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PEDIATRIC ONCOLOGIC IMAGING

Rare malignant liver tumors in children

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Abstract

Malignant hepatic tumors in children are rare, comprising 1.3% of all pediatric malignancies. Following hepatoblastoma, hepatocellular carcinoma is the second most common. Other malignant hepatic tumors seen in childhood include those of mesenchymal origin including undifferentiated embryonal sarcoma, angiosarcoma, rhabdomyosarcoma and epithelioid hemangioendothelioma, as well as biliary tumors such as cholangiocarcinoma. Diagnosis can be challenging because of their rarity, and the recognition of distinctive imaging features for certain tumors such as epithelioid hemangioendothelioma and biliary rhabdomyosarcoma can focus the differential diagnosis and expedite the diagnostic process. A complete MRI examination with hepatocyte-specific contrast media and diffusion-weighted imaging helps to focus the differential diagnosis, and, although findings are often nonspecific, in some cases typical features on MRI can be helpful in diagnosis. Histopathological analysis is usually required for definitive diagnosis. Hepatic tumors tend to be aggressive, and full staging is imperative to establish disease extent. Significant proportions are not amenable to upfront surgical resection and often require a multimodality approach including neoadjuvant chemotherapy within a multidisciplinary setting. Facilitating complete surgical resection is usually required for better survival. In this review, we emphasize pathology and imaging features for rare liver tumors that are useful in reaching a prompt diagnosis. We also discuss general clinical findings, prognosis and management of these tumors.

Keywords Children · Embryonal sarcoma · Hepatocellular carcinoma · Liver · Magnetic resonance imaging · Malignancy

Introduction

Malignant liver tumors are rare in children, accounting for just 0.5–1.5% of all childhood cancers [1]. Hepatoblastoma is the commonest malignant hepatic tumor in pediatrics and constitutes more than two-thirds of all hepatic neoplasms, especially in children ages 6 months to 3 years, followed by hepatocellular carcinoma (HCC), which comprises 20% of hepatic tumors [2, 3]. The remaining malignant liver tumors include metastases, malignant tumors of mesenchymal origin (~10%) such as undifferentiated embryonal sarcoma, angiosarcoma, rhabdomyosarcoma, and epithelioid hemangioendothelioma, and biliary tumors including cholangiocarcinoma [2, 4]. In 2011 the International Pediatric Liver Tumors Consensus Classification was developed by the International Pathology Symposium sponsored by Children's Oncology Group (COG) in Los Angeles [2]. This consensus classification (Table 1) has been instrumental in standardizing pediatric liver tumors and developing clinically relevant diagnostic criteria that are useful for international collaborative projects and trials.

Liver tumors in children typically present with an enlarged abdomen, palpable mass and elevated alpha-fetoprotein (AFP). Very elevated AFP levels suggest hepatoblastoma; levels can also be mildly raised in HCC, but raised AFP is less likely in benign liver tumors [4]. Patient age is also an important consideration in the differential diagnosis of hepatic tumors. Ultrasound serves as an initial screening modality for detection of the lesion and exclusion of other abnormalities. Complete characterization of the mass requires cross-sectional imaging such as CT or MRI. Both of these modalities have

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Table 1 Pediatric liver tumors consensus classification [2]

Epithelial tumors	
Hepatocellular	*Benign:* hepatocellular adenoma, focal nodular hyperplasia (FNH), regenerative nodules and dysplastic nodules *Malignant:* hepatoblastoma (various types), hepatocellular carcinoma (classic HCC and fibrolamellar HCC), hepatocellular malignant neoplasm not otherwise specified (NOS)
Biliary	*Benign:* bile duct adenoma, biliary hamartoma *Malignant:* cholangiocarcinoma, combined HCC-cholangiocarcinoma
Mesenchymal tumors	*Benign:* hemangioma, mesenchymal hamartoma *Malignant:* Embryonal sarcoma, rhabdomyosarcoma, malignant vascular tumors (epithelioid hemangioendothelioma, angiosarcoma)
Other rare malignancies	Malignant rhabdoid tumor, germ cell tumor
Metastases (and secondary)	From solid tumors: neuroblastoma, Wilms Acute myeloid leukemia

their advantages and disadvantages but MRI is preferable for liver tumor evaluation because it has superior soft-tissue contrast, functional assessment provided by diffusion-weighted imaging and hepatocyte-specific contrast agents, which increase specificity and detection. In most cases liver lesions are well characterized on imaging and provisional diagnosis is possible [5–7]; however biopsy is required for confirmation and, more important, to determine the type and grade of tumor and for genomic studies. Children usually require chest CT imaging because metastases from liver tumors are not uncommon at diagnosis and are most often seen in the lungs.

