Hepatic Tumors in Childhood

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75.1 Introduction

Primary neoplasms of the liver are rare in childhood and constitute 0.3–2% of all pediatric tumors. Malignant neoplasms account for 1% of all pediatric malignancies and are the third most common intra-abdominal neoplasm after neuroblastoma and nephroblastoma. The two primary malignant neoplasms of the liver are hepatoblastoma and hepatocellular carcinoma. For both these malignant tumors, complete resection of the tumor is necessary to achieve a cure. Detailed description of hepatic segmental anatomy has enabled surgeons to resect larger tumors in the recent years. This appreciation of the anatomy and the regenerative capability of the liver, which allows up to 85% of the liver to be safely removed in small infants, have greatly increased the scope for cure.

The incidence of benign liver tumors in children is less than their malignant counterpart, and in a large series of pediatric liver tumors, benign tumors accounted for less than 35%. The benign tumors include hemangiomas or vascular malformations, hepatocellular adenomas, focal nodular hyperplasia, mesenchymal hamartomas, and various types of cysts and cystic disease. With widespread use of ultrasonography, fortuitous discoveries of benign tumors are being made in a large number of children, and this raises the question of optimal surgical management for the surgeon.

75.2 History

A first glimpse of the hepatic anatomy was presented by Herophilus and Erasistratus between 310 BC and 280 BC. The first attempt at hepatic resection did not take place till the late 1880s. Though Martin et al.

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reported that hepatoblastomas could be treated by hepatic lobectomy in 1969, real progress in hepatic surgery was mostly seen following the detailed description of hepatic segmental anatomy by Couinaud. This knowledge allowed surgeons to get good vascular control before attempting to divide the liver parenchyma, and thereby avoid catastrophic bleeding.

Holton et al. showed that hepatoblastoma was sensitive to systemic chemotherapy in 1975. Following this, various authors have shown that neoadjuvant chemotherapy is useful in reducing the tumor size in hepatoblastoma and thereby enabling complete surgical resection of previously unresectable tumors. Presently, the standard of practice is to administer neoadjuvant systemic chemotherapy to patients with hepatoblastoma unless the tumor is clearly resectable at diagnosis.

The first application of hepatic transplantation to a childhood liver tumor was reported by Heimann et al. in 1987. Tagge et al. reported the first series of pediatric liver tumor patients treated by hepatic transplantation in 1992. Total hepatectomy with liver transplantation now has become a recognized treatment for unresectable hepatoblastoma confined to the liver and this treatment modality is part of the SIOPEL 3 protocol.

75.3 Surgical Anatomy

The liver has two main lobes, a large right and a smaller left and conventional description places their line of fusion on the upper surface of the liver along the attachment of the falciform ligament. However, knowledge of the detailed internal functional anatomy of the liver is essential for planning surgical resections. The anatomical description of the liver by Couinaud is the most complete and exact and also the most useful for the operating surgeon (Fig. 75.1). Essentially the three main hepatic veins within the scissurae divide the liver into four sectors each of which receives a portal pedicle with alternation between the hepatic veins and portal pedicles. The main portal scissura contains the middle hepatic vein and progresses from the middle of the gallbladder bed anteriorly to the left of the vena cava posteriorly. The right and left liver, demarcated by the main portal scissura, are independent in terms of portal and arterial vascularization and of biliary drainage. The distribution of the portal pedicles and hepatic veins delimits the hepatic segments, each of which has a unique portal vein, a branch of hepatic artery and bile duct. Knowledge of this anatomy allows control of the vascular structures before division of the hepatic parenchyma, thereby making major hepatic resections feasible.

