CHAPTER 107
Liver Tumours

Graeme Pitcher
V. T. Joseph

Introduction

The burden of tumours on African communities is often overshadowed by the immediacy of problems such as social and political instability and civil wars. Health problems such as communicable diseases and diseases borne from deprivation are in most places the priority of clinical care and the primary thrust for preventive strategies. Liver tumours, both benign and malignant, are uncommon in children and constitute only 3% of all solid organ lesions. Furthermore, overall figures show that malignant liver tumours account for less than 2% of all childhood malignancies. The incidence of the different histological types varies geographically and is related to hepatitis B and human immunodeficiency virus (HIV) prevalence.

In communities in Africa where access to medical care and sophisticated imaging technologies is limited, deep-seated visceral tumours often grow to an enormous size before they are detected and treated. In most areas, the facilities for the provision of good-quality, modern, multimodal and multidisciplinary care, which is so critical for a good outcome in these patients, simply do not exist. Little is known about the epidemiology and the outcomes of the management of liver tumours in children on the African continent as a whole because good-quality reports and registry data are generally lacking. The unique milieu of predisposing infectious diseases and other environmental influences and carcinogens results in a different pattern of malignant tumours on the continent, making research into their causes and treatment all the more pressing.

Demographics

Data reviewed recently from a tumour registry of paediatric oncology services in South Africa[1] provides a scarce and much-needed insight into the problem. An 18-year review provided 274 malignant liver tumours in children under the age of 14 years—amounting to 1 case per million at-risk children per year, in keeping with data from the United States.[2] The incidence of benign primary liver tumours is not known, but is probably similarly rare.

Of the malignant tumours, hepatoblastoma (HB) is the most common, occurring in 48% of tumour patients.[1] This tumour shows a distinct male preponderance (male-to-female ratio of 2:1), occurring at a mean age of 2.1 years of age and without any ethnic predeliction. Interestingly, in this series, no patient older than 4 years of age presented, and all patients had markedly elevated levels of alpha-foetoprotein (AFP).

Hepatocellular carcinoma is the second most common tumour, occurring in 27% of patients and showing a definite ethnic and gender bias.[1] The distribution of the other malignant tumours seen in the registry is depicted in Table 107.1. The incidence of HB is lower than reported from Western series (where the incidence appears to be increasing), which may be due to lower rates of such recognized risk factors as low birth weight and low maternal age,[3] genetic differences, or failure of diagnosis.

The study showed an interesting trend.[1] Over the course of the period of study, vascular tumours and Kaposi sarcoma seemed to increase in incidence, whereas hepatocellular carcinoma seemed to be occurring less commonly. The authors attributed this to the beneficial effect of the introduction of mandatory immunisation against hepatitis B in South Africa during the course of the period of study and possibly to the growing impact of the HIV epidemic in the country.

Aetiology

A thorough description of all the known causes and risk factors for liver tumours is beyond the scope of this book. This chapter therefore concentrates on the factors that are known or suspected of impacting the unique pattern of tumours seen on the African continent. The role of hepatitis B coinfection is well recognized as the most important risk factor for liver tumours in Africa.[4] Factors such as aflatoxin exposure, membranous vena caval obstruction, and excessive iron ingestion may play minor roles in placing African children at risk for liver tumours.

Table 107.1: Demographic of malignant liver tumours in childhood.

Tumour	Incidence of HB (%)	Gender bias (male-to-female ratio)	Age (years)	Racial distribution	Alpha-foetoprotein	Comments
Hepatocellular carcinoma	48	1.95:1	2.16	Equal	All ↑	Less than 4 years of age
Hepatocellular carcinoma	27	2.09:1	10.5	Black	85%↑	fibrolamellar variant, 12%; hepatitis B positive, 69%
Liver sarcoma	6	0.4:1	7.6			
Vascular tumours						
Kaposi sarcoma	5					All HIV positive
Haemangio-endothelioma	5					

Source: Moore SW, Davidson A, Hadley GP, Kruger M, Poole J, Stones D, Wainwright L, Wessels G. Malignant liver tumors in South African children: a national audit. World J Surg 2008; 32(7). Modified with permission.

The reasons for the lower-than-expected incidence of HB in Africa are not well understood, as mentioned above. The relationship between the Beckwith-Weidemann syndrome (BWS) and hemihypertrophy and the risk of HB (and more commonly Wilms' tumour and adrenocortical carcinoma) are well known. Regular screening of affected infants by three-monthly US and AFP monitoring is recommended. AFP is a serum protein produced by foetal liver cells, yolk sac, and the gastrointestinal tract.

The aetiology of most benign liver tumours is obscure. Adenomas associated with high-dose estrogen administration in oral contraceptives have become much less common after these drugs were reformulated. Patients with glycogen storage disease due to glucose-6-phosphatase deficiency or Fanconi anaemia are at risk for adenomas and should be monitored.

Clinical Presentation

Mass Presentation

In the majority of cases, the presentation of liver tumours in childhood is one of a progressively enlarging mass. The poor access of many children on the African continent to quality tertiary health care as well as the relatively hidden subcostal position of the liver result in many patients presenting with extraordinarily large tumours. Sometimes patients are erroneously referred for pulmonology assessments due to diaphragmatic elevation or to orthopaedics for apparent scoliosis. Patients with hepatoblastoma will occasionally show evidence of thrombocytosis and fever. Jaundice is usually not present except in the case of obstructing hilar tumours. As seen more frequently with Wilms' tumour, some unfortunate children will present in a very poor nutritional state with advanced cancer cachexia.[5]

Cirrhosis Presentation

In the Western world, most patients with de novo hepatocellular carcinoma (HCC) do not have underlying cirrhosis.[6] In sub-Saharan Africa, where the prevalence of hepatitis B is so much greater, the presentation with cirrhosis is much more common. Cirrhotic patients may present with symptoms of the underlying disease. In these cases, the presenting symptoms may be those of upper gastrointestinal haemorrhage due to varices, nosebleeds from thrombocytopaenia, lethargy, fatigue, failure to thrive, weight loss, or jaundice. In many patients with cirrhosis, the tumour will be detected on US or computed tomography (CT) scan screening at the time of the patient's first presentation with symptoms, but occasionally these will be detected during routine screening in larger centres.

