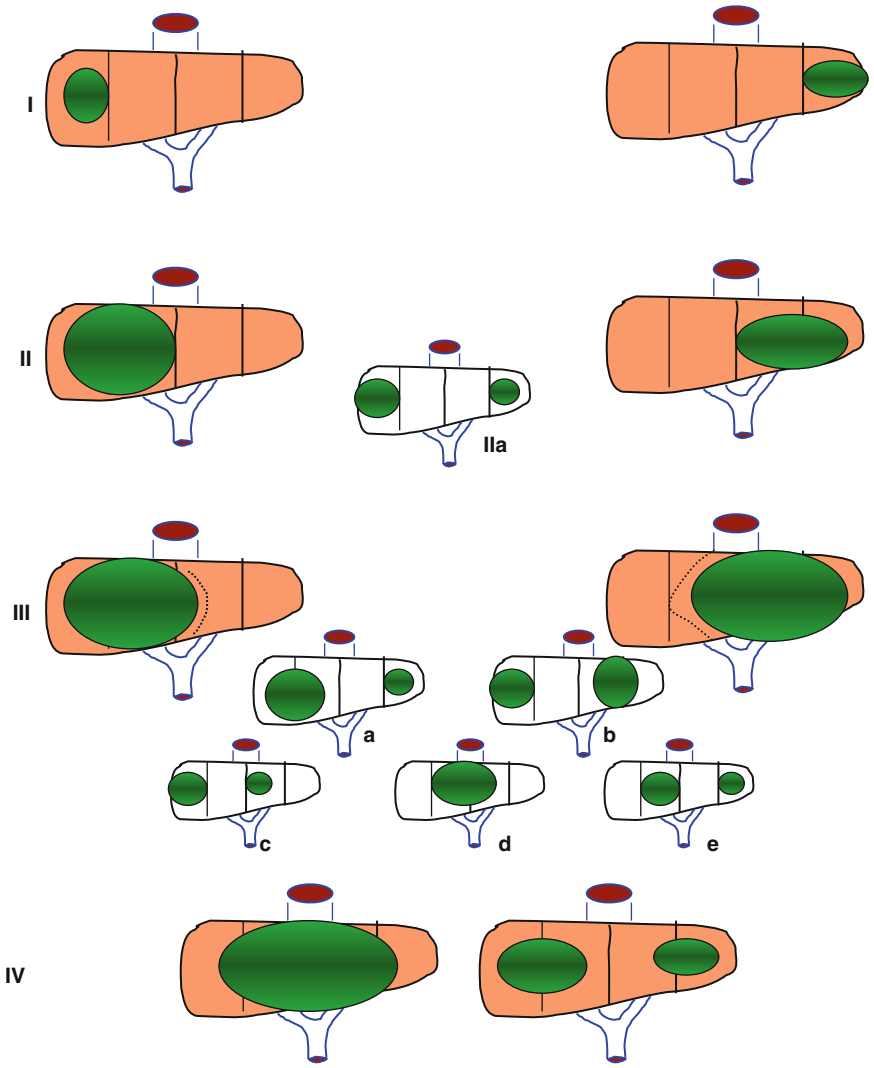

Fig. 16.4 PRETEXT and POST-TEXT groups I, II, III, and IV. Multifocal PRETEXT is IIa. Central or multifocal PRETEXT III is IIIa-e. PREEXT denoted prior to chemotherapy as "PRE-Treatment Extent of disease". POST-TEXT denotes imaging after chemotherapy as "POST-Treatment Extent of Disease"

Table 16.5 PRETEXT/POST-TEXT group (I, II, II, IV) and annotation (V, P, E, M, C, F, R) definitions

PRETEXT/POST-TEXT group	Definition
I	One section involved Three adjoining sections are tumor free
II	One or two sections involved Two adjoining sections are tumor free
III	Two or three sections involved One adjoining section is tumor free
IV	Four sections involved
Annotation:	
V	Venous involvement, V, denotes vascular involvement of the retrohepatic vena cava or involvement of ALL THREE major hepatic veins (right, middle, and left)
P	Portal involvement, P, denotes vascular involvement of the main portal vein and/or BOTH right and left portal veins
E	Extrahepatic involvement of a contiguous structure such as the diaphragm, abdominal wall, stomach, colon, etc.
M	Distant metastatic disease (usually lungs, occasionally bone or brain)
C	Caudate lobe
F	Multifocal tumor nodules
R	Tumor Ruptured at diagnosis

Table 16.6 Use of PRETEXT in risk stratification schemes of the major study groups

	COG-AHEP0731	SIOPEL-3,4,&6	GPOH-HB99	JPLT-2
Very low risk	PRETEXT I or II, pure fetal histology, primary resection			
Low risk/standard risk	PRETEXT I or II Any histology Primary resection	PRETEXT I, II, III	PRETEXT I, II, III	PRETEXT I, II, III
Intermediate-risk	PRETEXT II, III, IV Unresectable at diagnosis V+, P+, E+ SCU			PRETEXT IV Any PRETEXT with rupture, N1, P2, P2a, V3, V3a multifocal
High-risk	Any PRETEXT M+ : AFP level < 100 ng/ml	Any PRETEXT V+, P+, E+, M+ SCU AFP level < 100 ng/ml Rupture	Any PRETEXT V + E + P + M+ Multifocal	Any PRETEXT M1, N2 AFP level < 100 ng/ml

tion but after preoperative chemotherapy has been called POST-TEXT [76]. The precise definitions of vascular involvement differ somewhat between the SIOPEL and COG use of PRETEXT.

PRETEXT has been shown to be of moderate accuracy with a tendency to overstage patients, showed good reproducibility and superior predictive value for survival and possibility to monitor treatment response [75]. It is currently applied in all hepatoblastoma trials and indeed PRETEXT system has been accepted by all major international liver tumors study groups [80]. In HCC where some children may have concomitant hepatic cirrhosis, factors related to possible impairment of liver function should be taken into account in assessing the patient's resectability.

RISK GROUP Stratification

Risk group stratification has differed between the different study groups: COG, SIOPEL, GPOH, and JPLT (Table 16.6). Historically COG used the Evans staging system that relies upon the results of an attempt at surgical resection at diagnosis in all patients. In the current COG trial, AHEP-0731, the risk stratification is a hybrid of the traditional Evan's stage, PRETEXT resectability, AFP level at diagnosis, and presence or absence of unfavorable histologic subtype [81]. After SIOPEL 1, subsequent SIOPEL studies used two risk categories, standard and high risk based upon PRETEXT, presence of metastases and vascular invasion on imaging [82]. With the SIOPEL 3 and 4 studies low AFP tumors (<100 ng/ml) and spontaneously ruptured tumors were added to the high risk category showed that in addition to PRETEXT group, multifocalty AFP level, SCU histology, age over 5 where prognostically important. Recent prognostic analysis performed on the basis of the SIOPEL 2 and 3 trials [84]. An international cooperative effort by COG, SIOPEL, GPOH, and JPLT and coined the Children's Hepatic tumor International Collaboration (CHIC) has been established to identify and adopt an international risk group stratification schema which will be used by all study groups in the future [81]. The initial step in working towards this international risk stratification schema involved establishment of a large cooperative database housing outcome data from all of the multicenter trials shown in Table 16.8 and containing fully annotated data for 1605 patients. This database was then interrogated by univariate and multivariate analysis to yield risk groups comprised of multiple constellations of pretreatment prognostic risk factors (Table 16.7). The international multicenter trial groups are now in the process of integrating these statistical groups of prognostic factors into a global risk stratification scheme that will be used by all trial groups in the future.

Chemotherapy

The introduction of chemotherapy in the multidisciplinary treatment strategy for hepatoblastoma changed the prognosis dramatically. Cisplatin turned out to be the most effective tool. Chemotherapy regimens that included cisplatin achieved response rates up to 97 % which led to a resection rate of up to 80 % [83, 85–94]. Summary results of the major international trials over the past two decades are shown in Table 16.8. The SIOPEL group could even show that the treatment of standard risk hepatoblastoma with six courses of cisplatin monotherapy is equal to the treatment with the combination of cisplatin and doxorubicin [90]. Either used alone, or in combination with doxorubicin, etoposide, 5-fluorouracil, pirarubicin or vincristine, cisplatin has become the gold-standard for the treatment of hepatoblastoma. The different study groups developed on the basis of their experience risk adapted treatment strategies. In the current COG (Children's Oncology Group) study AHEP-0731 low risk patients receive two courses adjuvant cisplatin, vincristine and 5-fluorouracil (C5V). Intermediate risk patients receive neoadjuvant C5V plus doxorubicin (C5V-D), two to four course preoperative and two courses postoperative. High risk patients receive an upfront win-

Table 16.7 Summary results of hepatoblastoma cooperative trials

Study	Chemotherapy	Number of patients	Outcomes
INT0098 (CCG/POG) [85] 1989–1992	C5V vs. CDDP/DOXO	Stage: I/II: 50; Stage III: 83; Stage IV: 40	4-Year EFS/OS: I/II = 88 %/100 % vs. 96 %/96 %; III = 60 %/68 % vs. 68 %/71 %; IV = 14 %/33 % vs. 37 %/42 %
P9645 (COG) [86] 1999–2002	C5V vs. CDDP/CARBO[a]	Stage: I/II: pending publication Stage II = 38; Stage IV = 50	1-Year EFS: Stage III/IV: C5V 51 %; CDDP/Carbo 37 %
HB 94 (GPOH) [87] 1994–1997	I/II: IFOS/CDDP/DOXO; III/IV: IFOS/ CDDP/DOXO + VP/CARBO	Stage: I: 27; II: 3; III: 25; IV: 14	4-Year EFS/OS: I = 89 %/96 %; II = 100 %/100 %; III = 68 %/76 %; IV = 21 %/36 %
HB 99 (GPOH) [88] 1999–2004	SR: IPA; HR: CARBO/VP16	SR: 58 HR: 42	3-Year EFS/OS: SR: 90 %/88 %; HR: 52 %/55 %
SIOPEL 2 [89] 1994–1998	SR: PLADO; HR:CDDP/CARBO/ DOXO	PRETEXT: I = 6; II = 36; III = 25; IV = 21; Mets: 25	3-Year EFS/OS: SR: 73 %/91 %; HR: IV = 48 %/61 %; HR Mets: 36 %/44 %
SIOPEL 3 [90, 91] 1998–2006	SR: CDDP vs. PLADO; HR: SUPERPLADO	SR: PRETEXT I = 18; II = 133; III = 104; HR: PRETEXT IV = 74; +VPE = 70; mets = 70; AFP <100 = 12	3-Year EFS/OS: SR: CDDP 83 %/95 %; PLADO 85 %/93 %; HR: overall 65 %/69 %; mets 57 %/63 %
SIOPEL 4 [92] 2005–2009	HR: Block A: Weekly; CDDP/3 weekly DOXO; Block B CARBO/DOX	PRETEXT: I = 2; II = 17; III = 27; IV = 16; Mets: 39	3-Year EFS/OS: All HR = 76 %/83 %; HR: IV = 75 %/88 %; HR Mets: 77 %/79 %
JPLT 1 [93] 1991–1999	I/II: CDDP(30)/THPA-DOXO; III/IV: CDDP(60)/THPA-DOXO	Stage: I: 9; II: 32; IIIa: 48; IIIb 25; IV: 20	5-Year EFS/OS: I = ? /100 %; II = ?/76 %; IIa = ?/50 %; IIIb = ?/64 %; IV = ?/77 %
JPLT 2 [94] 1999–2010	I: low-dose CDDP Pirarubicin; II–IV: CITA Mets: High dose + stem cell transplant	Stage: *n* = 212; PRETEXT I:; II:; III ; IV	5-Year EFS/OS: I = ?/100 %; II = ?/89 %; III = ?/93 %; IV = ?/63 %; Mets 32 %