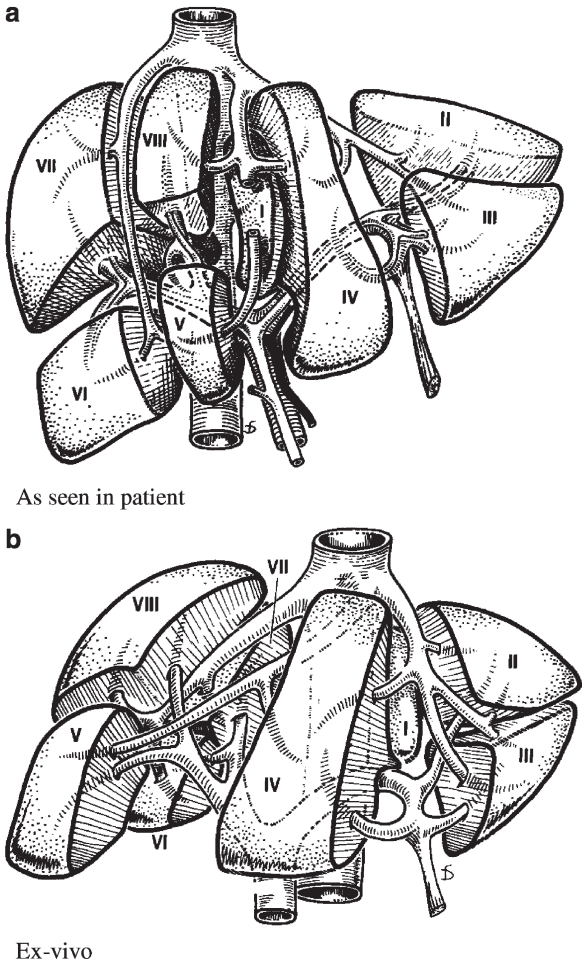


Fig. 75.1 Couinaud's description of liver into eight functional divisions. (**a**) As seen in patient (**b**) Ex-vivo. Each segment receives a branch of the portal vein, hepatic artery and is drained by a branch of either the right or left hepatic duct. The three main hepatic veins demarcate the liver into its four portal sectors (Blumgart 2000)

75.4 Evaluation of a Child with a Hepatic Mass

Most hepatic tumors present as an asymptomatic abdominal mass. Patients presenting with a suspected hepatic mass are first evaluated by history and physical

examination. Blood should be drawn for the following tests: complete blood count, liver function tests, coagulation studies, and measurement of tumor markers such as serum α-fetoprotein and β-human chorionic gonadotropin.

Usually the initial radiological evaluation is with ultrasonography. Ultrasonography will determine whether the hepatic mass is solid or cystic and the extent of the mass. A Doppler ultrasonography is useful in determining the patency of hepatic vasculature. This is followed with either a CT scan or magnetic resonance imaging (MRI). In our experience, MRI provides the greatest amount of information concerning both the lesion and surrounding veins and bile ducts. If a malignant liver tumor is suspected following the initial scans, then a thoracic CT scan is necessary for the purpose of tumor staging.

A tissue diagnosis is necessary to confirm malignancy. Percutaneous needle core biopsy is useful for the diagnosis of hepatoblastomas but may not be definitive in the case of hepatocellular carcinoma. When larger samples are needed, an open or laparoscopic liver biopsy is necessary. Once a diagnosis of malignancy is made it is advisable for the pediatric surgeon to include an oncologist and an experienced hepatobiliary surgeon in the planning of definitive surgery.

75.5 Malignant Liver Tumors

The most common malignant hepatic tumors are hepatoblastoma, hepatocellular carcinoma (hepatoma) and sarcomas. It is estimated that about 57.8% of these are hepatoblastoma, 33.4% are hepatocellular carcinoma and 8.8% are sarcomas.