Haemorrhage or Rupture Presentation

Intraperitoneal bleeding can rarely be the presenting symptom, either as a result of spontaneous rupture or more commonly after misguided attempts at needle biopsy. Rupture of large undifferentiated embryonal sarcomas has been described in older children. Newborns with antenatally undiagnosed hepatoblastoma or haemangioma are at particular risk of death during delivery.[7]

Prenatal Presentation

Routine antenatal US screening is not available to the vast majority of mothers on the African continent. In larger centres, both HB and haemangiomas may be diagnosed by antenatal US. This obviously aids in the overall care of the patient by directing the place and mode of delivery to diminish the risk of rupture and to expedite postnatal management. Large tumours (typically mesenchymal hamartomas and haemangiomas) can compromise foetal well-being and cause hydrops foetalis or even foetal death.[7,8]

Haematological Presentation

Rarely, infants with cutaneous or visceral haemangiomas may develop a consumptive coagulopathy. This has been named the Kasabach-Merritt syndrome. It can occur with any histological type of vascular lesion, but usually occurs in the kaposiform haemangioendothelioma or in the tufted angioma variants.[9] Its hallmarks are thrombocytopaenia and consumptive coagulopathy, which can be life threatening.

Investigations

Haematological Studies

All children with a suspected liver mass should be investigated by haematological and imaging studies. A full blood count, coagulation profile, and liver function tests, as well as a screen for tumour markers (AFP and β-HCG, or β-human chorionic gonadotropin) should be performed. Infants with haemangiomas should have thyroid function screening. AFP is the most useful single test. The results need to be interpreted in the light of normal high levels in the neonatal period. The 95% confidence intervals for AFP levels is 15.7–146.5 μg/ml.[10] Levels usually return to the normal adult range of <10 ng/ml by the age of 2 years. An encountered pitfall is that neonates with HB may have AFP levels scarcely higher than normal for their age. This limits its value as a screening tool but can also mislead the clinician. An elevated level can also occur in other tumours, such as mesenchymal hamartoma or in the face of hepatocellular regeneration.

If cirrhosis is suspected, viral studies seeking hepatitis A, B, C; cytomegalovirus; and Epstein-Barr virus should be included. In all patients, the HIV serology should be determined, either to aid in the diagnosis (e.g., for patients with vascular tumours) or to be able to optimize their condition for a potential major resection. In cases where parasitic disease is possible, hydatid serology should be considered.

Imaging

In the Western experience, imaging includes US, contrast-enhanced CT scan, and MRI. US is the most commonly used imaging modality for all masses in the liver. Haemangiomas are echogenic but cannot be differentiated from other vascular lesions such as tumours. The scan may be improved if colour Doppler is employed but US is probably most useful in follow-up of lesions that are being treated conservatively. US performed by an experienced operator is an excellent tool for the diagnosis of liver tumours and may be the only modality available in many African centres.

Contrast-enhanced CT provides good imaging of hepatic haemangiomas. The lesion shows peripheral enhancement during the arterial phase, which progresses towards the central area during the portal venous phase. For the planning of surgery, CT scanning is essential. It shows the operating surgeon the relationship of the tumour to major vessels and its exact location in the liver with greater accuracy, allowing a better assessment of resectability. In addition, the appearance may suggest the tumour type. Large, low-density lesions in the right lobe suggest mesenchymal hamartomas or undifferentiated embryonal sarcoma (Figure 107.1). Hepatoblastoma typically appears as a heterogenous solid tumour with ill-defined borders and may contain areas of calcification (Figure 107.2).

MRI provides the most accurate diagnosis of haemangiomas. Gadolinium can be given intravenously to produce enhancement of the lesion. In planning surgical resections, MRI can be extremely useful in defining the margins of the lesion in relation to adjacent vascular structures. Unfortunately, MRI is not routinely available in the African setting.

Radionuclide studies and hepatic angiograms are not used routinely in the imaging of haemangiomas in the liver.

Positron emission tomography (PET) scanning is not available in most African centres. Hepatic scintigraphy is no longer indicated except in the unusual incidence of differentiating uptake in an area of focal nodular hyperplasia (FNH) to distinguish it from an adenoma.

All patients with malignant tumours should receive chest x-rays as screening for metastases, and chest CT scans should be performed if any abnormality is detected. In patients with HCC, the screen should include a bone scan as well as CT of the brain.[11]

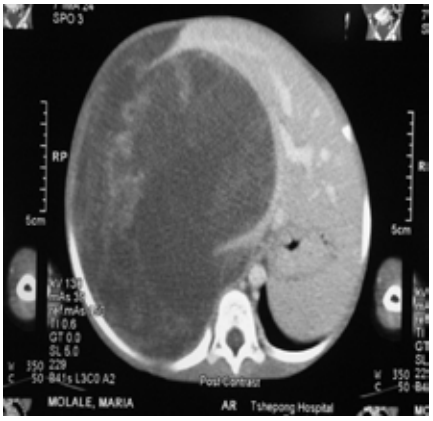

Figure 107.1: CT appearance of a large mesenchymal hamartoma in the right lobe of the liver

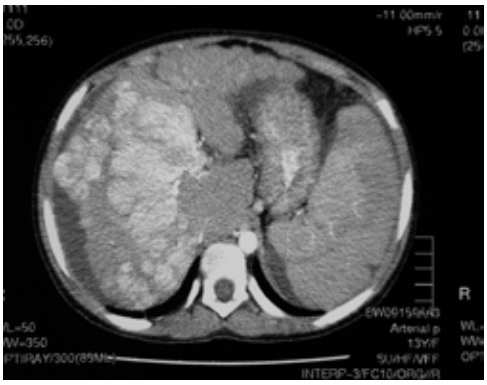

Figure 107.2: A large hepatoblastoma in the right lobe of the liver prior to neoadjuvant therapy.

Table 107.2: Main categories of liver tumours.

Malignant	Benign
Hepatoblastoma	Vascular neoplasm
Hepatocellular carcinoma	Haemangioma
Sarcoma	Haemanioendothelioma
Undifferentiated	Mesenchymal hamartoma
Angiosarcoma	Adenoma
Rhabdomyosarcoma	Focal nodular hyperplasia
	Adenoma
	Simple cyst

Types of Liver Tumours

The main categories of liver tumours are presented in Table 107.2.

Malignant

The two most important childhood liver malignancies are hepatoblastoma and hepatocellular carcinoma. The relative frequencies of these diseases shows a wide geographical variation and is influenced by the presence of environmental and genetic factors.