AFP alphafetoprotein, *CARBO* carboplatin, *CCG* Children's Cancer Group, *CDDP* cisplatin, *EFS* event-free survival, *C5V* cisplain + 5-flurouracil (5FU) + vincristin, *DOXO* doxorubicin, *OS* overall survival, *PLADO* cisplatin + doxorubicin, *POG* Pediatric Oncology Group SR, standard risk, *SUPERPLADO* cisplain + doxorubicin + carboplatin

[a]Study closed early because of inferior results CDDP/CARBO arm

Table 16.8 Multivariate analysis of risk groups in the Children's Hepatic tumor International Collaboration (CHIC) database [81]

PRETEXT	Age (years)	AFP	Other risk factors[a] (0, 1, ≥ 2)	#Patients in CHIC database[b]	5y-EFS
I & II	<3	>100	0	375	92 %
III	<1	>1,000	0	125	91 %
I & II	<3	>100	≥1	50	76 %
I & II	3–5	>100	Any	53	74 %
III	<1	>1,000	≥1	43	83–86 %
III	>1	>1,000	0	134	87 %
III	>1	>1,000	1	42	74 %
IV	<3	>100	0	58	77 %
I & II	>6	>100	Any	28	51 %
III	Any	100–1,000	Any	28	61 %
IV	<3	>100	1	59	66 %
III	>1	>1,000	>1	24	50 %
IV	<3	>100	>1	32	46 %
IV	>3	>100	Any	40	31 %
M+ (any PRETEXT)	Any	>100	Any and/or PRETEXT4	259	18–48 %
AFP <100 (any PRETEXT)	Any	–	Any	65	36 %

[a]Other Risk Factors statistically significant in multivariate analysis: (a) multifocal tumor, (b) major venous involvement +V (all three hepatic veins or IVC); (c) major venous involvement +P (portal bifurcation or both portal veins); (d) extrahepatic contiguous tumor extension +E; (e) Tumor rupture

[b]CHIC database includes patients from COG (INT-0098; P9645); SIOPEL (SIOPEL-2; SIOPEL-3SR, SIOPEL-3HR); JPLT (JPLT1; JPLT 2); and GPOH (HB89; HB 99)

Table 16.9 Current chemotherapy recommendations of the different study groups [81]

Study group	Risk group	Chemotherapy	Surgery
COG (AHEP 0731)	Very low risk	None	Primary
	Low risk	CDDP, 5FU, VCR × 2	Primary
	Intermediate risk	CDDP, 5FU, VCR, Doxo × 6–8	After 2–4 courses
	High risk	VCR, Irinotecan, Temsirolumus × 2 CDDP, 5FU, VCR, Doxo × 6	After 4–6 courses
SIOPEL (SIOPEL 6) (SIOPEL 3 HR)	Standard risk High risk	CDDP × 6 CDDP × 5 alternating Carbo/Doxo × 5	After 4 courses After 7 courses
GPOH	Standard risk	CDDP, Doxo × 3–4	After 2–3 courses
	High risk	CDDP × 5 alternating Carbo/Doxo × 5 (SIOPEL 3 HR)	After 5–7 courses
JPLT (JPLT 2)	PRETEXT I	CDDP, Pira × 4	Primary
	PRETEXT II	CDDP, Pira × 6	After 2 courses
	PRETEXT III/IV all V+P+E+	CDDP, Pira × 5–6 or CDDP, Pira × 2+Ifo/Carbo/Pira/Eto × 3–4	After 3–4 courses
	All PRETEXT M+	Additional high dose Eto/Carbo/Mel	After 4 courses

COG Children's Oncology Group, *SIOPEL* International Society for Pediatric Oncology, *GPOH* German Society for Pediatric Oncology, *JPLT* Japanese Study Group for Pediatric Liver Tumor, *CDDP* cisplatin, *5FU* 5-fluorouracil, *VCR* vincristine, *Doxo* doxorubicin, *Carbo* carbopaltin, *Pira* pirarubicin, *Eto* etoposide, *STS* sodium-thiosulfate, *Mel* melphalan

dow with vincristine and irinotecan in the first cohort of the study. Once this cohort is complete, a second cohort will receive an upfront experimental window of vincristine/irinotecan/temsirolimus. In both of these study cohorts the upfront experimental window will be followed by six courses of C5V-D, alternated every two courses with vincristine/ irinotecan or vincristine/ irinotecan/ temsirolimus in responders. If possible the tumor resection should be performed after four courses of the standard C5V-D backbone therapy. The aim of this study is to achieve with this risk adapted treatment a decrease in chemotherapy toxicity, while maintaining or improving the event free survival [95]. The current SIOPEL study for standard risk hepatoblastoma SIOPEL 6 uses the cisplatin monotherapy in six courses, already used in the previous SIOPEL 3 standard risk study. The patients are randomized for the additional administration of sodium thiosulfate (STS). The aim of this study is to assess the efficiency of STS preventing hearing loss, a frequent toxic side effect of cisplatin, and to evaluate the influence of STS on the tumor response to cisplatin. For high risk patients the SIOPEL 4 study investigated an intensified application of chemotherapy with weekly alternating cisplatin and doxorubicin/carboplatin. The results are promising but still with a short follow up. The interim recommendation of the SIOPEL is the chemotherapy strategy according to the SIOPEL 3 high risk study: High-risk patients are treated with cisplatin alternating every 2 weeks with doxorubicin/carboplatin for seven neoadjuvant and three adjuvant courses [83]. The recommendations of the other groups are listed in (Table 16.9).

So far, no controlled comparison has been done between the therapeutic strategies of SIOPEL and COG, primary chemotherapy for-all versus primary surgery for some. In terms of overall survival rates, the results of the different study groups have been more or less comparable. The improved results seen over the past two decades highlight some important lessons learned: (1) SIOPEL 4 weekly dose compressed chemotherapy, while toxic, is curing metastatic patients previously thought to be incurable; (2) In children not responding to chemotherapy, alternative chemotherapy and surgical resection of pulmonary metastatic disease should be considered; (3) After tumors have shown a good response to chemotherapy, the presence of a positive microscopic margin may not always portend a poor prognosis; (4) Liver transplant or complex resection (e.g., mesohepatectomy or resection with major venous resection and reconstruction) should be considered in every child with unresectable HB (about 15 % of cases) [79, 81, 93, 97].

Chemotherapy Toxicity

As cisplatin is the most important agent in the treatment of hepatoblastoma, cisplatin induced ototoxicity is a serious problem in the therapy of hepatoblatoma. Sixty percent of children treated with cisplatin develop some degree of bilateral hearing loss. The hearing loss is permanent and may have a delayed onset [96–100]. The risk of developing ototoxicity increases with lower age and a higher cumulative cisplatin dose, particularly when a dose of 400 mg/m^2 or more was reached [99, 100]. Different attempts have been made by the multicenter trial groups to reduce the risk of ototoxicity. The previously conducted COG study, COG P9645, tested amifostine in a randomized trial but failed to find significant otoprotection with this agent [101]. The current standard risk SIOPEL trial, SIOPEL 6, is investigating the potential otoprotective effect of sodium thiosulfate, which competitively binds at the cisplatin receptor site [83, 102, 103]. There are concerns that sodium thiosulfate, as a competitive receptor binder, could reduce the chemotherapy efficacy of cisplatin on the tumor, and results of this ongoing trial are pending at this time. Rather than added a chemoprotectant, the current COG trial, AHEP0731, attempts to reduce cisplatin toxicity by limiting the extended use of cisplatin in

low-risk patients, and using less platinum intensive regimens in intermediate/high risk patients.

Doxorubicin, also frequently used in the therapy of hepatoblastoma, can cause early and late onset of cardiac failure. The damage may be clinically significant only after years. The cumulative incidence of cardiac failure may not have a plateau, and can continue to be clinically significant several years after treatment [104].

Surgery

Surgical Guidelines COG

Contrary to early trials in America where decisions about surgical resection were made by individual surgeons, and hence were subjective and highly variable, the surgical guidelines of the current COG trial AHEP-0731 uses PRETEXT to define the recommended timing and extent of surgical resection. Surgical resection is recommended at diagnosis for PRETEXT I and II with clear venous margins on radiographic imaging. Surgical resection is after neoadjuvant chemotherapy for PRETEXT III (with POST-TEXT I, II or III with no major venous involvement -V and -P). Complete resection with liver transplant or extreme resection is recommended for POSTTEXT III +V +P, PRETEXT III extensive multifocal and for any PRETEXT IV [79, 105]. Resection at diagnosis is recommended only when a segmentectomy or a standard lobectomy will predictably yield a complete resection—i.e., PRETEXT I or II tumors based upon review of the diagnostic radiographic imaging.

Surgical Guidelines SIOPEL

SIOPEL and GPOH study groups recommend neoadjuvant chemotherapy be given to *all* patients with a rare patient going directly to transplant depending upon the recommendation of the transplant center [95].

Technique and Timing of Surgical Resection

Surgical approach differs somewhat between various international study groups and between HB and HCC. SIOPEL group favors initial biopsy followed by preoperative chemotherapy, while American COG group prefers primary resection in some cases with small localized tumors [78]. Current COG surgical guidelines recommend: (1) lobectomy or segmentectomy at diagnosis for PRETEXT I and II; (2) lobectomy or trisegmentectomy after neoadjuvant chemotherapy for POST-TEXT II or III which do not have macroscopic venous involvement (V-,P-); and (3) extreme/complex resection or liver transplant after neoadjuvant chemotherapy for POST-TEXT III with macroscopic venous involvement (V+, P+) or POST-TEXT IV. There is an option for resection of intermediate risk tumors after 2, rather than 4, cycles of chemotherapy given evidence that the majority of the chemotherapy response occurs in the first two neoadjuvant cycles [79, 106]. German GPOH group has recently joined the SIOPEL but in past it used to stand somewhere in between advocating primary resection in the small liver tumors and neoadjuvant chemotherapy in all others. Many surgeons reported that tumor resection after preoperative chemotherapy was easier due to its more solid character and better demarcation from the surrounding healthy liver tissue, as well as less bleeding, although the latter was not proven [77]. Although, no controlled comparison has been made between the therapeutic strategies of SIOPEL and COG, overall treatment results have been largely comparable between both study groups.