75.5.1 Hepatoblastoma

75.5.1.1 Incidence and Etiology

Hepatoblastomas are the most common primary hepatic tumors in children, accounting for up to 64% of hepatic malignant tumors. Hepatoblastoma affects one child in one million per year under 15 years of age. This translates into approximately 50–70 new cases per year in the United States with a male to female ratio of 1.7:1.0. Over 75% of these tumors occur in children less than 2 years of age. The median age at diagnosis of hepatoblastoma is 18 months. Though congenital hepatoblastomas and adult onset hepatoblastomas have been described in literature, these are rare. Blair et al. noted a borderline, but significant increase in the incidence of hepatoblastoma in 1994. However, Stiller et al. found no such increase in the incidence of hepatoblastoma between 1978 and 1997.

Hepatoblastoma may occur in siblings and there is an increased incidence in first degree relatives of the patients with familial polyposis coli. Other conditions associated with hepatoblastoma include Gardner's syndrome and the Beckwith-Wiedemann syndrome. Beckwith-Wiedemann Syndrome is also associated with several abdominal tumors, of which the majority are Wilms' tumors.

There is a significant association between hepatoblastoma and low birth weight. It is unknown as to whether developmental abnormalities associated with prematurity or interventions, such as early total parenteral nutrition, are the cause of the increased incidence of hepatoblastoma in these children. The increased survival of these children may somewhat explain the increased overall incidence of hepatoblastoma noted by some authors.

75.5.1.2 Histopathological Subtypes

There are five histological subtypes of hepatoblastoma reported based on the light microscopic findings. These subtypes are fetal (cells grow in trabeculae and resemble fetal hepatic cells), embryonal (cells grow in noncohesive sheets), mixed mesenchymal (contain mesenchymal tissue along with the epithelial component), macrotrabecular, and anaplastic or small cell. The histological subtyping of hepatoblastoma is important as there is an association between prognostic risk and the various subtypes as illustrated in Fig. 75.2. Some authors have indicated that the fetal histological subtype has a better prognosis compared to others. However, a review of 105 cases at the Armed Forces Institute of Pathology failed to confirm this finding. The histological subtype anaplastic or small-cell variant is a rare subtype, but is particularly virulent with a strong metastatic potential.

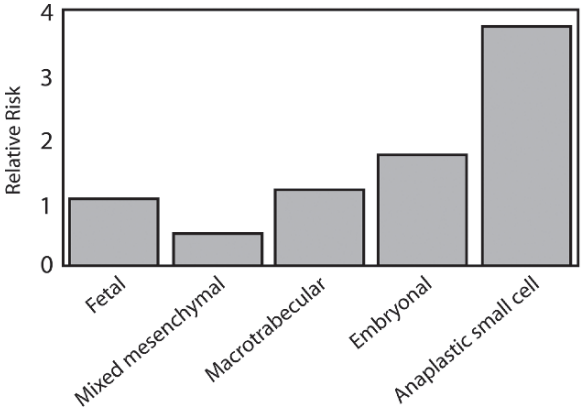


Fig. 75.2 Relative risk of death associated with histopathological subtypes of hepatoblastoma (La Quaglia 2000). The small cell undifferentiated or anaplastic variant has a very poor risk in comparison to the other three histopathological subtypes.