Hepatoblastoma

HB is a rare malignant neoplasm of the liver that occurs in children between the ages of 1 to 3 years. It is the most common primary malignant liver tumour, accounting for two-thirds of all cases. There is a male preponderance, with boys being twice as commonly affected as girls.

The prognosis for HB has improved in recent years, but the maxim still holds true that at some time in the course of the patient's treatment, a resection with complete peritumoural clearance is necessary for a good outcome.

The characteristic laboratory finding is the presence of an elevated AFP. At birth, it is normal to have high levels of AFP, which then decline over a period of time. In HB, the AFP is markedly elevated in at least 90% of the cases, and it can be also used as a marker to follow the response to therapy as well as to detect recurrence. The half-life of AFP is 4 to 9 days, and it returns to normal values approximately 6 weeks after tumour resection. Very high or very low levels of AFP in HB usually are associated with a poor prognosis.

A number of imaging studies are used in the diagnosis of children presenting with an abdominal mass that may be HB:

Plain abdominal x-ray shows a soft tissue mass in the right hypochondrium and occasionally may also show calcification within the mass.

Ultrasound shows HB as a hyperechoic mass in the liver; US is particularly good for showing the vascular anatomy using colour Doppler.

CT with contrast shows lesion contrast enhancement during the portal venous phase (Figure 107.3).

- *MRI* is the investigation of choice, but unfortunately for most children in this age group it will require general anaesthesia and it is not generally available in Africa. The images are sequenced after administration of gadolinium-based contrast agents, and three-dimensional (3D) reconstruction can be performed to provide an accurate anatomical picture (Figure 107.4).

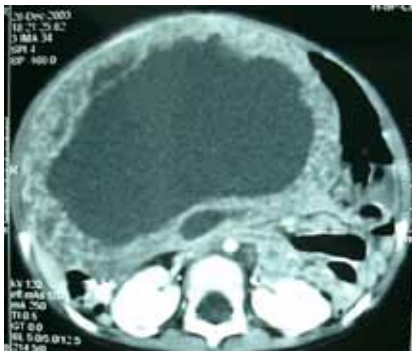

Figure 107.3: CT scan of hepatoblastoma.

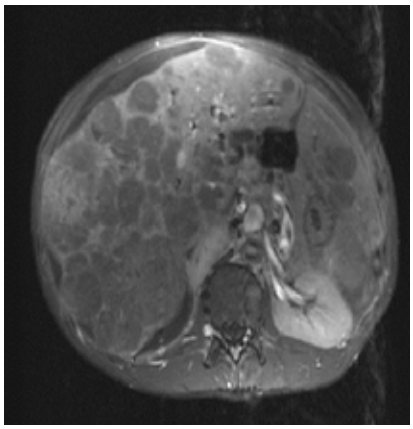

Figure 107.4: MRI of hepatoblastoma.

- *CT chest* is always performed to detect the presence of lung metastases.
- *Bone scans* are usually done to exclude any metastatic involvement.

The HB tumour is derived from immature liver precursor cells and it is usually a single lesion situated in the right lobe. On microscopic examination, microvascular invasion is often present, which must be taken into account when surgical resections are planned. The tumour has a pseudocapsule, and the surrounding liver tissue does not show

evidence of cirrhosis. Metastatic spread usually occurs to the lungs only, with bone secondaries being very rare.

Histologically, several subtypes have been described.

- Epithelial (56%)
  - Foetal (31%)—this has a good prognosis if completely resected
  - Embryonal + foetal (19%)
  - Macrotrabecular (3%)
  - Small cell undifferentiated (3%)
- Mixed epithelial/mesenchymal (44%)
  - Teratoid features present
  - Teratoid features absent

A large amount of data has now confirmed that HB is associated with a number of other conditions that are known to have a genetic basis. This is consistent with evidence that HB is derived from a pluripotent stem cell and arises as a result of developmental error during the formation of the liver.

- Beckwith-Wiedemann syndrome and hemihypertrophy: In these syndromes, there is loss of heterozygosity (LOH) of chromosome 11p.
- Familial adenomatosis polyposis (FAP): Mutations in the adenomatous polyposis coli (APC) supressor gene lead to alterations in the Wnt/Bcatenin signalling pathway contributing to the development of tumour.
- Talipes equinovarus
- Patent ductus arteriosus
- Tetralogy of Fallot
- Extrahepatic biliary atresia

Also, studies in Germany have shown the association with very low birth weight infants, and this has been confirmed elsewhere.

Two major staging systems have been used in the treatment of HB: The North American system, which uses postsurgical staging; and the European SIOPEL/PRETEXT,[12] which is a presurgical staging system. PRETEXT stands for PRETreatment EXTent of disease.

According to the PRETEXT system, which is assessed by CT scan, patients are divided into risk groups on the basis of the PRETEXT type and the behaviour of the tumour. The PRETEXT staging system involves dividing the liver into four sections (Figure 107.5):

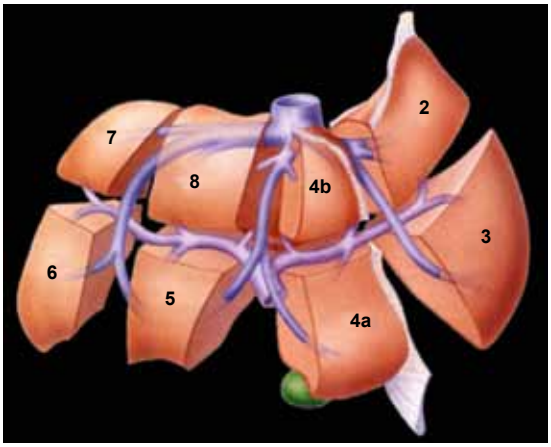

Figure 107.5: Anatomical liver segmentation.

- Segments 2 + 3 (left lateral section)
- Segments 4a + 4b (left medial section)
- Segments 5 + 8 (right anterior section)
- Segments 6 + 7 (right posterior section)

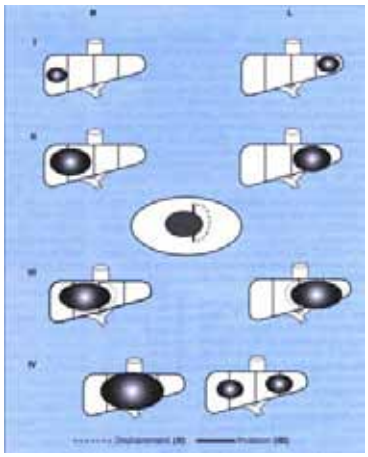

Figure 107.6: Four liver sections for PRETEXT staging.