Biopsy

Throughout consecutive trials diagnostic biopsy in hepatoblastoma has proven to be safe and reliable [77, 83]. There were no episodes of tumor seeding. Biopsy-related complications were infrequent (7 % in SIOPEL 1) and minor only, which mostly did not require any treatment. Initially open biopsy was advocated but now closed needle biopsy under ultrasonographic or laparoscopic guidance is preferred [83]. In the past COG recommended exploratory laparotomy, attempted surgical resection, and open biopsy in all patients. With refinements in preoperative imaging this has become unnecessary in many patients. Laparotomy and resection at diagnosis is recommended in patients with PRETEXT I and PRETEXT II tumors as long as a safe, margin free resection by either segmentectomy or standard anatomic lobectomy is felt to be feasible. If not, percutaneous or laparoscopic biopsy is generally performed. Biopsy is important in ruling out benign tumors such as infantile hemangioma in the youngest patients, in ruling out transitional HB/HCC tumors in intermediate age children, and in ruling out HCC in the older children. Real time ultrasound guidance makes liver tumor biopsy safer. The aim is to obtain sufficient tissue to allow an accurate diagnosis, whilst avoiding complications. Risk can be further minimized by using a percutaneous coaxial technique because it allows multiple samples to be obtained with a single tissue path. The biopsy tract may be embolized through the outer needle with a throbogenic plug of gelatin foam. Whenever possible, the outer needle should be passed through unaffected liver for a short distance to minimize the possibility of tumor seeding. Great care should be taken, however, to avoid crossing, and therefore possible contaminating, segments of liver that will not be resected at subsequent surgery and the surgeon is encouraged to discuss this in detail with the interventional radiologist prior to the procedure [107]. If any question remains about possibility of obtaining a safe path, laparoscopic biopsy with a tru-cut protecting needle is recommended. Sufficient tissue for pathologic subtyping and biologic study with percutaneous co-axial approach is of paramount importance. It has been postulated that even a small focus of small cell undifferenti-

ated (SCU) histology could affect tumor prognosis in a histologically heterogenous tumor. If any doubt about the adequacy of tissue for analysis is raised, an open biopsy is recommended. Recommendations from 2011 International Pathology Consensus Conference are for a minimum of 5-8 cores. At least 2 or 3 (or more) cores should be frozen for biology and one core or adjacent normal liver should be frozen.

Operative Technique

In general anatomic hepatic resections according to the segmental scheme of Couinaud, refined by Bismuth in the 80s are recommended as segmentectomies, hemihepatectomies and extended hepatectomies. As a general rule, POST-TEXT I tumors can be resected with a segmentectomy, if applicable, and POST-TEXT II ones with a standard hemihepatectomy. POST-TEXT III tumors are resected with extended hemihepatectomy or central hepatectomy. Any tumor with invasion of all major hepatic vessels as shown per imaging (+V, +P) or extensive liver involvement (PRETEXT IV) should be referred to a center with experience in liver resection and liver transplant [78, 79, 96, 108–110].

Atypical, non-anatomic, or wedge resections are not recommended. In two consecutive GPOH multicenter trials, HB89 and HB94, 38 % of the patients with an atypical resection were found to have post resection residual tumor and this was associated with a worse outcome [111]. This may be due to the known role of hepatocyte growth factor (HGF) stimulating post resection residual tumor cell proliferation [112]. Atypical liver resections should be used in selected cases only, mainly of multifocal tumors, when liver transplantation is not an option [113]. In any case adequate resection planning is crucial, which may be supported not only by the proper preoperative imaging, but also augmented with the special rendering software. This service is currently offered by the German company MeVis (MeVis Medical Solutions AG, Bremen, Germany) and it has also been recently developed by the French IRCAD (Research Institute Against digestive Cancer, Strasbourg, France). It may be very useful in cases of extensive tumors with vascular involvement, especially that it has been shown that liver anatomy and segmental division is correct in about 75–80 % of cases [114]. Not infrequently liver segments can receive the portal flow from the contralateral portal branch.

The ultimate goal of surgical resection is to achieve complete margin negative tumor clearance. Data from SIOPEL where patients have received preoperative chemotherapy suggest that any cleared margin (even <1 cm) might be acceptable [96, 110, 115]. No similar data exists for resection of a tumor at diagnosis and margins ≥1 cm are desirable if resection is done prior to chemotherapy. Patients should be referred to experienced medical-surgical Liver Specialty Centers with all technologies for major hepatic resections available and also access to liver transplantation. Hepatic resection begins with mobilization and anatomic definition of the extent of the tumor and satellite lesions, if any. Liver vascular supply should be identified before parenchymal dissection. Hepatic veins are preferentially secured suprahepatically prior to parenchymal dissection. If for some reason in extreme cases they are not able to be secured before parenchymal dissection they can be accessed and secured through liver parenchyma in the final phase of resection. This latter approach to the hepatic veins, while feasible, risks substantial increases in blood loss. Parenchymal dissection is done along the line of ischemia Blood loss can be minimized by adherence to above technical principles, as well as maintenance of a low central venous pressure with Trendelenburg position or application of the Pringle maneuver in the parenchymal phase of the resection which can be done safely up to 30–45 min. In special cases, total vascular exclusion of the liver can be used. Warm ischemia time should not exceed 30 min. In general, interrupted ischemia limited to 10–15 min with intervening 5–10 min periods of reperfusion is better tolerated continuous ischemia intervals [116]. Specialized equipment, such as ultrasonic CUSA-type dissector, water knife (Hydro-jet, ERBE), argon or infrared beam coagulator and intraoperative ultrasonography is usually very helpful in liver resections. Intraoperative ultrasound examination can determine safe resection plane assuring complete tumor removal and reliable detection and complete resection of satellite lesions [117, 118]. Topical thrombostatic agents, such as fibrin glue or special sponge sealants, are used for coverage of the hepatic resection plane.

Microscopic positive tumor margin after HB resection does not seem to guarantee a poor prognosis. In SIOPEL 1 trial only 2 of 16 patients (13 %), who died, had microscopic positive margin [77]. In SIOPEL 2 microscopic positive margin was identified in 13 SR patients and all 13 are long term survivors, even though 8 of them did not receive any additional treatment than prescribed by the protocol [89]. In the SIOPEL 3 SR arm only 2 out of the 28 patients with microscopic positive margin suffered an event and actually one of those was of higher risk of tumor relapse because of the initial intra-peritoneal tumor spillage [90]. Thus, it seems that microscopic positive margin does not confer worse prognosis per se. Beware that all of the data is from patients who have received preoperative chemotherapy, and that this has NOT been the experience in chemo-resistant tumors like HCC. Hence, radical tumor excision is recommended in every case.

Surgical Treatment Options for Preoperative Tumor Rupture

Bleeding from a preoperative tumor rupture occurs in about 2–3 % of HB. Intracapsular hematoma may tamponade the bleeding. Occasionally there may be an uncontained rupture

that decompresses into the peritoneal cavity presenting with uncontrolled bleeding and hypovolemic shock. Correction of clotting factors should be followed either by percutaneous embolization. Operative control of the hemorrhage may be necessary when percutaneous embolization is not immediately available [119]. Inadvertent injury to vital structures can be minimized if heroic, uncontrolled procedures are avoided. It is particularly important to avoid, if possible, massive blood loss, as massive blood transfusion during liver tumor resection has been correlated with an increased risk of tumor recurrence [120], surgical complication, and mortality.

Surgical Complications

Potential surgical complications include bleeding, impairment of blood flow in or out of the liver, bile blockage or leak, liver failure, infection, and others listed in [78] (Table 16.10). Bleeding from needle biopsy can almost always be stopped with correction of clotting factors and with direct pressure. In contrast, massive bleeding during complex tumor resection may be life threatening. Bleeding risk is minimized by avoiding inappropriate aggressive attempts at tumor resection in proximity to major vessels [117, 120]. In the event of a failed initial resection, reoperation is associated with increased perihepatic bleeding with adhesions to the diaphragm, retroperitoneum, and right adrenal gland. Unrecognized anatomic origin of a replaced right or left hepatic artery may lead to bleeding or inappropriate ligation. Normal liver can occasionally survive permanent interruption of arterial or portal venous inflow, but not both [121]. In the rare instance that both portal and arterial inflow of the remaining liver tissue has been disrupted, survival requires immediate revascularization or transplant. Loss of adequate venous drainage from the residual liver remnant will cause congestion and some loss of parenchymal viability. It's important to prevent inadvertent hepatic venous occlusion with ill-placed sutures into the hepatic parenchyma in an attempt to control bleeding. Potential causes of postoperative liver failure include small liver remnant, liver devascularization, interruption of venous drainage, excessive liver warm ischemia due to prolonged vascular occlusion or massive bleeding, major bile duct obstruction, halogenated anesthetic agents, viral infections, and drug reactions. Unless definitive signs of improvement are seen in the first few days, liver transplantation may need to be considered.

Intraoperative cardiac arrest occurs in 1–2 % of major liver resection procedures. The most common cause is uncontrolled massive blood loss. Close communication between the operative surgeon and anesthesiologist is of paramount importance in not allowing the patient to develop life-threatening hypovolemia, acidosis, and coagulopathy. Cardiac arrest may also occur from tumor emboli or, more commonly, an air embolus from an uncontrolled hole in the IVC or major hepatic vein. Risk of an air embolism can be minimized by the use of higher PEEP (Positive End-Expiratory Pressure) settings during the suprahepatic vein and IVC dissection portion of the procedure. It is also very important to preoperatively evaluate cardiac function in all

Table 16.10 Potential surgical complications of major liver resection

Type of surgical complication	Most common	Less common Regularly reported
Bleeding	Intraoperative hemorrhage Postoperative hemorrhage	Intraoperative cardiac arrest Hepatic hematoma Hemobilia Gastrointestinal bleeding Side effects of massive transfusion
Blood flow	Postoperative sequelae of intraoperative inflow and outflow obstruction	Venous outflow obstruction Hepatic artery injury or thrombosis Portal venous injury or thrombosis Hepatic necrosis
Liver failure	Coagulopathy Hypoglycemia Ascites	Too small-for-size liver remnant (<25 % of normal liver, <50–60 % cirrhotic liver)—isn't this a cause, rather than an effect?? Encephalopathy
Bile drainage	Bile leak Biliary stricture	Bile fistula Biloma Bile peritonitis Cholangitis
Infection	Wound infection Hepatic or perihepatic abscess Pneumonia	Sepsis Cholangitis Peritonitis
Miscellaneous	Adhesive bowel obstruction Pleural effusion	Diaphragm injury Wound dehiscence Recurrent or persistent tumor

patients who have been treated with doxorubicin as their post-chemotherapy cardiac function may be compromised and their ability to tolerate hypovolumic stress decreased.

Bile leak occurs in 10–12 % of cases and its frequency has not decreased over the years [112]. The bile ducts, particularly at the level of the hilum, are more easily disrupted than the vessels. If a minor injury is recognized it can usually be directly repaired. Major injury with loss of ductal wall, complete division, or loss of length mandates debridement back to healthy, well-perfused ducts and drainage with a Roux-en-y limb of jejunum. Bile leak from the cut surface is minimized by close inspection and avoiding non-anatomic resection. When any question of potential leak exists a retrograde cholangiogram, before closure of the abdominal wall, is recommended both to detect leaking biliary radicals and confirm appropriate drainage of all remaining segments. Although placing drains at the time of operation does not lessen the rate of bile leakage, it does facilitate postoperative management in the event of a leak. Bile leaks that do not respond to appropriate drainage may be associated with distal obstruction, such as a retained section of viable liver excluded from the biliary drainage system, iatrogenic occlusion (clip, ligature, thermal injury), hematoma, stone, residual obstructing tumor, or ischemic stricture. Appropriate time for reoperation is unclear as wait-and-see treatment is successful in most cases. An adult review recommends that patients with drainage output greater than 100 mL 10 days of bile leakage diagnosis should be scheduled for interventional treatments [112]. No such comparable data exist for children.

Liver Transplant for HB

Cases of "unresectable" hepatoblastoma (HB) due to involvement of the entire liver, extensive multifocality, or major hepatic venous or portal venous involvement comprise 10–20 % of all HB treated in multicenter trials [102]. The best results for high risk HB reported to date were in SIOPEL 4, and these improvements in outcome seen in the high risk group appear to be at least partly due to an increase in the use of liver transplant [79, 92]. The recommendations for transplant used in this most recent studies are: (a) tumor clearly involving all four sections of the liver, especially those with extensive multifocality as judged by MRI or CT angiography; (b) tumor location so close to both main portal vessels at the hilum of the liver and/or all three hepatic veins that it is unlikely that a tumor-free excision plane will be achieved without risking life threatening hemorrhage. These patients should be identified early in their treatment and their clinical course and imaging followed closely throughout their initial chemotherapy, in conjunction with a liver specialty surgeon.