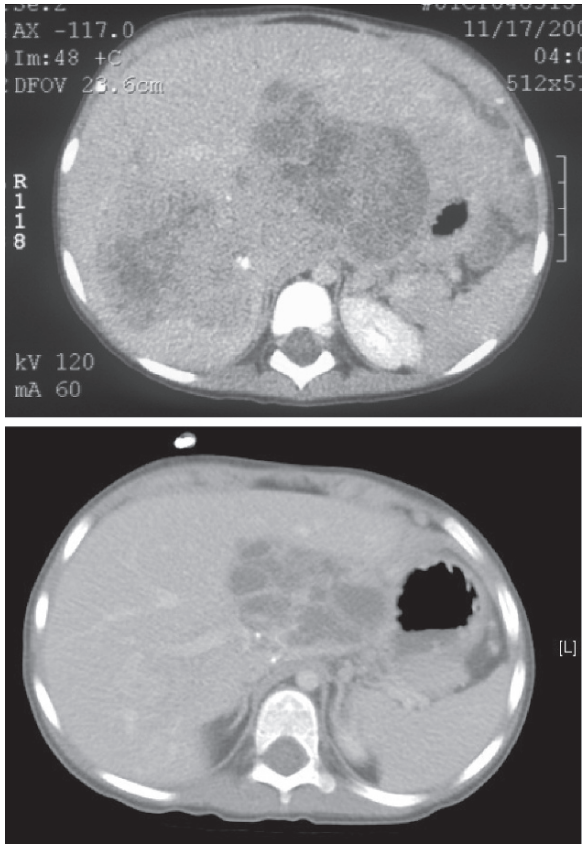


Fig. 75.3 Typical response of hepatoblastoma to neoadjuvant chemotherapy. CT findings at diagnosis in a child with hepatoblastoma. The tumor involves both right and left hepatic lobes and is inoperable. CT scan in the same child following four cycles of chemotherapy. The tumor is confined to left lobe and is eminently resectable.

75.5.1.3 Clinical Findings

As mentioned above, the most common presenting sign of a hepatoblastoma is an asymptomatic abdominal mass. The child is often in good health and the tumor mass is discovered incidentally when an attentive parent, grandparent, or clinician discovers the mass on a routine examination or while bathing the child. A small minority may have other symptoms such as pain, irritability, minor gastrointestinal disturbances, fever, pallor, failure to thrive and even tumor rupture. Patients with the anaplastic variant of hepatoblastoma who often have distant metastases at diagnoses are more frequently symptomatic. A mild anemia associated with a markedly elevated platelet count is observed in the majority of patients at diagnosis. The platelet count can range into the millions and the etiology is probably secondary to an abnormal cytokine release.

Measurement of the serum α-fetoprotein is well established as an initial tumor marker in the diagnosis of hepatoblastoma and a means of monitoring the therapeutic response. When interpreting the α-fetoprotein level it is important to realize that normal α-fetoprotein levels are very high at birth and decrease over the first 6 months of life. Usually by 6 months of age, the levels should be below 100 ng/mL, though in some children this may take up to 1 year of age. It is estimated that the α-fetoprotein will be markedly elevated in 84–91% of patients with hepatoblastoma. Low initial α-fetoprotein levels have been associated with poor survival outcome.

75.5.1.4 Imaging

As mentioned earlier, the first imaging study is usually an abdominal ultrasound and, if duplex technique is employed, tumor vascularity can be gauged and the hepatic veins assessed. This is usually followed by computerized axial tomography or magnetic resonance imaging. A computerized axial tomography with oral contrast is useful in identifying any pulmonary metastases, and in determining the hepatic involvement and resectability (Fig. 75.3).

75.5.1.5 Staging

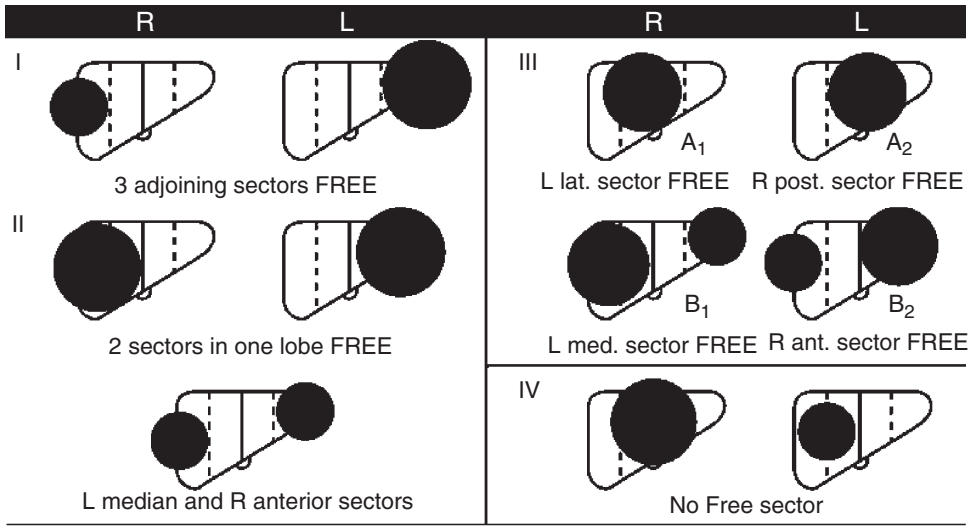
Most studies to date have used the clinical grouping defined by the Children's Cancer Group and the Pediatric Oncology Group as listed in Table 75.1. This classification is based on the postoperative extent of disease. Although this classification is useful in predicting postoperative prognosis, it does not provide preoperative information. To assess tumor response and resectability before and after neoadjuvant chemotherapy, the International Society of Pediatric Oncology (SIOP) developed the PRETEXT (pretreatment extent of disease) staging system (Fig. 75.4). The PRETEXT system is based on the radiological findings and describes both the number and the location of involved liver sectors and takes into account the invasion of the hepatic and portal veins as well as extrahepatic and metastatic disease. More recently, the TNM classification has been used (Table 75.2).