The PRETEXT number (Figure 107.6) is derived by subtracting the number of adjacent sections not involved with a tumour from the number 4. Thus,

- PRETEXT I: One section involved, three sections free
- PRETEXT II: One or two sections involved, two adjoining sections free
- PRETEXT III: Two or three sections involved, one adjacent section free
- PRETEXT IV: All four sections involved

Additional criteria include:

- caudate lobe involvement;
- inferior vena cava involvement;
- hepatic veins;
- portal veins;
- extraabdominal disease;
- tumour rupture/intraperitoneal haemorrhage;
- lymph node metastases; and
- distant metastases.

Based on these criteria, patients can be classified into high-risk and standard-risk groups. Standard-risk patients are those classified as PRETEXT I, II, and III with no spread outside of the liver. High-risk patients are those classified as PRETEXT IV or with extrahepatic spread, distant metastases, or vascular invasion.

Most patients are asymptomatic, and the first indication of the tumour may be an enlarging abdomen. This accounts for the finding that 40% of cases are in an advanced stage at the time of presentation and 20% already have pulmonary metastases. Among other symptoms are:

- anorexia, loss of weight, and failure to thrive;
- osteopaenia;
- rupture with haemorrhage; and
- precocious puberty associated with β-hCG secreting tumours.

The HB tumour is usually fairly responsive to chemotherapy with cisplatin and doxorubicin (known as PLADO), and in most cases, resection is facilitated by using these drugs as neoadjuvant chemotherapy. In high-risk cases, carbopalatin is often added to the regimen. These approaches have yielded high resection rates and 3-year tumour-free survival rates of 89% for standard-risk patients and 48% for high-risk patients.[13] Liver transplantation, in countries where that modality is available, has greatly improved the outcome of patients with extensive high-risk disease. Recent data clearly show that posttransplant outcomes are much more favourable in borderline

patients who were subjected to primary transplantation compared to those in whom transplantation was attempted after unsuccessful resection (i.e., as rescue therapy).[14,15] Recently, liver transplantation has been shown to play a significant role in the treatment of unresectable HB with 5-year disease-free survivals of 80%.

Hepatocellular carcinoma

HCC accounts for only 23% of paediatric malignant liver tumours, but the actual incidence varies in different geographical areas. In countries where hepatitis B and HIV are prevalent, the incidence can rise to almost 50%. Two peak age groups can be identified: the first from 0 to 4 years and the second from 10 to 14 years. Unlike HB, this tumour is associated with cirrhosis of the liver. Predisposing factors therefore include metabolic liver disease, hepatitis B, biliary atresia, and total parenteral nutrition.

Clinically, patients present with an abdominal mass, pain, weight loss, anaemia, and fever. The AFP is elevated in 50% of cases. Imaging studies are similar to HB, and tissue diagnosis by liver biopsy is required for confirmation of the disease and to assess the extent of cirrhotic involvement of the liver.

The outlook for the African child with HCC remains dismal. The majority present with multicentric disease, and most tumours (85%) are not amenable to resection from the outset.[5,16] Most patients with unresectable disease are best treated by palliation. Response rates to chemotherapy with or without radiation treatment tend to be poor, although newer agents that have been tried in adults with HCC in the developed world may improve the outlook. Transplantation has been offered to a small, select group of patients with exclusively intrahepatic disease in whom resection is not possible, but results have been mixed.

Hepatic sarcoma

Undifferentiated embryonal sarcoma is the third most common malignant tumour in the liver. These tumours occur in children between 5 and 10 years of age. They are mesenchymal in origin and are closely related to the vascular tumours. Angiosarcoma of the liver is a highly malignant tumour and has a poor outlook. Embryonal rhabdomyosarcoma arises from intrahepatic biliary ducts and often presents clinically as obstructive jaundice. The treatment and outcomes follow those of the rhabdomyosarcoma protocols.

As these are rare tumours, it is essential to have tissue diagnosis before appropriate therapy can be instituted. Although US-guided percutaneous biopsy has been advocated, it is safer to do an open biopsy or laparoscopic-assisted biopsy due to the risk of bleeding. This approach will also provide better tissue samples for histology and specialised examination.

The undifferentiated embryonal sarcoma classically presents with a large, usually right-lobed, low-density or sometimes frankly cystic lesion on imaging, which may easily be mistaken for a simple liver cyst,[17] or hydatid disease[18] in high prevalence areas for that disease. AFP levels are usually normal in this tumour. Careful planning to enhance the possibility of complete resection is mandatory, with misdiagnosis significantly diminishing the chance of cure.

The only hope of cure in patients presenting with one of the variants of sarcoma is complete resection. Neoadjuvant treatment may be helpful in rendering tumours resectable, particularly in embryonal rhabdomyosarcoma and in some cases of undifferentiated embryonal sarcomas.[19] Results in patients in whom resection can be achieved are good, with cure achieved in 20–30% of cases and useful palliation achieved in many[5] (Figure 107.7).

Kaposi sarcoma and malignant vascular tumours in AIDS patients

Malignant vascular lesions in the HIV-positive patient tend to be more aggressive, being more commonly anaplastic and frequently metastatic at presentation. This is commonly a terminal manifestation of severe immunodeficiency and carries a very poor prognosis.

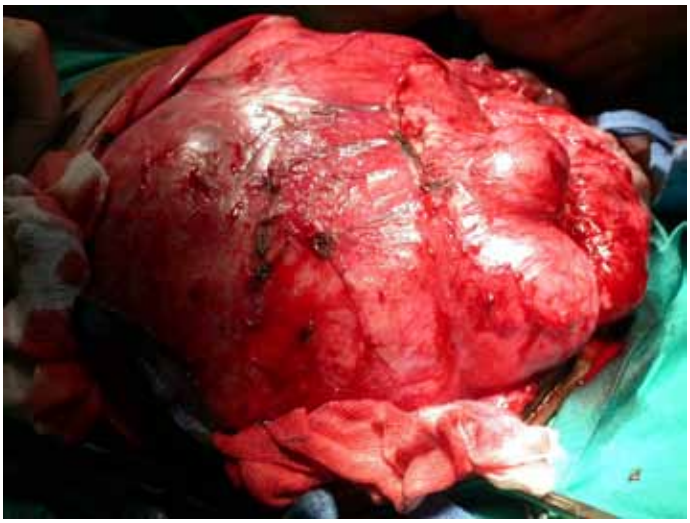

Figure 107.7: Massive undifferentiated embryonal sarcoma, successfully resected with adjuvant chemotherapy and disease-free at 2 years.