Advances in treatments and surgical techniques have improved the prognosis of hepatoblastoma significantly. There is now a 5-year event-free survival of greater than 80% for localized and 30–60% for advanced disease [3, 8]. However, the prognosis of other pediatric hepatic tumors remains poor, with a <30% 5-year event-free survival for hepatocellular carcinoma [3, 9–11]. Because hepatoblastoma has been well described in the literature, this review focuses on other rare malignant liver tumors in children. We describe general clinical features and discuss pertinent histopathology and radiologic findings that help differentiate the tumor and anticipate prognosis and management of these tumors (Table 2).

Hepatocellular carcinoma (HCC)

HCC is a malignant tumor of hepatocyte cell differentiation with an annual age-adjusted incidence of 0.05 cases per 100,000 in 2009, and this has remained stable over the years [11]. It typically presents as a painless abdominal mass and is seen in older children 10–14 years of age with slight male predominance [10]. AFP level is elevated in approximately 70% of cases [4]. Unlike adult HCC, which is seen with preexisting chronic liver disease in 70–90% of cases, the majority (approximately 70%) of pediatric HCC in the Western world is seen in an otherwise normal liver [10]. In contrast, in some parts of the world where viral hepatitis is endemic, most pediatric HCC occurs with background chronic liver disease; in Taiwan 100% of pediatric HCCs are hepatitis-B seropositive [10]. In non-endemic countries, predisposing conditions are noted in approximately 30% of HCCs and include chronic liver disease secondary to biliary atresia, progressive familial intrahepatic cholestasis, glycogen storage disease, alpha-1-antitrypsin deficiency, tyrosinemia and chronic viral hepatitis infection, among others [12]. Rarely, causative association with both classic and attenuated familial adenomatous polyposis syndrome has been reported [13].

Pathology

Two pathologic types of HCC seen in children include classic type and fibrolamellar HCC. A transitional histological entity between hepatoblastoma and HCC is seen rarely, in older children and adolescents, and has been termed "hepatocellular malignant neoplasm, not otherwise specified" in the consensus classification [2]. The gross and microscopic features of classic HCC in children and adults are similar. However some molecular differences have been reported, including mutation of the *c-MET* gene (the gene that encodes the hepatocyte growth factor receptor), lower cyclin D1 expression and higher frequency of loss of heterogeneity of chromosomal arm 13q in childhood HCC, as compared to adult HCC [10]. HCC can be solitary, multinodular and diffusely infiltrative. The morphological appearance of cells in HCC varies, from well-differentiated tumor cells closely resembling normal hepatocytes with minimal to mild nuclear atypia and low mitotic activity to poorly differentiated cells dispersed in a macrotrabecular growth pattern, containing hyperchromatic, pleomorphic markedly atypical nuclei with high mitotic activity [2, 4]. There are different grading systems, including the Edmondson and Steiner and the World Health Organization (WHO) 2010 schemes, which are based on nuclear features and morphologic differentiation, respectively [12, 14]. The College of American Pathologists advocates the use of American Joint Committee on Cancer (AJCC) cancer grading

Table 2 Key differentiating clinical, pathology and imaging features for rare liver tumors