Table 75.1 Post-surgical clinical group staging

Stage I	No metastases, tumor completely resected
Stage II	No metastases, tumor grossly resected with microscopic residual disease (positive margins or tumor rupture/spill at the time of surgery)
Stage III	No distant metastases, tumor unresectable or resected with gross residual tumor or positive lymph nodes
Stage IV	Distant metastases regardless of the extent of liver involvement

75.5.1.6 Treatment and Prognosis

Following initial assessment, the first decision regarding treatment is whether to initiate neo-adjuvant chemotherapy



Liver is divided into four sectors, based on its surgical anatomy.

- PRETEXT I- three adjoining sectors are free of tumor
- PRETEXT II- two adjoining sectors are free of tumor
- PRETEXT III- one non Sector or two non-adjoining sectors are free of tumor
- PRETEXT IV- no tumor free sectors

In addition, extrahepatic tumor is expressed as follows:

V - tumor involving hepatic vein
P - tumor involving pertal vein
E - extrahepatic direct spread, limited to enlargement of the hilar lymph nodes
M - presence of distant metastases

Fig. 75.4 International Society of Paediatric Oncology PRETEXT staging (Brown, Perilongo et al. 2000)

Table 75.2 TNM staging of hepatic tumors

Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T1, N1, M0
	T2, N1, M0
	T3, N0, M0
Stage IVA	T4, any N, M0
Stage IVB	Any T, any N, M1

T0 = no tumor
T1 = solitary tumor </= 2 cm
T2 = solitary tumor </= 2 cm with vascular invasion or multiple tumors limited to one lobe without vascular invasion
T3 = solitary tumor >/= 2 cm with vascular invasion or multiple tumors limited to one lobe with vascular invasion
T4 = multiple tumors in more than one lobe or involvement of a major branch of the portal or hepatic vein
N0 = no nodal disease
N1 = nodes involved
M0 = no distant metastases
M1 = distant metastases

or proceed with resection. About 46% of hepatic malignancies are resectable at diagnosis. Resection at diagnosis will avoid or lessen the need for chemotherapy and its associated morbidity. However, when resection at presentation is not feasible, neo-adjuvant chemotherapy can shrink the tumor size extensively and enable safer and complete resection at a later stage. This requires good clinical judgment and good communication between the pediatric surgeon, oncologist, radiologist, and if necessary, an experienced hepatobiliary surgeon.

For unresectable tumors at diagnosis, the initial surgical procedure should include a diagnostic biopsy and placement of a vascular access device for neo-adjuvant chemotherapy. At present, the recommendation for initial treatment of hepatoblastomas is with Cisplatin, 5-fluorouracil, and vincristine. Single agent doxorubicin is sometimes used in very young infants who undergo complete resection. This regimen consists of just three doses and may be associated with less long- and short-term toxicity than multi-agent regimens. Definitive resection of tumor is undertaken after four cycles of chemotherapy, if complete resection is feasible. With complete resection of the primary tumor, overall survival of 60–70% is achievable with non-stage IV hepatoblastoma except in the very small group of children with aggressive anaplastic variant.