Benign Tumours

Benign lesions of the liver presenting as tumours account for one-third of all hepatic masses. Most of these lesions are not neoplastic in origin and may be better regarded as malformations. Benign tumours can be divided into two groups:

- Mesenchymal
  - Haemangioma
  - Hamartoma
- Epithelial
  - Cysts
  - Focal nodular hyperplasia
  - Hepatic adenoma

Haemangiomas

Haemangiomas are the most common benign lesions seen in the liver and are frequently seen in the first 6 months of life. They vary from small lesions that are incidentally detected on scans done for other reasons to massive lesions that may precipitate high-output cardiac failure. Large lesions that are symptomatic present with abdominal pain, abdominal mass, or with complications of which bleeding is the most frequent.

The natural history is one of spontaneous regression, and in asymptomatic cases a conservative approach with regular monitoring may be all that is needed. In the presence of symptoms that may be life-threatening, treatment is initiated with high-dose steroids. Alpha interferon has also been used, but it is toxic and the response is slow, occuring over a period of months. Focal lesions may be resected or controlled with hepatic artery embolisation. Hepatic irradiation and radio frequency ablation have been successfully used to treat large lesions in some cases, but the experience is limited. Extensive lesions that cannot be managed in this way may require liver transplantation.

Infantile haemangioendothelioma

Infantile haemangioendothelioma is the third most common liver tumour in childhood (12% of all paediatric liver tumours in the Western world), and is the most common liver tumour in infancy. It is usually seen in infants younger than the age of 6 months; 85% of cases present within this age group. There is a female preponderance with a female-to-male ratio of 2:1. Fifty percent have cutaneous haemangiomas and the lesions themselves may show calcifications. They are usually benign, but malignant sarcoma can occur.

The natural history of these tumours is that they grow in the first year of life and then start regressing probably due to thrombosis in the vascular

channels. Histologically, they are mesenchymal tumours with vascular channels lined by endothelial cells. Two subtypes are recognised:

- *Type 1* consists of multiple small vascular channels with calcification and a fibrous stroma containing bile ductules.
- *Type 2* consists of vascular channels with disorganised endothelial lining and there is no stroma containing bile ductules.

Haemangioendothelioma is generally managed conservatively, as spontaneous regression will usually occur. Intervention is required if the lesion becomes symptomatic or due to its size. Steroids have been used to induce regression, but they are not usually effective. Surgical resection provides cure and is the treatment of choice when feasible.

Mesenchymal hamartoma

Mesenchymal hamartoma is a rare benign tumour of the liver that is more properly classified as a malformation. In the Western world, it accounts for only 6% of liver tumours in childhood and generally occurs between the ages of 1 to 2 years. The right lobe of the liver is almost always the site of involvement (Figure 107.8).

Histologically, the lesion consists of an overgrowth of mesenchymal tissue with a marked tendency to cyst formation. This is reflected in the CT findings of a heterogenous, complex mass with multiple cystic spaces. The treatment is either marsupialisation of the cysts or surgical resection, which can be successfully done because the tumour is always confined to one lobe only.

All mesenchymal hamartomas are best treated by complete resection. Incomplete resection has been associated with the development of sarcoma.[20] Infantile haemangiomas can be managed expectantly without biopsy if their imaging appearance is typical. Careful medical management, consisting of treatment of cardiac failure and occasionally hypothyroidism (due to expression of type 3 iodothyronine deiodinase in the tumour, resulting in consumption of thyroxine) is critical to a good outcome.

Liver cysts

Nonparasitic cysts of the liver may be simple cysts or part of the spectrum of polycystic disease (Figure 107.9). Simple cysts are usually incidental findings and are generally single. They vary in size from small lesions to very large ones that occupy the whole lobe of the liver. The wall is thin and composed of mature connective tissue. The treatment of large, symptomatic simple liver cysts is surgical, as percutaneous aspiration is always associated with recurrence. Most cysts can be unroofed, leaving the interior open to the peritoneal cavity. This may be done laparoscopically with good results. It may sometimes be necessary to carry out hepatic resection if the cyst is very large and occupies the whole lobe of the liver.

The cysts of Caroli's disease arise from the intrahepatic biliary ducts and are filled with bile. They may involve a single lobe, in which case hepatic resection is the treatment of choice. However, both lobes of the liver may also be involved, and transplantation is then the only possible mode of treatment.

Polycystic liver disease is associated with polycystic kidney disease in 50% of cases. The cysts may be diffuse throughout the liver or may occupy one lobe. The hepatic parenchyma between the cysts is normal and liver function is well preserved.

Liver abscesses may present as cystic lesions, or an infected cyst may subsequently appear as an abscess. The aetiology may be pyogenic or amoebic. Pyogenic abscess is usually secondary to infection from the biliary tract. It may sometimes be associated with immune deficiency states, especially chronic granulomatous disease. Rarely, tuberculous abscess of the liver may occur without any evidence of lung disease.

Amoebic abscess is endemic in certain parts of Africa and Asia. The parasite enters the portal venous channels through the intestine and lodges in the liver, causing abscess formation.

Simple liver cysts can be treated expectantly unless they are large or symptomatic, in which case they should be treated by resection if possible or by aspiration, sclerotherapy or fenestration as circumstances permit.[21]

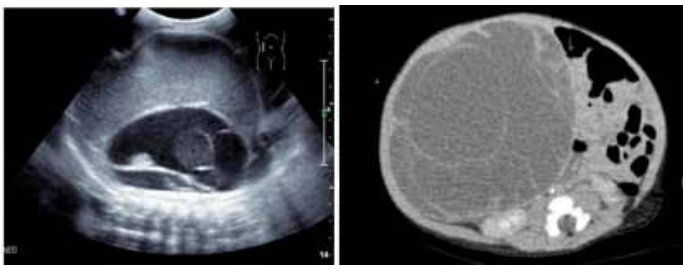

Figure 107.8: Mesenchymal harmatoma.