Liver tumor	Epidemiology	Clinical	Pathology	Imaging		
				Ultrasound	CT	MRI
Hepatocellular carcinoma (HCC)	10–14 yrs M:F, 3:1	Abdo pain/ distension; systemic symptoms	Malignant hepatocytes of varying differentiation; bile pigment IHC: + HepPar1, EpCAM, Glypican 3	Hypoechoic nodules/ masses	Heterogeneous hypoattenuation on unenhanced CT	T1 hypointense; T2 hyperintense; heterogeneous arterial enhancement and washout in portal venous and delayed venous phases; hypointense fibrous capsule
Fibrolamellar HCC	Adolescents M:F, 1:1.3	Indolent, nonspecific, abdo pain/ distension/ mass; normal underlying liver; >50% metastasize, usually nodal disease; normal AFP; gynecomastia in some cases	Large polygonal tumor cells with eosinophilic cytoplasm, arranged in cords, separated by lamellar fibrosis; IHC: + CD68, CK7; DNAJB1-PRKACA fusion transcript	Nonspecific, well-defined mass with variable echogenicity, hyperechoic central scar	Large heterogeneous well-defined lobulated lesion, ±calcifications	T1 hypointense and T2 hyperintense; low attenuation of large central scar on T2
Hepatocellular malignant neoplasm, not otherwise specified	Older children/ adolescents	Often advanced at presentation; elevated AFP	Transitional histology with equivocal/overlapping HCC and hepatoblastoma morphology; mixed immunophenotype; associated with telomerase (TERT) gene expression		Large multifocal vascular invasion common	
Undifferentiated embryonal sarcoma	6–10 yrs M=F	Abdo mass, pain, nausea, vomiting, anorexia; usually normal AFP	Sarcomatous cells are pleomorphic, stellate, spindle-shaped, ±eosinophilic globules; high mitotic activity; myxoid background IHC: variable CD56, vimentin, alpha1 antitrypsin	Solid heterogeneous hyperechoic solitary mass, usually right lobe (myxoid elements, cystic spaces, blood)	Hypoattenuated mass with a cystic appearance, presence of solid nodules, septa, ±serpiginous vessels; ±fluid-fluid levels	Solid–cystic with delayed enhancement of peripheral solid components and septa; intratumoral bleeding+
Biliary rhabdomyosarcoma	<5 yrs	Jaundice, abdo distension and pain, vomiting, fever	Embryonal with botryoid and spindle cell subtypes; pleomorphic rhabdomyoblasts with eosinophilic cytoplasm IHC: myogenin (nuclear uptake), ±desmin	Biliary dilation; hypo- or iso-echoic intraductal soft-tissue mass with vascularity	Hypo- and heterogeneous attenuated intraductal mass ±biliary dilatation	T1 hypointense; T2 hyperintense. Could show frond-like growth and cystic areas giving similar appearance to botryoid rhabdomyosarcoma in bladder and vagina
Cholangiocarcinoma	15–18 yrs M:F, 1.5:1	Often underlying disease such as primary sclerosing cholangitis, immune deficiencies + congenital hepatobiliary disorders	Well to poorly differentiated adenocarcinoma with glands dispersed in dense fibrous stroma, resembles any extrahepatic adenocarcinoma IHC: + CK7, CK19	Dilated intra- and extra-hepatic ducts; hypo- to isoechoic soft-tissue mass; intraluminal filling defects	Hypodense ill-defined lesion along porta on unenhanced CT; may be mistaken as periportal fibrosis	T1 hypointense; T2 hyperintense; very minimal enhancement of delayed images; diffusion restriction
Epithelioid hemangioendotheli-oma	10–18 yrs M:F, 2:3	Abdo pain/ distension, weight loss; often multifocal, multiorgan disease	Epithelioid and dendritic cells forming lumina, sometimes containing RBCs, in a fibromyxoid stroma IHC: + factor VIII Ag, CD31, CD34, ERG; WWTR1-CAMTA1 and YAP1-TFE3 fusion transcripts	Hypoechoic multiple nodules and coalescing masses	Hypodense target nodules; peripheral contrast enhancement with central hypoenhancement; ±capsular retraction; ±calcification	T1 hypointense; heterogeneous hyperintensity on T2; characteristic target-like enhancement, centripetal enhancement and capsular retraction
Angiosarcoma	3–5 yrs M:F, 1:2	Abdo pain and distension; tumor can bleed and rupture; metastasizes to lung	Large solitary mass, multiple nodules or diffusely infiltrating lesion; sinusoidal and cavernous vascular channels; hypercellular whorls of sarcomatous spindle cells and eosinophilic globules	Solitary or multifocal, heterogeneous hypoechoic to isoechoic lesions	Peripheral nodular and irregular hypervascularity with arterial enhancement; ± necrosis and hemorrhage	Well-defined round multifocal lesions, T1 hypointense, T2 hyperintense; bizarre progressive enhancement rather than centripetal filling of hemangioma

Abdo abdomen, *AFP* alpha-fetoprotein, *F* female, *IHC* immunohistochemistry, *M* male, *RBC* red blood cells, *Yrs* years

and staging manual, composed of a four-tier grading scheme based on morphologic differentiation as described in the WHO 2010 scheme [15]. Regardless of the grading system applied, vascular invasion and poor differentiation are independent risk factors for an adverse outcome.