It is estimated that approximately 20% of children will have stage IV disease at the time of diagnosis. The overall survival rates are lower in this group of children, but in our experience a rate of 50% is achievable as long as complete resection at the primary site is accomplished. Some patients with microscopic residual at the primary site are curable with continued chemotherapy and may benefit from external beam radiotherapy to this primary hepatic site. Most pulmonary metastases will resolve fully with chemotherapy while resection is reserved for larger or persistent metastatic lesions.

Hepatic transplantation for unresectable primary lesions can be effective for tumors confined to the liver. Cases with extensive extrahepatic extension or vascular invasion have had poor outcomes with total hepatectomy and hepatic transplantation. Chemoembolization shows promise and involves arteriographic injection of occluding thrombogenic materials (Angiostat collagen) or stainless steel coils combined with chemotherapeutic agents like Cisplatin or doxorubicin, into the arterial circulation to the tumor. Using this technique the concentration of chemotherapeutic agents can be increased 50- to 100-fold in the embolized tumor. Others have treated pulmonary metastases with external beam radiotherapy in an approach similar to that used for Wilms' tumors but with 18–20 Gy administered. Pulmonary radiation may be associated with significant pulmonary toxicity.

75.5.2 Hepatocellular Carcinoma (or Hepatoma)

75.5.2.1 Incidence and Epidemiology

Hepatocellular carcinoma accounts for 23% of pediatric liver tumors and affects about 0.5 children in one million per year under the age of 15. The incidence is bimodal with an early peak before the age of 5 years, and a second peak between 13 and 15 years of age. It is rare in infancy, though historical series without pathological review may report a higher rate of infantile hepatocellular carcinoma due to misdiagnosis of some early hepatoblastomas. The Liver Cancer Study Group of Japan reported no cases below the age of 4 years in a series of 2,286 patients (Japan 1987). There is a male predominance that ranges from 1.3 to 3.2:1 for

hepatocellular carcinoma. In areas endemic for hepatitis B the male to female ratio may be reversed at 0.2:1.

The relative risk for the development of hepatocellular carcinoma is 250 for patients with chronic active hepatitis compared to those without hepatitis surface antigen positivity. This knowledge has enabled the health workers in Taiwan to reduce their incidence of hepatocellular carcinoma in children from 0.70 per 100,000 children to 0.36 per 100,000 in 5 years following the introduction of a universal vaccination program against hepatitis B. Other conditions associated with the development of hepatocellular carcinoma include cirrhosis, alpha-1-antitrypsin deficiency, tyrosinemia, aflatoxin ingestion, hemochromatosis, hepatic venous obstruction, androgen and estrogen exposure, the Alagille syndrome (arteriohepatic dysplasia), and thorotrast administration.

75.5.2.2 Clinical Findings

Unlike children with hepatoblastoma, children with hepatocellular carcinoma are usually symptomatic at diagnosis. Pain is common (38%) and may even occur in the absence of an obvious mass. But most of these symptoms are nonspecific and include anorexia, fatigue, nausea, and vomiting and weight loss. The α-fetoprotein is elevated in approximately 85% of patients with most levels more than 1,000 ng/mL. Though elevated, these levels are usually lower than those measured in hepatoblastoma patients. Up to 10% may present with tumor rupture with signs and symptoms of a hemoperitoneum. The tumors that rupture are not necessarily large and long-term survival with complete resection has been reported.

75.5.2.3 Staging

The staging schemes listed for hepatoblastoma are also used for hepatocellular carcinoma in childhood.