The following guidelines have been developed over the years and are currently recommended by COG, SIOPEL, and GPOH. It is important that consultation with a transplant center with special expertise in pediatric liver surgery be considered early in the treatment in order to prevent delays and unwanted extended courses of chemotherapy while awaiting resection and transplantation. Most of these patients should be treated with standard on-study chemotherapy protocols with the same number of cycles of chemotherapy, before and after transplant, as patients submitted to partial hepatectomy. An occasional patient with an extensively multifocal PRETEXT IV, or with tumor thrombosis in the main portal vein, might be recommended for primary transplant with minimal preoperative chemotherapy [109].

Multifocal PRETEXT IV

Multifocal PRETEXT IV HB in the absence of any metastatic disease after chemotherapy (POST-TEXT IV, multifocal, –M) is a clear indication for liver transplantation. Clinicians should resist the temptation to intensify chemotherapy in a vain effort to avoid transplant because of the high likelihood of inducing tumor resistance to chemotherapy [123]. Apparent clearance of tumor nodules from one section of liver after preoperative chemotherapy should not distract from transplant because of the high probability of persistent microscopic viable neoplastic cells despite radiographic "clearance" [79, 123]. COG and SIOPEL recommend transplant in these patients, although there are controversial reports of successful piecemeal resections of such tumors [93, 114, 115].

Solitary PRETEXT IV

Large solitary PRETEXT IV tumors usually have neoadjuvant chemotherapy and many of these tumors may "downstage" to a POST-TEXT III with clear retraction of the tumor from the anatomic border of one lateral section and would allow performance of a trisectionectomy. A POST-TEXT IV, –M tumor is a clear indication for transplant.

PRETEXT III +P, +V

In a subgroup of PRETEXT III tumors there will be major vascular invasion that does not clear with neoadjuvant chemotherapy. A POST-TEXT III tumor with persistent +V and/or +P that may preclude safe and prudent performance of a extended hepatectomy. Resection in the face of major venous invasion runs the risk of leaving viable neoplastic tissue behind if the surgeon must peel off viable tumor directly from the involved vein. Some have argued in favor of venous resection and reconstruction ("extreme" or "complex" resection) as opposed to transplant in these cases. There are no trials comparing the results of partial resection with extensive venous dissection versus complete resection with transplantation. Again, clinicians should resist the temptation to intensify chemotherapy in a vain effort to avoid transplant because of the high likelihood of inducing tumor resistance to chemotherapy and worsening outcome [122]. Complex

resection carries an increased risk of surgical complication, including bleeding and/or venous outflow obstruction and positive tumor margin [80]. Whether resection is partial, or complete with transplant, any suspicious invasion of the retrohepatic vena cava should be resected "en bloc" and reconstructed either with autologous internal jugular vein, donor iliac vein, or a preserved cadaveric whole organ with donor IVC.

Transplant in Patients with Pulmonary Metastatic Tumor at Diagnosis

An absolute contraindication to liver transplant is persistent pulmonary metastases nonresponsive to neoadjuvant chemotherapy and not amenable to surgical resection. The tumor should show at least partial response to chemotherapy (decrease in tumor size, decrease in serum AFP, and decrease in size or disappearance of pulmonary nodules). Unresponsive or progressive metastatic disease in the face of neoadjuvant chemotherapy is a relative contraindication to transplant because even if the nodules can be surgically resected microscopic foci of chemoresistant tumor are highly probable [79, 109, 124]. Lung metastasis that do respond to chemotherapy, but do not entirely clear, should be surgically resected [79, 125]. Some have advocated sternotomy and bilateral lung palpation, rather than unilateral wedge resection, although this remains controversial.

Rescue Transplant for Relapse or Persistent Tumor

Multiple series have shown superior outcome with primary transplant (about 80 % overall survival) compared to rescue transplant (about 30–40 % overall) [108, 126–130]. The basis for this is undoubtedly multifactorial but two important concerns are the likelihood of chemotherapy resistance in relapse tumors [123, 131, 132], and the debilitated state of the patients when transplanted in the face of end-stage disease.

Pediatric Liver Unresectable Tumor Observatory (PLUTO)

SIOPEL, together with support from COG, GPOH, Study of Pediatric Liver Transplantation (SPLIT), and individual pediatric liver transplant centers all over the world, has established a worldwide electronic registry for liver transplant for childhood tumors (hepatoblastoma, hepatocellular carcinoma, infantile hemangioma, and others) [108]. The link to obtain a password to register patients on this database can be accessed via the PLUTO Registry Website: http://pluto.cineca.org

Surgery for Local Relapse in the Liver

Management of relapse tumor has varied across study groups [131, 132]. In SIOPEL studies, only 5 % of patients who had achieved a complete remission and a local relapse and were treated with salvage chemotherapy and surgery [131]. In JPLT 1 four locally relapsed patients underwent a redo liver resection with short-term survival (17 months) in all four, long-term follow-up not reported [133]. In the liver transplant experience overall survival for "rescue" transplant, transplant for a local relapse, was 30 %, compared to 82 % for patients transplanted at the first operation. PET CT has begun to be used in pediatric surgical oncology of solid tumors although experience is limited; caution is warranted as false positive results are possible in normally regenerating liver

Hepatic Arterial Chemo-embolization (HACE) and Trans-arterial Chemoembolization (TACE)

HACE/TACE is occasionally used in children with HB whose tumors remain unresectable after chemotherapy AND who are not liver transplant candidates due to uncontrollable extrahepatic tumor. Recently available doxorubicin eluting beads are a particularly attractive option for embolization in this situation. TACE, however, is more common in HCC and is discussed below in the HCC surgical discussion.

Hepatocellular Carcinoma

Epidemiology, Biology, Genetics

Hepatocellular carcinoma (HCC) accounts for about 87 % of the malignant liver tumors of children between 15 and 19 years of age [134]. In most countries HCC is less common than HB, but there is considerable geographic variation with rates ranging from 0.2 per million in England and Wales to 2.1 per million children in Hong Kong. Hepatitis B and C viral infections are the most common cause of chronic liver diseases and hepatocellular carcinoma in adult. In pediatric HCCs, most pediatric HCCs are "de novo" cases, usually not related to hepatitis B and C viral infections, but in some Asian populations e.g. Hong Kong and Taiwan HCC occurs more frequently due to the high infectious rates of hepatitis virus [135]. Recent decline in HCC may be attributed to immunization of infants against perinatal transmission of hepatitis virus.

There are two distinct groups of HCC patients in childhood: sporadic or "denovo" HCCs without preceding liver disease and those developed in the context of chronic or congenital liver disease. The former group typically affects older children and shows a relatively poor outcome, while HCC developing in congenital liver diseases [94, 136, 137] are sometimes diagnosed as tiny nascent nodules in the resected liver at liver transplantation [138]. Some biologic differences may exist between HCCs developing in adults and children. Kim and colleagues [139] have observed that expression of cyclin 1 was lower and LOH higher at 13q in pediatric malignancies. Fibrolamellar carcinoma is a rare primary malignant liver neoplasm that usually affects ado-

lescents and young adults with no underlying liver disease and the lack of cirrhosis [15]. This expresses markers associated with both biliary (CK7 and epithelial membrane antigen) and hepatocytic (heppar-1 and glypican-3) differentiation, as well as markers associated with hepatic progenitor cells (CK19 and EpCAM) and stem cells (CD133 and CD44), indicating that subsets of HB and HCC share a molecular pathway in their pathogenesis. Genetic alterations seen in fibrolamellar carcinoma include gains in 1q and 8q and loss of 18q [140], and a recently reported DNAJBI-PRKACA chimeric transcript [141].

Pathology

In the pediatric age group, more than two-thirds of HCC occur in children older than 10 years of age, but only 0.5–1 % of all HCC manifest before 20 years of age, and very few HCCs are diagnosed in children less than 5 years old. About 20–35 % of children with HCC have underlying chronic liver disease. It is still disputed whether "adult-type" HCC in children is the same or a different disease. Zimmermann and others have suggested that HCC forms a tumor family, consisting of adult-type HCC and its variants, fibrolamellar HCC, and a novel entity occurring in older children and young adolescents with features of both hepatoblastoma and hepatocellular type histologies [7]. The gross presentation is in the form of solitary or multiple (multifocal) lesions. Solitary tumors display four main growth patterns, expanding (or pushing) mass lesions, pedunculated (or hanging) lesions, invading tumors with poor delineation, and mutifocal tumors resembling metastatic disease. These growth patterns exert a considerable influence on the surgical resectability of the tumors.

Fibrolamellar Hepatocellular Carcinoma (FL-HCC)

This tumor usually arises in non-cirrhotic livers of adolescents or young adult patients and is encountered more frequently in Western countries [15]. Overall, FL-HCC accounts for less than 10 % of all HCCs. Unlike adult HCC where fibrolamellar has a better prognosis, recent review of fibrolamellar HCC in the SIOPEL experience shows no improved outcome with this subtype in pediatric patients [143]. FL-HCC shows vascular invasion in up to 35 % of cases, frequently metastasizes into locoregional lymph nodes (about 50 % of cases), and tends to show unusual spreading patterns, including intraperitoneal spread. FL-HCC is typically a solitary lesion which has a predilection for the left liver lobe (two-thirds; unusual for hepatic primary tumors). It reveals well-defined margins and a central scar in 70 %. The cut surface often shows a firm and tan to brown tissue with radiating septa, sometimes closely resembling focal nodular hyperplasia. Histologically the cells form strands embedded in the typical fibrosclerotic stroma which may form a central stellate scar. Typically, cells of FL-HCC show marked immunostaining for cytokeratin 7 [7, 55].

Transitional Liver Cell Tumor (TLCT)

TLCT is now called Hepatocellular neoplasm - Not Otherwise Specified (HC-NOS) by the Pediatric Consensus Classification [7]. The term, transitional, had previously been used to denote a putative intermediate position of the tumor cells between hepatoblasts and more mature hepatocyte-like cells although significant confusion regarding the exact histology still exists [7]. These tumors are highly aggressive lesions that have a treatment response pattern clearly different from hepatoblastoma [14]. The usual presentation is that of a large or very large solitary hepatic tumor (mostly in the right liver lobe), commonly associated with very high serum AFP levels. Grossly, the tumors display an expanding growth pattern and sometimes exhibit a large central necrosis. Histologically, the tumor cells vary between and HCC-type cell and cells found in hepatoblastoma, sometimes with formation of multinuclear giant cells.

PRETEXT and Staging HCC

No staging or grading system has been found that accurately predicts prognosis in pediatric HCC. In the pediatric multicenter trials, PRETEXT has been used because of its utility in HB and the crossover between these two tumors in the intermediate age group. The Edmondson and Steiner histologic grading system seems to add prognostic value to the 6th edition of the TNM grading system in adults [142]. Neither COG nor SIOPEL has current open trials for HCC, although an international cooperative trial is in the planning stages. Prior trials in the USA have used the traditional Evan's staging system (I, II, III, IV) [17], but current discussions with colleagues describing the extent of tumor involvement of the liver are based upon PRETEXT to aid in making key decisions about surgical resectability. In HCC where some children may have concomitant hepatic cirrhosis, factors related to possible impairment of liver function should be taken into account in assessing the patient's resectability.