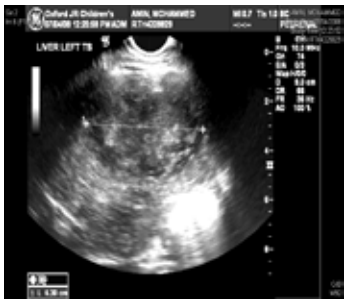

Figure 107.9: Liver cyst.

Focal nodular hyperplasia

FNH represents a localised proliferation of hepatocytes in response to a vascular malformation. It is the second most common benign tumour of the liver, accounting for 8% of the lesions seen; it has a predilection for females. The lesions usually present as solitary, well-defined nodules, and the characteristic feature is the presence of a central scar with radiating fibrous septa. Bile duct proliferation is seen on histology.

Two types of FNH have been described:

- Classic (80%) contains all three components: abnormal nodular architecture, malformed vessels, and cholangiolar proliferation.
- Nonclassic (20%) contains two of the three components of the classic type but always includes bile duct proliferation and is further subdivided into three subtypes: telangiectatic FNH, FNH with cytologic atypia, and mixed hyperplastic and adenomatous FNH.

Clinically, most FNHs are asymptomatic and are discovered during routine scanning. They can, however, present with abdominal pain and with a palpable mass. Although oral contraceptives do not cause these lesions, they may aggravate them and precipitate complications such as infarction and bleeding.

The diagnosis can be made on imaging studies when the characteristic central scar with a stellate appearance is seen. Unfortunately, a positive diagnosis can be achieved in only two-thirds of the patients, and other lesions (particularly hepatocellular carcinoma) can mimic the appearance on scans. It is therefore advisable that in all cases where the diagnosis is not clear and in patients who are symptomatic, surgical exploration and biopsy or resection of the affected area should be carried out.

Hepatic adenoma

Hepatic adenoma is a rare, benign tumour arising from liver cells. It most often occurs in young women and is associated with the use of oral contraceptives. The lesions are generally solitary (80%) but may be multiple (20%). Histologically, the tumour is composed of sheets of hepatocytes containing fat and glycogen with an absence of bile ducts and portal tracts. These lesions have a propensity to rupture and bleed and may rarely also undergo malignant transformation to hepatocellular carcinoma.

The diagnosis in the Western experience is made on the history and imaging findings on CT and gadolinium-enhanced MRI. Typically, adenomas show arterial phase enhancement and the presence of fat and haemorrhage. Nuclear medicine studies are also helpful.

Surgical exploration is advised in all cases due to the risk of haemorrhage. Withdrawal of oral contraceptive use does not lead to regression of the lesions. Solitary lesions are managed by localised resections. Multiple lesions may require biopsy and follow-up evaluation.

Other benign tumours

Some tumours, most recently described as the diffuse type,[22] are large, occupying almost the entire liver (Figure 107.10); these will require systemic steroid or alpha-2A-interferon therapy. In life-threatening circumstances, hepatic artery embolisation (or ligation at open operation) can show dramatic results. Adenomas of the liver are considered premalignant and should be resected where possible. Patients with FNH should be treated expectantly because this condition has no premalignant potential.

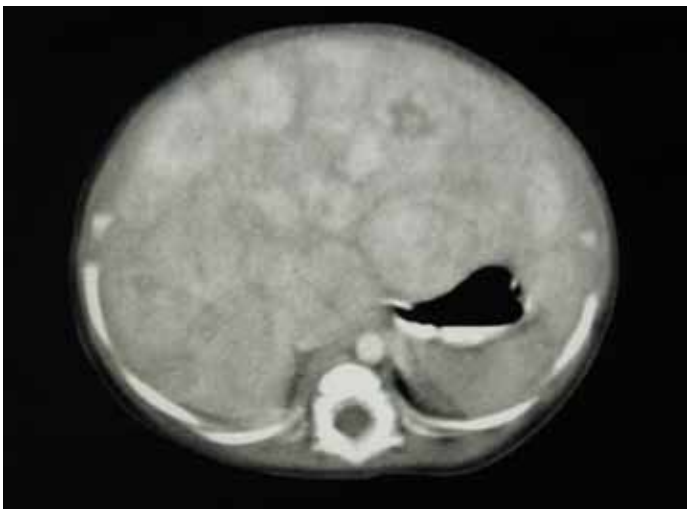

Figure 107.10: Typical CT scan appearance of large, diffuse infantile hepatic haemangioma, typical of the type associated with cardiac failure, coagulopathy, and life threat.

Management

Work-up should be expeditious, and children should be aggressively nutritionally supported, particularly in neglected cases. Treatment depends on the suspected histological type of the tumour (see Table 107.2), its resectability, the presence of metastatic or extrahepatic spread, and the general condition of the patient, including the presence or absence of cirrhosis. Social factors, such as parental compliance, concordance of beliefs with respect to the cause of illness, and access to medical services, need to be assessed. In some cases, these factors will sadly mitigate against any attempt at curative treatment.

Biopsy

The role of biopsy is somewhat controversial. For patients with a typical clinical picture of HB (between 6 months to 3 years of age, elevated AFP more than three times the normal for age, and perhaps fever and thrombocytosis), chemotherapy can usually be started without biopsy confirmation,[23] although not all units follow this approach. All other patients must be submitted to histological biopsy, either by submission of the completed resection specimen if the tumour is deemed safely resectable, or by a percutaneous, laparoscopically guided, or open biopsy at laparotomy. A core-cutting (Trucut®) needle usually gives adequate tissue for the pathologist to make an accurate assessment. It is very important for the clinician to liase closely with the pathologist if there is any doubt as to the diagnosis. A serious pitfall of management is to falsely assume one kind of pathology and to treat incorrectly. A typical example is the management of HB in a young infant or neonate as a presumed haemangioma.