75.5.2.4 Treatment and Outcome

Again, complete resection of the primary tumor is essential for long-term survival. However, this is usually difficult at presentation due to the multifocal nature of the tumor with its extrahepatic involvement of regional lymph nodes and distant metastases. Infiltration with thrombosis of portal and hepatic venous branches is common and even the vena cava may be involved. Chen et al. reported a 18.2% complete resection rate in their series of 55 children. Combination chemotherapy with doxorubicin, cyclophosphamide, vincristine and 5-fluorouracil has not been found effective in reducing tumor size in hepatocellular carcinoma. All this translates into an overall survival rate of zero for children with hepatocellular carcinoma that is not fully resectable at presentation.

Liver transplantation has shown to be useful in selected patients with unresectable tumor. However, positive hepatitis B viral serology, non-fibrolamellar histological type and high frequency of local or metastatic spread make most patients unsuitable for liver transplantation.

75.5.3 Rhabdomyosarcoma of the Extrahepatic Bile Ducts

This form of rhabdomyosarcoma is a very rare tumor with 40% of patients presenting with distant metastases. But mortality is most often due to the effects of local invasion. Rhabdomyosarcoma of the liver, not involving the bile ducts, has also been reported, but is extremely rare. The patients' ages range from 1 to 9 years at presentation. The typical symptoms include intermittent jaundice and sometimes loss of appetite and episodes of cholangitis (Charcot's triad). Hepatomegaly or a palpable abdominal mass is usual, and the diagnosis may be confused with hepatitis or a choledochal cyst.

As with hepatoblastoma and hepatocellular carcinoma, tissue diagnosis is necessary. Neo-adjuvant chemotherapy will reduce the tumor size and allow a cleaner resection at second-look surgery. During the initial biopsy, hilar and left gastric lymph node sampling is performed to determine whether these nodal echelons require added radiotherapy. Resection appears to improve survival. Whether these patients may be treated by chemotherapy alone after establishment of the diagnosis and simply observed if a complete radiologic response is documented remains to be confirmed with future studies.

75.5.4 Primary Hepatic Non-Hodgkin's Lymphoma

Primary non-Hodgkin's lymphoma of the liver occurs in childhood and may account for up to 5% of primary hepatic malignancies. These tumors respond well to chemotherapy, and surgery is not necessary.

75.5.5 Metastatic Hepatic Tumors

Several tumors, including non-Hodgkin's lymphoma, neuroblastoma, rhabdomyosarcoma, rhabdoid tumors, Wilms' tumor, the desmoplastic small round cell tumor, adrenal cortical carcinoma, and osteogenic sarcomas are known to metastasize to the liver in children. There is little data to determine the correct surgical approach to these lesions. Criteria for surgical removal of hepatic metastases include control of the primary site, a solitary or limited number of metastases, good performance status, and a reasonable expectation of prolonged survival or cure.

Hepatic metastases from neuroblastoma are seen in newborns and infants with Stage 4S disease, and are a distinct characteristic of this disease. These lesions usually resolve with time. Wilms' tumor metastasizes to the liver in about 12% of cases and this is usually associated with unfavorable histology. In selected patients, resection of these lesions may have a survival benefit. Most of the other tumors metastasize to the liver in the late stages of disease, and surgical resection does not appear to provide any survival advantage.

75.5.6 Benign Hepatic Tumors

Benign tumors of the liver that occur in childhood include hemangiomas or vascular tumors, hepatocytic adenomas, focal nodular hyperplasia, mesenchymal hamartomas, and various types of cysts or cystic disease. Vascular tumors are the most common and compose greater than 50% of these benign hepatic tumors.

75.5.6.1 Vascular Tumors

Hemangioma: Hemangiomas are lesions characterized by endothelial-lined vascular spaces that can vary in size and extent. They are sometimes classified as hamartomas. The overall incidence of endothelial lined vascular tumors of the liver in childhood is probably unknown since many are asymptomatic. Vascular lesions taken together represent 13–18% of symptomatic hepatic tumors in childhood. Hepatic hemangiomas are twice as common in females as in males.