Chemotherapy

Chemotherapy for HCC is discussed controversially. In adult HCC no or little response to chemotherapy is described. Gemcitabine plus oxicisplatin has recently been reported in a large multicenter trial in adults, although no such comparable data exists in children [144]. Children have usually been treated in the last years according to hepatoblastoma trials where cisplatin or carboplatin was combined with one or more drugs (doxorubicin, 5 FU, vincristine, etoposide). It has been postulated that the response rate to chemotherapy is higher in children and in about 1/3 of the children who have preoperative chemotherapy will get a complete resection [16] (Table 16.11). Better chemotherapy response in children may be due to the higher rate of "de novo" tumors with normal liver function and the transitional liver cell tumors

Table 16.11 Chemotherapy for pediatric hepatocellular carcinoma (HCC) [16, 17]

Trial	Chemotherapy	Partial response rate (%)
INT 0098	Cisplatin, doxorubicin versus Cisplatin, vincristine, 5-fluorouracil	16
SIOPEL 1	Cisplatin, doxorubicin (PLADO)	49
SIOPEL 2	Cisplatin, carboplatin, doxorubicin	50
JPLT	Cisplatin, tetrahydropyranyl-adriamycin	32
HB 99 (GPOH)	Carboplatin, etoposide with stem cell transplantation	47

(TLCT) described by Prokurat et al [14]. The true advantage of the use of adjuvant chemotherapy for stage I disease is unknown [17].

Antiangiogenesis, Sorafanib

Despite a moderate response rate to chemotherapy in children with HCC, the overall survival rates are still extremely poor. Novel therapeutic approaches were investigated over the last years in HCC in adults. The recent adult experience with Sorafenib, a multikinase inhibitor with anti-angiogenic and anti-proliferative activities has been most promising. It demonstrated a significantly improved time to tumor progression (median 5.5 months vs. 2.8 months) and OS time (10.7 months vs. 7.9 months) in prospective trials in the treatment of HCC in adults with unresectable tumors [145, 146]. Sorafenib in combination with doxorubicin demonstrated a significantly better progression free survival compared with doxorubicin and placebo [147]. Information about novel therapeutic approaches in childhood HCC is rare. One series of 12 children with HCC treated with Sorafenib in combination with PLADO (cisplatin, doxorubicin) showed a promising approach in childhood HCC: Four of seven patients with unresectable tumors had a partial response and two of them achieved resectability [148].

Other antiangiogenic agents, epidermal growth factor receptor (EGFR) inhibitors and mTOR inhibitors where evaluated in phase II and III studies in HCC in adults: Bevacizumab (VEGF antibody), sunitib (multikinase inhibitor), brivanib (VEGFR inhibitor), erlotinib (EGFR inhibitor), cetuximab (EGFR antibody) [148]. Bevacizumab was the most promising agent especially in combination with erlotinib with a response rate of 25 % In adult tumors the combination of cetuximab with gemcitabine/oxaliplatin (GEMOX) achieved a response rate of 20 % [149].

Surgery

The technical aspects of liver surgery have been discussed in detail above in the surgical section dealing with hepatoblastoma. Topics above with particular relevance to pediatric HCC include biopsy, resectability, surgical technique, HACE/TACE, preoperative portal vein embolization, and surgical complications of liver surgery. Given the poor response of HCC to chemotherapy and radiation, the mainstay of treatment is surgery. This means that in contrast to hepatoblastoma a primary radical tumor resection should be attempted whenever possible, and patients with the clinical constellation for advanced HCC should always be treated in consultation with a specialized center with experience in childhood liver surgery.

In HCC patients with hepatic cirrhosis, the liver remnant volume calculation is essential and can be predicted by CT scan and/or MRI. In childhood, the usual limit for resection (a ratio obtained dividing the remnant liver volume by the patient body weight) can be exceeded from the usual 0.8 value to 0.6 and even more. Sampling of lymph nodes from the hepato-duodenal ligament should be performed in every HCC case, as their involvement is relatively frequent and has a significant impact on prognosis. In general in HCC, extended lymphadenectomy of the hepatic pedicle is recommended.

When an older child or a young adult presents with a resectable tumor thought most likely to be HCC, primary resection should be attempted. Although all studies have confirmed the importance of complete tumor resection for obtaining cure, less than 20 % of patients are amenable to initial surgery. After HCC resection the 5-year survival is on average of 35–51 %, while recurrence-rate is about 20–30 % at the same interval and with little change in the last decade [134]. This is on the contrary to survival rates in completely resected HB that exceed the range of 90 % [102].

Liver Transplant for HCC in Children

The role of liver transplantation in pediatric HCC is in greater evolution than in pediatric HB and because of HCC's relative chemoresistance transplantation may offer an important chance for cure with tumor confined to the liver [150–152]. Transplant is absolutely contraindicated in the presence of any extrahepatic tumor, even in the occasional patient where it clears with chemotherapy. Some argue that an exception might be made in the intermediate case of children with transitional cell liver tumors. Outcome for transplant in adult HCC has improved over the years due to our recognition that strict selection criteria, Milan or UCSF criteria, are important in preventing post-transplant tumor relapse. However, Milan criteria are NOT strictly applied in pediatric HCC [151, 153]. This is because of increased chance of respon-

siveness to chemotherapy, and studies which fail to show a correlation between survival and Milan criteria in children [154, 155]. Despite the excellent overall survival in this pediatric series, the only child in their series who fulfilled all four criteria was a child with tyrosinemia with a small incidental tumor found on surveillance screening. In view of the lack of improvement in results from conventional treatment of pediatric HCC over the past two decades, most pediatric transplant surgeons will offer transplantation to children with large denovo tumors, regardless of size, as long as there is no evidence of extrahepatic spread.

TACE/HACE with Doxorubicin Beads or Yttrium Radioactive Beads

Hepatic arterial chemoembolization (HACE), also called transarterial chemoembolization (TACE), is an established method of treatment of HCC in adults. Experience with TACE in children is limited [156–159]. It has been used not only in pediatric HCC, but also in a small number of children with HB [156–159]. TACE produces a marked reduction in tumor size associated with a significantly decreased AFP levels and tumor necrosis. In the reported experience TACE rendered resectable 2 out of 3 pediatric HCCs or served successfully as a bridge to OLT in three other pediatric cases [159]. According to the report of Li, tumor shrinkage after TACE ranged from 19.0 to 82.0 %, with a mean value of 59.2 % [158]. AFP levels decreased 99.0–29.0 % from initial levels, with a mean decrease of 60.0 %. TACE allowed for the subsequent complete surgical resection in 13 HB cases and the other three underwent partial resection [158]. One patient received successful orthotopic liver transplantation after receiving TACE therapy. Pathological examination showed that the mean percentage of necrotic area in the surgical specimens was 87 %. In Xuewu's experience 6 out of 8 children (75 %) had a marked response after the first TACE and were judged as being surgically resectable, but one boy died of pneumonia just before the scheduled operation, while another boy preferred further TACE [160]. On the other hand, severe complications, such as pulmonary embolism, have been associated with this technique [156]. Although complications with the older lipiodol/cytostatics (doxorubicin, cisplatin and sometimes mitomycin or vincristine with a possible addition of verapamil to break potential tumor resistance) emulsion technique were more frequent, chemoembolization is now possible with doxorubicin loaded capsules of the prolonged release or spheres which develop radiation effect. Embolizing agents are usually Gelfoam or Spongostan particles, or steel coils.

TACE may be of particular use in children with advanced HCC where treatment options are very limited. In some cases tumor resection not only might become possible, but also technically facilitated as tumors become firm and calcified. Main indications for TACE are: a bridge to liver transplantation (while waiting for a liver donor to become available) or to resection (with an attempted conversion of non-operable, systemically chemoresistant tumors to resectability). Potential advantages of TACE include the delivery of a higher concentration of cytotoxic drugs to the tumor, which is mostly vascularized by the hepatic artery branches, prolonged "dwell time" of drug in the tumor and reduced systemic toxicity. TACE may be particularly safe in children and adolescents with HCC who do not have cirrhosis. However, TACE requires high technical expertise in radiology suited with large volume of interventional procedures. The effectiveness of TACE is limited by the development of neovascularity in the periphery of the tumor [161, 162]. The procedure should be repeated every 4–6 weeks.

Pre-operative Portal Venous Embolization

Portal venous embolization has been used in adults with HCC to induce hypertrophy of the remaining liver remnant [163], and reported experimentally in children. This technique may be particularly useful in children with large tumors. The portal venous branch on the side of the tumor is cannulated percutaneously and polyvinyl alcohol and coils are inserted to induce portal vein occlusion under fluoroscopic control. This has a dual effect of alcohol thrombosis of the embolized tumor and compensatory hypertrophy of the unharmed opposite liver lobe increasing the potential hepatic functional reserve in patients with cirrhosis and underlying liver dysfunction in preparation for hepatic resection of the tumor

Percutaneous Ablative Therapies

Ablative percutaneous methods of local control are more relevant to pediatric HCC than HB, as HCC is more often advanced at diagnosis, and therapy often more directed toward palliation than cure. Available ablative therapies include percutaneous radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI), and cryotherapy. Cryotherapy refers to cold injury produced by cryoprobe delivery of liquid nitrogen and although once popular in adults, it has now fallen out of favor due to superior results achieved with RFA and PEI. In most cases, these treatment approaches are palliative and are suitable for smaller size tumors only, generally below 3–4 cm maximum diameter. RFA provides slightly better tumor kill than PEI (90 % versus 80 % complete tumor necrosis) with less sessions (mean of 1.2 versus 4.8) [164]. It is also associated with fewer side effects; thus in many centers, RFA is now preferred over PEI; however, RFA is contraindicated in lesions located adjacent to the major biliary ducts or to bowel loops. Complications of these ablative techniques occur in about 8–9 % of cases, mainly in the form of pain, fever, bleeding, tumor seeding,

and gastrointestinal perforation [165]. Percutaneous ablation has not been well studied in children.

Rhabdoid Tumor

The definition of a rhabdoid tumor classically relies on a characteristic morphology and loss of hSNF5/INI1 tumor suppressor gene expression [166]. In cases lacking the typical histological features, the loss of expression of the INI1 gene product is the essential diagnostic tool. Although pediatric rhabdoid tumors are most common in the kidney and brain, they do occur at other sites including the mediastinum and liver. When primary to the liver, rhabdoid tumor is difficult to distinguish from the small cell undifferentiated (SCU) variant of hepatoblastoma (HB) [58]. Given the aggressive biologic behavior and poor prognosis seen with the SCU variant of HB, it has been suggested that tumors previously classified as SCU-HB were actually hepatic rhabdoid tumors. The differentiation of an SCU-HB from a rhabdoid tumor is challenging and is important in terms of research, but possibly clinically irrelevant at present as both are biologically aggressive with poor response to chemotherapy. Malignant rhabdoid tumor of the liver is a rare and aggressive tumor of toddlers and school age children which may present with spontaneous rupture [167]. These rare tumors are often chemoresistant and fatal, although a recent case report documents the potential for cure with multimodal therapy including ifosfamide, vincristine, and actinomycin D [168]. As with all locally aggressive liver tumors that respond poorly to chemotherapy, the most important treatment goal is complete surgical excision.

Hepatic Sarcomas

Primary hepatic sarcomas are rare, and their outcome depends primarily on tumor histology, sensitivity to chemotherapy and/or radiotherapy, and the ability to achieve complete tumor resection [169].