Surgery

Liver surgery is a major undertaking and requires a specialist team for both the intraoperative and postoperative care of the patient. Thorough preoperative evaluation using appropriate imaging studies is carried out to plan the surgery. The abdomen is opened through an upper transverse or bilateral subcostal incision. Special retractors are available that are clamped to the sides of the operating table and hold the blades to retract the costal margins. The liver is mobilised by dividing the falciform and both triangular ligaments (Figure 107.11). The line of resection is then marked on the surface, and division of the hepatic paenchyma is started. This can be done in several ways: finger fracture, crushing with clamps, bipolar diathermy, LigaSure™ , harmonic scalpel, or Cavitron® ultrasonic surgical aspirator (CUSA®). As the division proceeds, the vessels need to be controlled with coagulation or ligatures. The procedure can be made easier by vascular control. Usually, only portal triad occlusion with a clamp that controls hepatic artery and portal venous inflow into the liver is all that is required. The clamp must be released after 30 minutes, and then it may be reapplied after a short interval. The operation should be completed by that time to avoid ischaemic damage to the liver. With very large or vascular tumours, particularly in the right lobe, it may be necessary to obtain total vascular control by clamping the suprahepatic and infrahepatic vena cava as well. Bleeding from the cut surface can also be reduced by keeping the central venous pressure low. At the end of the procedure, the cut surface is sealed with fibrin glue, and the right subhepatic space is drained (Figure 107.12).

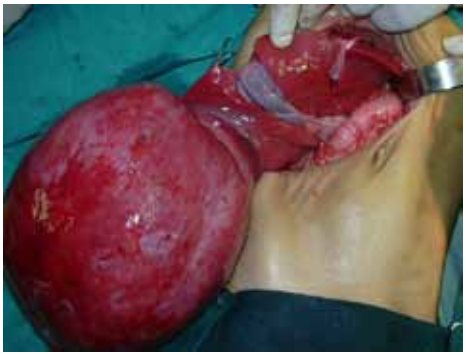

Figure 107.11: Operative view of right lobe hepatoblastoma.

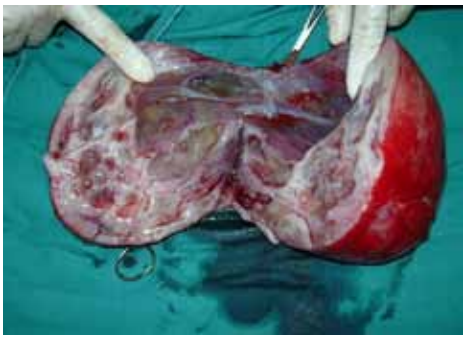

Figure 107.12: Cross section of the tumour from Figure 107.11.

Resection Techniques

Liver resection surgery should always be performed by a surgeon with operative experience with the liver and a thorough knowledge of its segmental anatomy. Before embarking on any liver resection, it is vitally important to assemble the required personnel and facilities as these are not universally available in developing countries (see the checklist

in Table 107.3). The most important facilitator of surgical safety and comfort is good exposure. Optical magnification in the form of 2.5 to 3.5 loupes is essential. A headlight illuminates the darker corners and enhances safety. The bilateral subcostal incision affords excellent exposure, and when combined with a strong mechanical retractor such as a Thompson retractor, usually suffices without the necessity for a midline extension except in older children with narrow subcostal angles. On entering the abdomen, a routine inspection of the abdominal cavity and assessment of extrahepatic spread is performed. The liver should be completely mobilised, allowing access and slinging of the inferior vena cava both above (subdiaphragmatically) and below the liver and to the hepatoduodenal ligament. Although the "Pringle manoeuvre" should be avoided, if possible, to ensure normal liver function and production of coagulation factors during the procedure, it is best to have it exposed preemptively in the event that it is required.

Table 107.3: Checklist of essential equipment, personnel, and drugs for liver resection

Surgical equipment	Personnel and facilities	Drugs, blood, pumps
Vascular instruments	Experienced anaesthetist	Good venous access
Mechanical retractor	Able first assistant	Packed cells and fresh frozen plasma (FFP)
Optical magnification	Able scrub nursing team	Blood pumps
Electrocautery	Postoperative intensive care unit (ICU)	Infusion pumps for inotropes
Sutures	Warming device	
Parenchymal dividers	Intraoperative ultrasound	
Argon beam	Pathologist	
Topical haemostatic agents		

Most resections are best carried out anatomically. This has the advantage of minimising blood loss, injury to biliary structures, and inadequate resections leaving a residual tumour.[11] Hilar dissection prior to parenchymal transection facilitates the performance of major resections by determining the anatomical location of vital structures providing inflow and bile drainage from the liver remnant. It is not necessary to perform cholangiography routinely.

A slightly head-down position lowers the inferior vena caval venous pressure, minimising bleeding, and facilitates venous return, optimising the patient's haemodynamic stability. The line of transection is marked on the liver capsule with electrocautery. An almost bloodless field can be achieved by the placement of pledgeted sutures through the hepatic parenchyma prior to starting division.[24] If this is not possible in larger tumours, then the first assistant can usually achieve very useful bimanual liver compression, which provides haemostasis as well as stabilising and exposing the plane of transection.

Parenchymal division can be safely achieved by a number of techniques, according to the availability of specialised equipment or the surgeon's individual preference. Instruments such as the ultrasonic dissector, LigaSure, harmonic scalpel, and TissueLink™ are useful adjuncts to a good operation, but safe transection of the parenchyma can be achieved by the use of electrocautery alone in most cases. Large veins (both portal and hepatic) will be encountered periodically and are best suture ligated, or clipped with a clip applicator. For this purpose, the LigaSure certainly facilitates an easier and safer division of such vessels. Transecting the parenchyma in the direction of the inferior liver margin up towards the hepatic veins is preferred because it allows for maximal exposure (towards the end of tissue transection) of the most dangerous area of the procedure at the hepatic veins. These veins are most commonly suture ligated with a polypropylene suture. Raw surface bleeding can be managed by a combination of suture, electrocautery, argon beam laser (if available), or various topical haemostatic agents. The liver bed is always drained by an active suction drain, as it is an area of negative pressure.

Postoperative Complications

A vast number of complications can potentially occur following major liver resection. Among the most important and specific to the operation are postoperative haemorrhage and postoperative liver dysfunction due to an insult to an insufficient-sized liver remnant—the "small for size syndrome". A safe remnant liver is usually considered to be >25% of the functional liver volume, or 0.8–1.0% of body mass. As long as that guideline is respected and there has not been a significant insult to the remnant, then this complication should occur very rarely.[25] Postoperative bleeding can usually be avoided by maintaining liver function by limiting periods of cross-clamping, judicious blood and product use, and maintenance of normal haematological parameters and meticulous haemostasis of all areas, including the liver raw surface.

Other less dangerous but more common problems include bile leaks, prolonged ascitic drainage, pleural effusions, atelectasis, and pulmonary infections. These can be managed on their merits. Limiting the use of postoperative ventilation can dramatically reduce pulmonary complications and is safe if used with discretion.