Diagnosis can be fortuitous on a routine ultrasonography or when presented with an abdominal mass. Multiple hemispherical cutaneous hemangiomas may be present and warn the physician of possible visceral lesions. MRI study is all that is needed to confirm diagnosis and asymptomatic lesions are best left alone, as they tend to regress after the 1st year of life. Large lesions may cause congestive heart failure; if medical treatment is not successful, either hepatic artery embolization or direct surgical ligation may be necessary.

Hemangioendothelioma: These are highly proliferative cellular lesions of variable malignant potential. In one report of 16 infants and children, 15 presented with hepatomegaly, 7 with congestive heart failure, and 4 had associated cutaneous lesions. The Kasabach-Merritt syndrome, a platelet-trapping coagulopathy, has also been observed. These lesions may appear very cellular but do not metastasize. If a primary lesion produces symptoms, resection is indicated for relief.

Hemangioblastoma: Hemangioblastoma of the liver is usually associated with Lindau-von Hippel disease. In infancy and childhood these lesions appear very cellular but distant metastases are uncommon. Complete resection should be performed and is usually curative.

75.5.6.2 Mesenchymal Hamartoma

Mesenchymal hamartomas account for six percent of primary liver tumors in childhood and there is a male predominance. Two-thirds of these tumors are diagnosed at less than 1 year of age. These are usually multicystic and the cysts are lined with flattened biliary epithelium, or endothelium. It is postulated that mesenchymal hamartomas arise in areas of focal intrahepatic biliary atresia. This results in distal bile duct obstruction and hepatocellular necrosis.

The majority of mesenchymal hamartomas present as an enlarging abdominal mass or hepatomegaly, and are usually not symptomatic. They can grow to great sizes causing respiratory distress or evidence of caval

obstruction. Often an open biopsy is necessary to make the diagnosis. Anatomical resection is the recommended treatment for large lesions. Because of the mesenchymal component, these lesions have a definite capsule that facilitates enucleation of large central mesenchymal hamartomas that are not amenable to lobectomy. Prognosis is good and in one study of 18 patients, 13 who were available for follow-up were alive and well 1 month to 24 years after treatment (mean = 5 years).

75.5.6.3 Focal Nodular Hyperplasia and Hepatocellular Adenoma

These are benign hepatocellular proliferations that are rare in children. Less than 2% of hepatic tumors in childhood are focal nodular hyperplasia or hepatocellular adenomas. The presence of fibrous septa containing bile ducts and inflammatory infiltrate distinguishes focal nodular hyperplasia from hepatocellular adenoma. These fibrous septa are seen as a distinct central scar in the ultrasound and computerized axial tomogram images. Most patients are less than 5 years of age at presentation and there is a female predominance. There is an association with contraceptive use in adults but no such association is reported in childhood and adolescence.

It is best to remove adenomas because of the difficulty in histologically differentiating them from low-grade hepatocellular carcinomas, and because of the uncertainty surrounding future malignant degeneration. Resection may also result in symptomatic relief in some children. In general anatomic resection is preferred for focal nodular hyperplasia and most do well after the hepatic resection. However, asymptomatic lesions can be observed using serial abdominal ultrasonography.

75.5.6.4 Cysts and Cystic Disease

There are multiple case reports of solitary, congenital, non-parasitic liver cysts in childhood. They are extremely rare but have been increasingly noted as incidental findings on ultrasounds or computerized axial tomograms performed for other reasons. These usually are simple cysts and are asymptomatic. To the best of our knowledge, there has been no report indicating any malignant degeneration of these cysts.

If there are associated symptoms, such as pain or jaundice, then aspiration followed by ethanol injection (sclerotherapy) may be of benefit. If this is not successful, surgical intervention including resection, marsupialization or cyst wall excision may be considered.

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