Biliary Rhabdomyosarcoma

The classic presentation of biliary rhabdomyosarcoma is in young children (average 3 ½ years) with jaundice and abdominal pain, and is often associated with abdominal distension, vomiting, and fever [170]. Histology is either embryonal or botryoid, both histologic subtypes of rhabdomyosarcoma that have a favorable prognosis. It is important to definitively distinguish in differentiated embryonal sarcoma the cuniform biliary rhabdomyoscarcoma as patients with UESL are often erroneously included on COG RMS protocols [171]. Because the tumor most often involves the central biliary tree and porta hepatis, the ability to achieve gross total resection is rare. Fortunately the tumor is often sensitive to both chemotherapy and radiation and long-term survival is seen in 60–70 % of patients. Surgical intervention has two goals: to establish an accurate diagnosis and to determine the local-regional extent of disease. Although chemotherapy is generally effective at relief of the associated biliary obstruction, patients remain at risk for biliary sepsis until the obstruction abates as the tumor shrinks with chemotherapy.

Undifferentiated Embryonal Sarcoma of the Liver

The undifferentiated embryonal sarcoma of the liver (UESL) is an aggressive hepatic tumor of mesenchymal origin. It accounts for about 5–15 % hepatic tumors in childhood [172, 173]. The typical presentation is an 8–18 year old with a liver mass, nausea, vomiting, jaundice, fever, and weight loss. PET CT has been reported to monitor treatment response as recent significant improvement in survival has been seen with chemotherapy, aggressive surgery, and salvage radiotherapy [173]. On MRI the tumor is heterogeneous with focal areas of T1 hyperintensity and T2 hypointensity. On CT, the prominent myxoid stroma has high water content and cystic appearance. The peripheral rim of dense enhancement corresponds to the pseudo capsule [66]. Diagnosis often requires an open biopsy because needle aspiration or true cut biopsy frequently yields only necrotic material [174]. Histologically, the UESL is a mesenchymal lesion with polygonal spindle cells, stellate cells, highly polymorphous cells and a variable component of myxoid stroma. Multiple eosinophilic globular inclusions in giant cells are typical for UESL. Sometimes also dilated bile ducts are present, especially in the peripheral areas. Immunohistochemical analysis shows that the tumor stains positively for vimentin, alpha-1 antitrypsin [171]. UESL has been reported to arise within mesenchymal hamartoma, an hypthosis that was recently shown to be associated with t (11, 19) (q11; q13.4) translocation [175, 176].

The best chance of cure is achieved with a multidisciplinary treatment strategy based on neoadjuvant and adjuvant chemotherapy, surgical resection, and sometimes radiotherapy. The chemotherapy regimens are usually based on guidelines designed for childhood sarcomas, including vincristin (V), actinomycin D (A), cyclophosphamid (C), ifosfamide (I), Doxorubicin (A) (CWS Protocol: VA, VAI, VAIA; IRS protocol: VAC) [171, 172]. The unresectable tumors are treated with neoadjuvant chemotherapy followed by delayed surgery and postoperative chemotherapy, and about two-thirds will show tumor shrinkage after neoadjuvant chemotherapy [174, 177].

Liver transplantation is a treatment option to achieve a complete resection after neoadjuvant chemotherapy [173, 178]. Cure is usually possible following complete tumor resection. Patients with unresectable tumor after chemother-

apy, multifocal or ruptured tumor and patients with distant metastases have been associated with a poor prognosis. The overall survival in single institution series in the last years was 70–100 % [172–174, 179].

Angiosarcoma

Although rare, the authors' personal experience, and multiple case reports in the literature, support the potential for malignant transformation of an infantile hepatic hemangioma to angiosarcoma [180, 181]. Histologic verification of malignancy can be difficult and angiosarcoma should be suspected if the biologic behavior of an infantile hepatic hemangioma shows unusual progression or recurrence after a period of relative quiescence. Relatively chemoresistant, prognosis is generally poor unless diagnosed early. There are case reports of successful transplantation.

Metastatic and Other Malignant Tumors Involving the Liver

Metastatic Liver Tumors

In children, especially infants, hepatic metastasis is sometimes detected in neuroblastoma. Patients with neuroblastoma younger than 12 months of age with metastases limited to liver, skin, and bone marrow is called a stage 4S and have better outcomes than infants with stage 4 disease [182]. The majority of 4S liver tumors will regress spontaneously, even when persistent, and may not require aggressive therapy [182]. Multiple solid tumors of childhood are known to metastasize to the liver including: germ cell tumors (GCTs), neuroendocrine pancreatic tumors, pancreatoblastoma, gastrointestinal stromal tumor, desmoplastic small round cell tumor, nephroblastoma, and brain tumors, especially glioblastoma, and medulloblastoma [183–185]. In cases with metastasies to the liver or lung, chemotherapy, radiotherapy, and surgical approaches have not been standardized. Neoadjuvant chemotherapy often yields a partial response; however, tumors may remain surgically unresectable. An aggressive approach to treatment is required to maximize long-term remission, and multiple case reports document occasional survivors after hepatic metastasectomy.

Hepatic Involvement in Hematologic Malignancies

Hemophagocytic Lymphohistiocytosis (HLH)

Hemophagocytic lymphohistiocytosis (HLH) may occasionally present as an abnormal liver mass in a newborn with coagulopathy. Predisposing factors include familial, herpes simplex virus, and severe combined immunodeficiency [186]. Diagnostic criteria according to HLH-2004 include fever, splenomegaly, bicytopenia, hypotriglyceridemia, hypofibrinogenemia, hemophagocytosis, low NK cell activity, hyperferritinemi a, and high IL-2 receptor levels [187]. Treatment is with combination chemo-immunotherapy, including etoposide, dexamethasone, cyclosporine A, and anticipated mortality of about 40 % is increased if the diagnosis or appropriate therapy is delayed.

Langerhans' Cell Histiocytosis (LCH)

Morphologic changes and clinical findings in Langerhans' cell histiocytosis (LCH) of the liver may resemble primary sclerosing cholangitis or a chronic non-suppurative destructive cholangitis [188]. Therefore, LCH is an important differential diagnosis of chronic destructive cholangitis with cholestatic liver disease, especially in children and young adults. Other involved organs include bone, pituitary, thyroid, lungs [189]. The diagnosis can be verified by S-100 and CD-1a immunohistochemistry. There have been rare reports of pediatric liver transplantation in toddlers with multisystem LCH who developed end stage liver disease despite intensive chemotherapy [190, 191].

Acute Megakaryoblastic Leukemia (AMKL)

Rarely congenital acute megakaryoblastic leukemia (AMKL) may present isolated to the liver with ascites caused by massive infiltration of hepatic sinusoids by leukemic cells [192]. The bone marrow by microscopy and flow cytometry and the peripheral blood smear may not initially show the presence of blasts. Because the marrow fibrosis may not manifest until after the massive hepatic infiltration it may initially be difficult to diagnosis as leukemia. In most children with liver involvement the spleen, lymph nodes, and marrow will also be involved at diagnosis. But even in these cases the diagnosis may be difficult, both clinically and pathologically, and the hepatic and lymph node involvement is not uncommonly misinterpreted as solid tumor [193].

Hepatic Veno-occlusive Disease (VOD)

VOD is a major manifestation of liver toxicity associated with conventional and high-dose chemotherapy in children affected by hematologic malignancies and certain solid tumors [194]. Clinically, patients present with jaundice, painful hepatomegaly, and fluid retention, which may evolve into multi-organ failure, a hallmark of severe disease. The pathogenesis is complex and not completely understood, but the damage to sinusoidal endothelium, typically caused by toxic metabolites released from antineoplastic drugs, is thought to play a crucial role, together with cytokine activation, immune deregulation, and coagulopathy [195]. This results in primarily vascular changes in the liver affecting small hepatic venules (VOD), sinusoids (sinusoidal dilatation, peliosis, and perisinusoidal fibrosis) and the portal vein and its branches. Diagnosis is based on clinical criteria supported by characteristic ultrasound findings, with the gold standard investigation being hepatic-venous pressure gradi-

ent measurement and biopsy. The most convincing approach is the use of defibrotide, a novel oligonucleotide with antithrombotic and antiplatelet aggregating properties, as well as endothelial-stabilizing effects. This agent, together with other specific forms of supportive care, has shown efficacy in the treatment of established VOD and promising results in the prevention of VOD in pediatric patients receiving chemotherapy [196].

Liver Tumors as Secondary Malignancies

Secondary liver tumors, especially focal nodular hyperplasia, have been reported in children previously treated with chemotherapy and radiotherapy for tumors including neuroblastoma, leukemia, germ cell tumor, and Ewing's sarcoma [81, 197]. Another case report of FNH in a child with a history of stage IV neuroblastoma showed foci of small cell undifferentiated hepatoblastoma in the resection specimen so very close follow-up is necessary if treatment of the FNH is nonoperative [198]. Although it is difficult to conclude that a specific chemotherapy agents or radiotherapy can cause FNH, liver tumors have been recognized as potential late effects and/or secondary malignancies in children who have previously undergone chemotherapy and radiation as toddlers.

Benign Tumors

Benign Epithelial Tumors

Benign epithelial tumors that are common in adults may infrequently occur in childhood. These include focal nodular hyperplasia (FNH), nodular regenerative hyperplasia (NRH), large regenerative nodules (LRN), and hepatic adenoma. All are composed of hyperplastic hepatocytes similar to surrounding liver parenchyma and may be difficult to discern at imaging [66]. Preferential hepatic arterial phase enhancement helps distinguish FNH and hepatic adenoma from uninvolved liver. Hepatic adenoma often has intracellular fat and a propensity for intratumoral hemorrhage, neither of which are seen in FNH. Unlike adenoma, FNH often contains enough Kupffer cells to show uptake at sulfur colloid scintigraphy. Nodular regenerative hyperplasia is often associated with portal hypertension.

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) may be diagnosed at any age, from newborns to the elderly. In children, it usually is diagnosed between 2 and 5 years of age [199]. It is a benign epithelial tumor that has been referred to by various names in the literature including benign hepatoma, solitary hyperplastic nodule, focal cirrhosis, cholangiohepatoma, and even mixed adenoma. FNH has been seen in association a variety of different conditions and situations including previous trauma to the liver [200], other liver tumors [201], hemochromatosis [202], Klinefelter's syndrome [203], itraconazole [204], smoking [205], oral contraceptives [205], congenital absence of the portal vein (Abernathy syndrome) [206] and a history of pediatric treatment with chemotherapy for a Wilms tumor or neuroblastoma [198, 207]. Focal nodular hyperplasia is a well-circumscribed, lobulated lesion whose typical architecture on gross examination consists of bile ducts and a central stellate scar containing blood vessels that supply the hyperplastic process. Usually, there is no real capsule, but often the fibrous tissue surrounds the liver in lesions varying in size from a few millimeters to more than 20 cm in diameter and may be single or multiple. Microscopically, the proliferating cells are practically identical to the surrounding hepatocytes.

Like other benign liver tumors, small lesions may be asymptomatic incidental findings. Larger lesions may occasionally present with mass symptoms, usually abdominal pain. The diagnosis of FNH is suggested by the ultrasonographic appearance of a well-demarcated, hyperechoic and homogenous lesion; the tumor may be much more evident on CTA or MRA after intravenous contrast enhancement; and usually has normal accumulation of ^{99m}Tc sulfur colloid on liver scintigraphy. Old case reports have reported false positive imaging with ^{9m}Tc sulfur colloid, but recent review has shown that the diagnosis of FNH by imaging alone without biopsy can be highly specific, and MRI was the most sensitive study [208, 209]. In fact, FNH can be a radiographic chameleon, and although a radiographic "central stellate scar" is a pathogneumonic finding, it is lacking in 40–50 % of patients. Spontaneous regression is rare although it may be seen after cessation of oral contraceptives. Asymptomatic patients do not require resection. Symptomatic patients in whom the diagnosis of malignancy has not been definitively ruled out will require surgical excision. Symptomatic patients in whom the benign diagnosis has been confirmed may be candidates for ablative therapy with transcatheter arterial embolization [210].