Prognosis and Outcomes

The prognosis for benign tumours is excellent overall. The two exceptions to this rule are large mesenchymal hamartomas and infantile haemangiomas. Children with large central mesenchymal hamartomas (Figure 107.13) present a specific challenge; these can be resected with innovative nonanatomic resections and by a technique of dissection in the immediate peritumoural plane in order to avoid injury to major portal or venous structures.[5] Concerns about malignant transformation of the residual tumour should not override safety concerns. Multimodal therapy combined with medical treatment and embolotherapy or hepatic artery ligation of the infant with diffuse haemangioma have improved the outcomes for these infants as well. Whereas transplantation has been used in that scenario in the developed world,[26] it will rarely be feasible on the African continent, even in transplant centres.

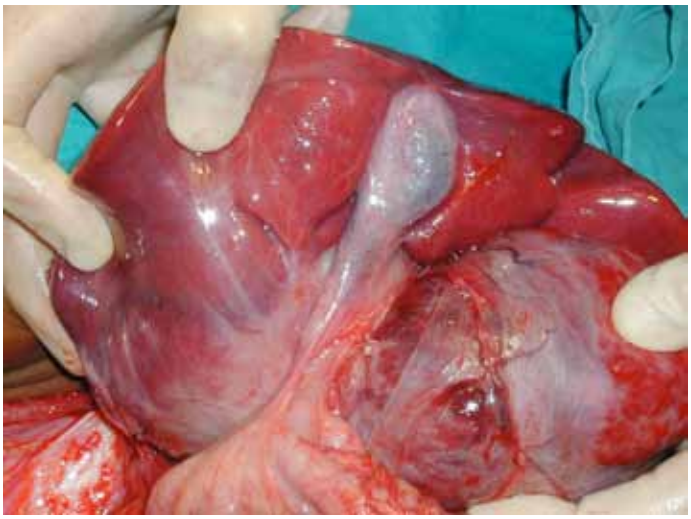

Figure 107.13: Intraoperative appearance of central mesenchymal hamartoma in a 2-year-old child.

Prevention

Immunisation against hepatitis B provides a wonderful opportunity for the prevention of hepatocellular carcinoma in childhood. For example, compulsory hepatitis B immunisation commenced in the United States in 1992,[27] and it has been predicted that deaths in children due to hepatitis B could be decreased by 80% as a result of effective vaccine programs.[28] Within the last few years, many African countries have commenced hepatitis B immunisation programs.[29,30] Although some encouraging reports of declining hepatocellular carcinoma incidence are emerging, the full benefit will probably not be seen until the next decade.

Hepatocellular carcinomas are well known to be associated with diseases such as biliary atresia, hereditary tyrosinaemia type I, progressive familial intrahepatic cholestasis (PFIC), Alagille syndrome, and other causes of cirrhosis in children.[31] Although these patients probably represent only a small percentage of tumours in African children, it is important that they are provided surveillance in appropriately staffed and funded units.

With the mainly unchecked progression of the HIV epidemic in many countries on the African continent, the upsurge of Kaposi sarcoma contributing to the malignant tumour burden of African children is to be expected.[1] The management of this epidemic should be accorded top priority to prevent the millions of deaths occurring annually in children and to contribute to improving the quality of life of these children.

Ethical Considerations

In most instances, the treatment of children with liver tumours follows the lines of maximum effort (with available resources) to help the patient with the presumption of beneficence (i.e., that the patient will benefit from the treatment). The treatment of patients with advanced and unresectable hepatocellular carcinoma certainly falls within the ambit of *futile treatment*. This term is used advisedly, as no care (such as the provision of analgesia, tapping ascitic collections) is futile, but no heroic measures should be adopted in the oncologic treatment of these children. Similar considerations exist in the patient with AIDS who presents with an aggressive malignant vascular tumour.

A controversial and difficult circumstance arises when treatment by transplant would be advisable but the child and the family are deemed unsuitable due to either geographic, educational, or financial reasons, or are expected not to adhere to the rigorous posttransplant treatment and surveillance strategies. This scenario occurs not uncommonly, and the usual outcome is exclusion of the child from access to such treatment. The harsh realities of transplantation in the developing world often offer no other solution.

Evidence-Based Research

Table 107.4 presents an observational study of different patterns of disease in malignant liver tumours based on African children's cancer registry data. Table 107.5 presents a review of the current state of the art in management of liver tumours in children in Germany.

Table 107.4: Evidence-based research.

Title	Malignant liver tumors in South African children: a national audit
Authors	Moore SW, Davidson A, Hadley GP, Kruger M, Poole J, Stones D, Wainwright L, Wessels G
Institution	Multiinstitutional in South Africa—children's cancer registry data
Reference	World J Surg 2008; 32(7):1389–1395
Problem	Epidemiology and outcomes of treatment in South Africa for malignant tumours.
Intervention	Collation of registry data.
Comparison/ control (quality of evidence)	Observational study.
Outcome/ effect	Showed different patterns of disease.
Historical significance/ comments	This is the largest registry-based study of malignant liver tumours in Africa and provides unique insights into the problem of malignant disease in an area with high seroprevalence of HIV and hepatitis B.

Table 107.5: Evidence-based research.

Title	Management of liver tumors in childhood
Authors	Von Schweinitz D
Institution	Paediatric surgery clinic, University of Munich, Germany
Reference	Semin Pediatr Surg 2006; 15(1):17–24
Problem	Review of management of liver tumours in children.
Intervention	Review.
Outcome/ effect	Education.
Historical significance/ comments	An excellent review of the current state of the art from a developed country.

Key Summary Points

1. The prevalence of liver tumours related to infection with HIV and hepatitis B, the Kaposi sarcoma, and hepatocellular carcinoma is higher in African children than in the Western world, with poor prognosis.
2. The most common presentation is an enlarging abdominal mass, but practitioners should be wary of the other modes of presentation.
3. Carefully performed work-up with haematological investigation as well as good-quality imaging are the critical first steps in evaluation.
4. Many patients with advanced multicentric hepatocellular carcinoma as well as patients who have terminal AIDS and aggressive malignant vascular tumours are best treated by palliation.
5. Good results can be achieved by combining good-quality surgery with multimodal treatment for hepatoblastoma, and for sarcomas even in partially resource-deprived communities.
6. Prevention by promoting hepatitis vaccination programs and encouraging specific treatment and support for patients with HIV infection are critical.

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