Macroregenerative Nodules

Nodular regenerative hyperplasia (NRH) are macroregenerative nodules in a non-cirrhotic liver. This is a rare entity of unknown etiology but has been associated in children with a variety of other diseases and drugs. In about half of the children there is some component of associated portal hypertension. Nodular regenerative hyperplasia has been reported in children with portal hypertension and hepatopulmonary syndrome, celiac disease, mimicking metastatic nodules in children with prior treatment of Wilms' tumor or Neuroblastoma, azathioprine treatment of inflammatory bowel disease intrahepatic occlusive venopathy in children treated with six thioguanine for acute lymphoblastic leukemia, Budd-Chiari Syndrome, pulmonary arterial hypertension and connective tissue disorders, chronic granulomatous disease, and a spec-

trum of other disorders many of which involve some sort of perturbation of the hepatic vasculature [211]. Radiologically its nodular appearance may look like neoplasia and open wedge biopsy is occasionally required to definitively rule out malignancy [212]. Prognosis in the absence of portal hypertension is good and complications are rare.

The group in Pittsburgh feels that nodular regenerative hyperplasia (NRH) and large regenerative nodules (LRN) are distinct types of hepatocellular nodules with terminology that has historically often been used interchangeably in the literature [213]. NRH and LRN may have different predisposing factors and imaging findings. Nodular regenerative hyperplasia (NRH) is often associated with portal hypertension, organ transplantation, myeloproliferative disease, or autoimmune processes. The nodules in NRH typically do NOT enhance. Although Rha et al. report a child with NRH secondary to Budd Chiari, the group from Pittsburgh refer to these enhancing lesions in Budd Chiari as LRN [213]. The differentiation may be important if there is a suspicion of malignant degeneration of the nodule and biopsy may be necessary.

Hepatic (Hepatocellular) Adenoma

Hepatocellular adenomas are benign liver neoplasms with specific but varied histopathologic findings and tumor biology. Recent studies of their genetic and histopathic features lead to categorization into three distinct subgroups: (A) inflammatory hepatocellular adenomas; (B) hepatocyte nuclear factor 1x-mutated hepatocellular adenomas; and (C) B-catenin-mutated hepatocellular adenomas. Treatment depends upon subtype and an algorithm was recently proposed in a comprehensive review [214]. The differential diagnosis from focal nodular hyperplasia (FNH) remains a challenge. Other associations have been reported with glycogen storage disease types 1 and 3, galactosemia, hyperthyroidism, polycythemia, diabetes, Fanconi's anemia, polycystic ovary syndrome, and contraceptives or anabolic steroids. When associated with oral contraceptives or anabolic steroids the tumor may regress with cessation of the hormonal therapy. Persistent or progressive adenomas are at risk of rupture and bleeding and surgical excision is often recommended. Alternative contemporary management may include percutaneous radiofrequency ablation [215].

In patients with glycogen storage disease type 1A multiple adenomas may develop progressively in about 50 % of patients. In these patients there is a risk of hepatocellular carcinoma in up to 18 % of patients and HCC has been reported as early as 6 years of age. These patients need to be monitored very closely with serial AFP, radiographic imaging, and biopsy if any question of HCC is raised [216]. In glycogen storage 1A patients in whom the adenomas are multiple and growing, liver transplant not only corrects the underlying metabolic disorder, but also eliminates the risk of tumor rupture, and eliminates the risk of HCC. Apart from the special circumstance of glycogen storage disease, surgical excision has been recommended for lesions >5 cm, dysplastic foci, enlarging size or features of malignant change on imaging, B catenin activation, male gender [216].

Mesenchymal Hamartoma

Although mesenchymal hamartoma of the liver is the second most common benign liver tumor in children, its biology and pathogenesis are poorly understood [174]. Historically, mesenchymal hamartoma has been described in the literature by various names including pseudocystic mesenchymal tumor, hepatic and giant cell lymphangioma, cystic hamartoma, bile cell fibroadenoma, hamartoma, and cavernous lymphangiomatoid tumor. Edmondson recognized these to be similar lesions and described them as mesenchymal hamartoma in 1956. Mesenchymal hamartoma typically presents before 2 years of age with abdominal swelling as the initial symptom. Before sophisticated diagnostic imaging became so readily accessible, many of these tumors became very large, eventually presenting with mass effect such as vena cava compression, feeding difficulties, and respiratory distress. With the widespread use of ultrasound and CT these tumors are now usually detected early as a palpable mass in an otherwise asymptomatic child. The alpha-fetoprotein (AFP) may be variably elevated in this tumor confounding the differentiation from hepatoblastoma. The pathogenesis of mesenchymal hamartoma is unclear. The three leading theories postulate (1) abnormal embryologic development of the mesenchyme producing obstruction of the developing biliary tree that results in cystic, anaplastic, and proliferating bile ducts with most of the proliferative growth just before or after birth, because no mesenchymal mitotic activity in seen histologically [169]; (2) Abnormal development of blood supply with ischemic necrosis and reactive cystic changes [217]; (3) Abnormal proliferation of embryologic hepatic mesenchyme with increased expression of fibroblast growth factor −2 (FGF-2) [218]. Microscopically, the tissue consists of a mixture of bile ducts, liver cell cysts, and mesenchyme. The cysts may simply be dilated bile ducts, dilated lymphatics, or amorphous fluid surrounded by mesenchyme. Elongated or tortuous bile ducts surrounded by connective tissue are unevenly distributed with the bile ducts at the periphery often exhibiting active proliferation [169].

Mesenchymal hamartoma is more common in the right lobe of the liver, although any lobe may be involved. On ultrasonography one sees multiple echogenic cysts although, if the cysts are small, the entire tumor may appear as an echogenic mass. The typical CT scan shows a well-circumscribed, multilocular, multicystic mass that contains low-density cysts separated by solid septae and stroma The stroma and septae may be vascular and occasionally show contrast enhancement on CT scan similar to that seen in infantile hepatic hemangioma. When the cysts are small the tumor may appear solid rather than cystic and biopsy is

required to rule out malignancy. Occasionally a highly vascular tumor in a neonate may present with hydrops, high output heart failure, and respiratory distress [219]. More commonly the tumor tends to increase in size during the first several months of life and subsequently may either stabilize, continue to grow or undergo spontaneous regression.

Traditionally, the surgical treatment has been complete tumor excision, either nonanatomically with a rim of normal tissue or as an anatomic hepatic lobectomy. If the tumor is considered unresectable, the surgical options include enucleation and marsupialization. Although facile, marsupialization may result in tumor recurrence [220]. Management continues to evolve, however, with debate in the literature regarding the advisability of nonoperative management in the asymptomatic patient [221]. Caution is warranted if expectant management is chosen due to reports of malignant transformation or association with undifferentiated (embryonal) sarcoma [174, 222–224].

Hepatobiliary Cystadenoma

Hepatobiliary Cystadenoma is a benign liver tumor most commonly found in middle-aged women. Rare case reports include a 4-year-old boy who had a large mucin-hypersecreting hepatobiliary cystadenoma [225, 226]. The tumor in this little boy caused a hepato-colo-cutaneous fistula, which produced a large amount of external fluid loss. Total excision and repair of the fistula was possible after shrinkage of the tumor with the use of selective embolization of the feeding artery by interventional radiology [226].

Benign Vascular Tumors

Infantile Hepatic Hemangioma

Infantile hemangioma is the most common benign tumor of the liver in infancy [9] illustrates the striking variability of three subtypes focal, multifocal, and diffuse. Many focal lesions are often discovered incidentally and are localized and small enough to be of little clinical significance. Symptoms seen with larger lesions may include abdominal distention, hepatomegaly, congestive heart failure, vomiting, anemia, thrombocytopenia and consumptive coagulopathy, jaundice secondary to biliary obstruction, and associated cutaneous or visceral hemangiomas [227]. The diagnosis of infantile hepatic hemangioma is usually straightforward and based on the combination of clinical symptoms and radiographic appearance on ultrasound and CT scan. Contrast enhanced CT scan shows an area of diminished density, and after bolus injection of intravenous contrast there is contrast enhancement from the periphery toward the center of the lesion, and, after a short delay, there essentially is complete isodense filling of the lesion and liver. MRA has been used in complex cases to identify atypical radiographic features that may portend a poor prognosis [28]. Unfavorable radiographic features include: central varix with arteriovenous shunt, central necrosis or thrombosis, and diffuse hemangiomatous involvement of the liver with abdominal vascular compression [28]. Arterial angiography may be used in infants with refractory symptoms in whom either hepatic artery ligation or embolization is considered. If a definitive diagnosis of simple infantile hepatic hemangioma can be made radiographically, management can be noninvasive because spontaneous regression occurs in most cases—especially those with focal tumors. The terminology is confusing, however, with different authors often using the terms hepatic hemangioma, infantile hepatic hemangioma, infantile hepatic hemangioendothelioma (IHEE), and kaposiform hemangioendothelioma interchangeably [228]. A European pathologic classification recognizes two types in infantile hepatic hemantioendothelioma (IHEE). Type I is more common is composed of a single layer of plump but bland endothelial cells with rare mitotic figures. Type 2 has more pleomorphic endothelial cells and is considered by some to be a low-grade angiosarcoma [229].

A treatment algorithm has been proposed by the vascular anomalies treatment center at Boston Children's Hospital and can be reached at www.liverhemangioma.org (Fig. 16.5). Treatment in this algorithm is based upon whether or not the tumor is solitary, multifocal, or diffuse [230, 231] whose radiographic appearance is shown in Fig. 16.6. About 65 % of

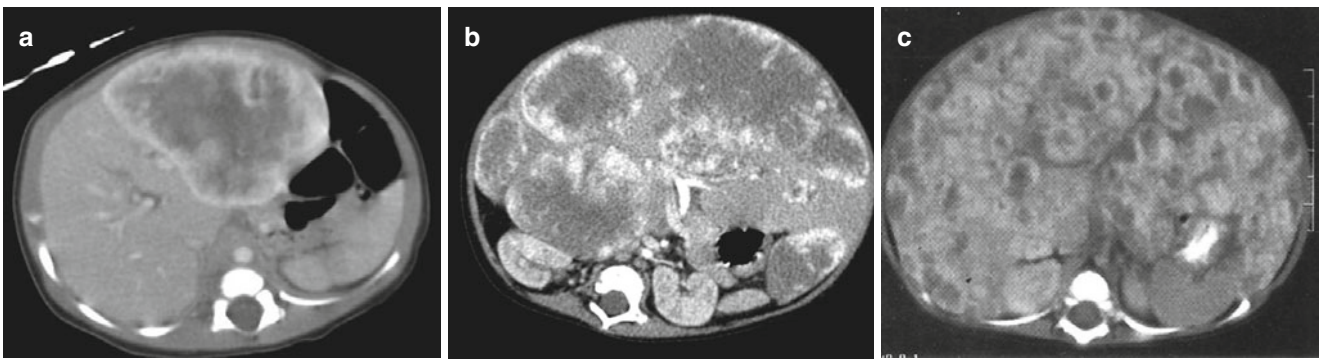

Fig. 16.5 Three subtypes of infantile hepatic hemangioma: (**a**) focal, (**b**) multifocal, and (**c**) diffuse

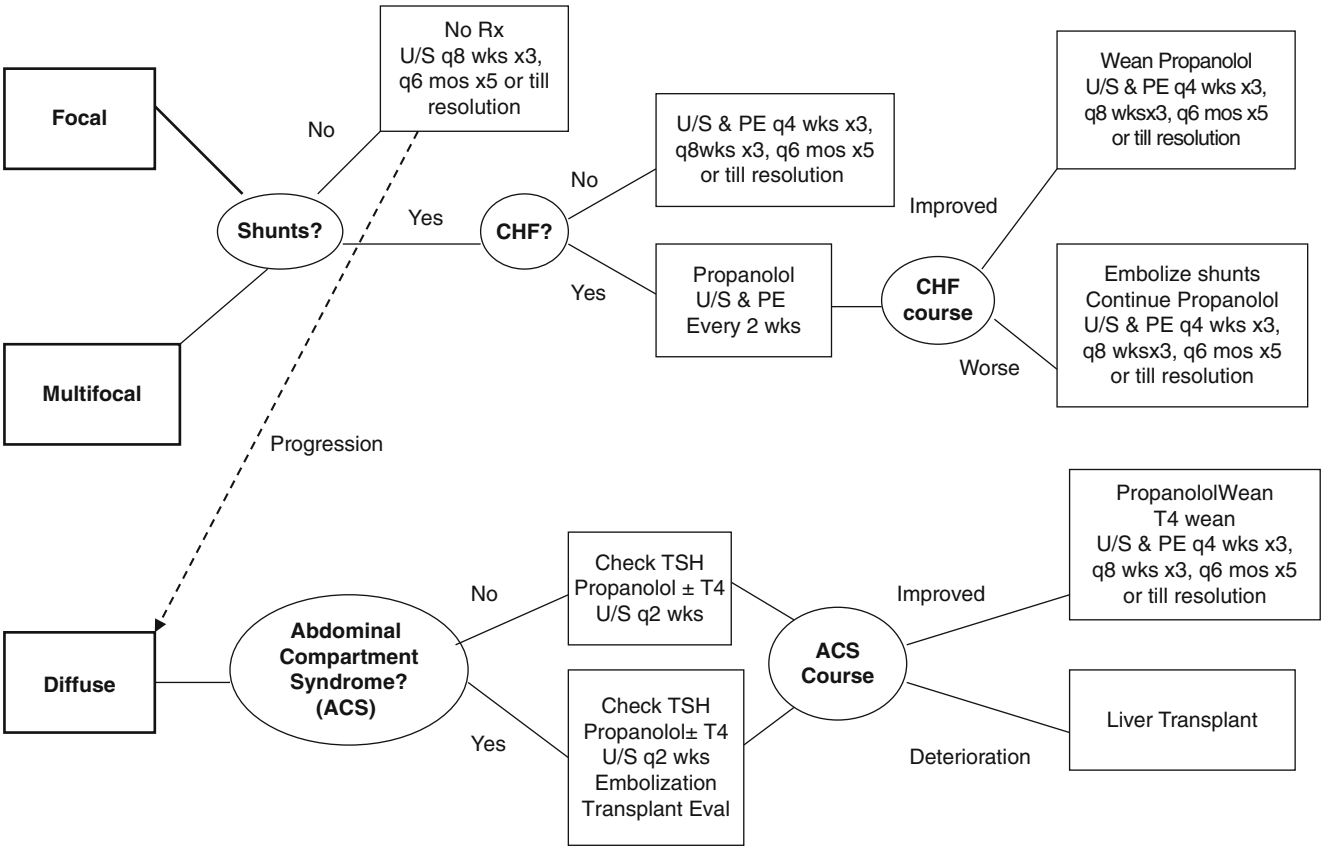

Fig. 16.6 Treatment algorithm: infantile hepatic hemangioma (Adapted from Fishman et al., www.liverhemangioma.com)

tumors are solitary or unifocal with a survival of 86 % and death usually not caused by the tumor but by a co-morbidities [9]. 35 % of tumors are multifocal or diffuse with a survival somewhere between 60 and 100 % with death usually secondary to cardiorespiratory compromise caused tumors refractory to medical and interventional management [9, 231, 232]. Sometimes a large rapidly growing infantile hepatic hemangioma can be life-threatening with intractable high-output cardiac failure from intrahepatic arteriovenous shunting, intraperitoneal hemorrhage, respiratory distress as a result of pulmonary congestion, and massive hepatomegaly compressing abdominal vasculature and producing abdominal compartment syndrome. Historically, the initial medical intervention for symptomatic tumors has been corticosteroids although many are increasingly choosing to start with propranolol [241]. Other medical treatment options exist, although no single treatment has been shown to be universally effective. Congestive heart failure is treated with supportive care, digitalis and diuretics. Anemia and coagulopathy are treated with corrective blood product replacement therapy. Both success and complete failure have been reported variously with many other treatments including epsilon-aminocaproic acid, tranexamic acid, low-molecular-weight heparin, vincristine, cyclophosphamide, interferon 2-alpha, AGM-1470, and newer generation antiangiogenic drugs [233–236]. The angiogenesis inhibitor interferon-alpha may be clinically efficacious, however it must be avoided or used with great caution in children less than 1 year of age because of the risk of producing an irreversible spastic diplegia [237]. Recent studies have shown that the large tumors may produce antibodies to TSH and screening to rule out secondary hypothyroidism is recommended [238]. Treatment is with thyroid hormone replacement therapy and reports demonstrate resolution of the hypothyroidism after liver transplantation in cases that fail medical management [239]. Most recently propranolol has been shown to inhibit the growth of infantile hemangioma [240]. Potential explanations for the therapeutic effect of propranolol, a non-selective beta-blocker, include vasoconstriction, decreased expression of VEGF and bFGF genes through down-regulation of the RAF-mitogen activated protein kinase pathway, and the triggering of apoptosis of capillary endothelial cells [240, 241]. Although rare, malignant transformation to angiosarcoma has been reported and close followup is recommended [180, 181, 242, 243].

In infants who fail medical management, symptomatic solitary tumors may be treated by excision, hepatic arterial ligation or selective angiographic embolization. Although potentially hazardous, hepatic arterial embolization can be especially help-

ful in tumors causing high output cardiac failure due to arteriovenous shunts within the tumor [232]. Orthotopic liver transplantation may be life-saving for cases with diffuse angiomatous change in which the lesion is progressive with intractable high-output cardiac failure, abdominal compartment syndrome, and failure of lesser treatment options.

Kaposiform Hemangioendothelioma

The term "hemangioendothelioma" is sometimes used in the literature when describing a tumor that seems more consistent with a diffuse infantile hemangioma of the liver and hence the terminology can be confusing. Nevertheless, a biologically distinct tumor of infants presenting in the first year of life is kaposiform hemangioendothelioma which may involve the retroperitoneum, extremities, neck or chest wall. Isolated liver involvement is not seen; rather retroperitoneal tumors expand without regard to anatomic planes and may encase the porta hepatis and directly invade the liver, pancreas, mesocolon, colon, and kidneys [244, 245]. Kaposiform Hemangioendothelioma is biologically aggressive, and Kasabach Merritt phenomenon is common with a life threatening coagulopathy and thrombocytopenia. Platelets are consumed by the tumor with a half-life of 1–24 h, and platelet transfusions may actually promote tumor growth through intralesional clotting and the release of vascular endothelial growth factors such as platelet derived growth factor (PDGF). Because of these phenomena, platelet transfusions should only be given when the patient is actively bleeding or as a preparation for surgery [246]. Tumor growth can be so rapid that it causes fibrosis and destruction of the neighboring tissues and mortality ranges from 12 to 24 % for tumors at all sites [244, 247], but may be as high as 60 % for those tumors involving the retroperitoneum due to porta hepatis vascular and biliary obstruction [244]. Successful treatment has been reported with alpha-interferon [248], however, in tumors refractory to antiangiogenic therapy, multidrug chemotherapy regimens may be required and success has been reported with propranolol and vincristine combined with cyclophosphamide, actinomycin D, and methotrexate [246].

Epithelioid Hemangioendothelioma

Epithelioid hemangioendotherlioma is a slow growing vascular tumor which consists of endothelial cells that morphologically resemble epithelial cells. Mainly a tumor in adults, pediatric cases are rare and usually involve children in their teenage years.

Hepatic Teratoma

Primary teratomas (germ cell tumors: GCTs) are rare neoplasms (incidence 0.7/100.000 children/year) with tissue derivatives of all three germ layers [249]. Teratomas mostly occur in the ovaries, the sacrococcygeal region, the testes, and the central nerves system and GCTs of the liver is extremely rare, and accounts for <1 % of all liver neoplasms [250, 251]. Most of them are in children aged <3 years old, and about half of these tumors have been malignant, about half benign [252]. The characteristic histological finding is the predominance of hepatic tissue in the resected specimen. Malignant GCTs have been reported as teratoma [253, 254], choriocarcinoma [255, 256] or yolk sac tumor [251]. Serum AFP levels are sometimes elevated because it is produced by yolk sac, embryonal liver, and embryonal gastrointestinal tract.

Inflammatory Myofibroblastic Tumor

In past inflammatory myofibroblastic tumor (IMT) was often called Inflammatory Pseudotumor. These tumors are usually found in children and young adults and, although most frequently occur in the lungs, can occupy the liver, too [257–260]. Fever, abdominal pain, weight loss and anemia are typical clinical symptoms of IMTs. In some cases of hepatic hilar localization obstructive jaundice develops [257]. There are no specific imaging features of IMT. Thus, surgical biopsy is needed for the final diagnosis. Since the microscopic diagnosis may be quite difficult primary excisional biopsy may be the best option.

Pathologically IMT is a non-neoplastic solid mass consisting of proliferated myofibroblasts with a various degree of infiltration with inflammatory cells. Plasma cells are often predominant. Myofibroblasts are spindle cells sharing features of smooth muscle cells and fibroblasts and stain positively for vimentin, actin, and keratin in most cases [261]. The differential diagnosis are lymphomas and granulomatous lesions. Particularly, when multinucleated giant cells and foamy histiocytes are found [262]. The stroma is typically quite fibrotic with a laminated appearance or dense sclerotic zones, which can be confused with sarcomas [262]. IMT etiology is still largely unclear [257, 262]. There have been several hypotheses like atypical inflammatory response, infectious processes (such as Epstein-Barr virus) [258, 261, 263–265]. These theories are supported by hypergammaglobulinemia or immunologic deficits found in some patients [266]. Recent findings identified clonal, nonrandom, balanced chromosomal translocations resulting in rearrangement of the ALK gene in 50 % of patients [267]. Up to 70 % of IMTs are positive for ALK-1, a tyrosine kinase oncogene found to be rearranged in anaplastic large-cell lymphoma, rhabdomyosarcoma, and peripheral nerve sheath tumor, suggesting that IMTs may represent rather true neoplastic pathway than reactive proliferation. For this reason some are classified as low-grade sarcomas with myofibroblastic differentiation and the World Health

Organization classification puts them among, so called intermediate neoplasms [267]. This is further supported by the fact that some IMTs have a potential for local recurrence or even distant metastases [267]. DNA aneuploidy was identified as another denominator of the malignant IMT behavior [268]. In fact IMTs may be quite a heterogenous group. Surgical excision has been a cornerstone of therapy for IMTs, although spontaneous or antibiotic- and steroid-induced regressions have been noted [262]. Recently, also the use of non-steroid antiinflammatory drugs and imatinib has been tested with some success [267].

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