Various histological patterns have been described including trabecular, acinar, pseudoglandular, clear cell, steatotic, compact and scirrhous, with trabecular pattern being the most common. Morphologic appearance, paucity/disruption of reticulin framework, presence of endothelialized sinusoids (CD34-positive, which is negative in normal sinusoidal endothelium) and bile production by tumor cells help to differentiate HCC from benign hepatocellular adenomas, hepatoblastoma and other primary or metastatic tumors. In difficult cases, use of immunohistochemical methods can be helpful in differentiating other tumors from HCC, but not always from hepatoblastoma [16]. Metastatic involvement might be found within the portal veins, hepatic veins and vena cava. Expression of epithelial cell adhesion molecule (EpCAM) has been reported to be more frequent in children than adults with HCC and p53 is more common in hepatic HCC than hepatoblastoma [12, 17]. Immunoreactivity for HepPar1, glypican 3, glutamine synthetase and alpha-fetoprotein is variable in HCC. Therefore immunohistochemical staining pattern should be carefully interpreted in association with histological features in cases of HCC.

Imaging

Pediatric HCCs are usually large lobulated heterogeneous masses, compared to smaller nodules detected in adults because of screening and earlier detection [4]. HCCs are usually hypoechoic to surrounding liver parenchyma on ultrasound. They are heterogeneously hypoattenuating on unenhanced CT because of hemorrhage, fat, necrosis and calcification. HCCs are slightly hypointense on T1-weighted MR images and usually hyperintense on T2-weighted MR images. On dynamic imaging with CT or MRI, HCCs show prompt enhancement in the arterial phase and washout in portal venous or equilibrium phases [7]. Avid arterial enhancement in HCC is usually heterogeneous, especially in larger lesions, contrary to homogeneous arterial enhancement in focal nodular hyperplasia and adenomas. The washout could also be heterogeneous, with avid enhancing areas in the arterial phase showing prompt washout (Fig. 1). A fibrous capsule that is present in some HCC cases is hypointense on T1- and T2-weighted images and shows enhancement in delayed phases. Most HCCs are hypointense on hepatobiliary-phase imaging performed with injection of hepatocyte-specific contrast media. HCCs show diffusion restriction. Both diffusion-weighted imaging and hepatocyte-specific contrast media increase the lesion detection and confidence in characterization of lesions. Intravascular spread, multifocal lesions and metastases tend to be more frequently associated with HCC as compared to hepatoblastoma.

Staging

Imaging plays an essential role in management and is the mainstay for staging. Various staging systems have been proposed. The risk stratification and disease extent of HCC are determined using the Pretreatment Extent of Disease (PRETEXT) system, originally proposed by the International Society of Pediatric Oncology Liver group (SIOPEL) for hepatoblastoma in 1990 [18]. Response Evaluation Criteria in Solid Tumors (RECIST) is used for HCC staging and response assessment in adult HCC and relies on single-dimension measurement and follows target lesions. However, anatomical size might not be a reliable measure in which response is assessed and hence the amount of viable tumor defined as showing uptake of contrast agent in arterial-phase CT or MRI is incorporated within the criteria, now termed modified RECIST (mRECIST) [19]. RECIST had been used for research studies but currently PRETEXT is used for both clinical and research purposes at our institution.

Management and prognosis

Long-term survival in pediatric HCC remains dismal. Pediatric HCC has relatively higher response to chemotherapy (up to 50%) as compared to adult HCC (30%) [3, 9]. Conventional chemotherapy such as cisplatin and doxorubicin, along with sorafenib, a multikinase inhibitor, might add some survival benefit [20]. In general, though, sensitivity of HCC to chemotherapy is poor and surgical resection is essential for cure. Survival rates of approximately 50% are reported in resectable pediatric HCC [9]; however only 30% of the tumors are resectable at presentation. The 5-year overall survival remains <20% in children in whom surgical resection is not possible [21]. Adults with advanced HCC limited to the liver are offered liver transplantation using Milan criteria. However, encouraging results have been shown with advanced disease exceeding Milan criteria in children, hence some authors recommend offering liver transplantation to children even with vascular invasion [3, 22]. Alternative interventional treatment options including radiofrequency ablation, transarterial catheter chemoembolization (TACE) and transarterial radioembolization using yttrium-90 (^{90}Y) have proved to be effective in local disease control for advanced disease and to control tumor burden as a bridge to resection or liver transplantation [23]. TACE is standard of care for treatment of HCC in adults. Data in children are scarce but reveal similar favorable response in children and adolescents with advanced disease [23, 24].

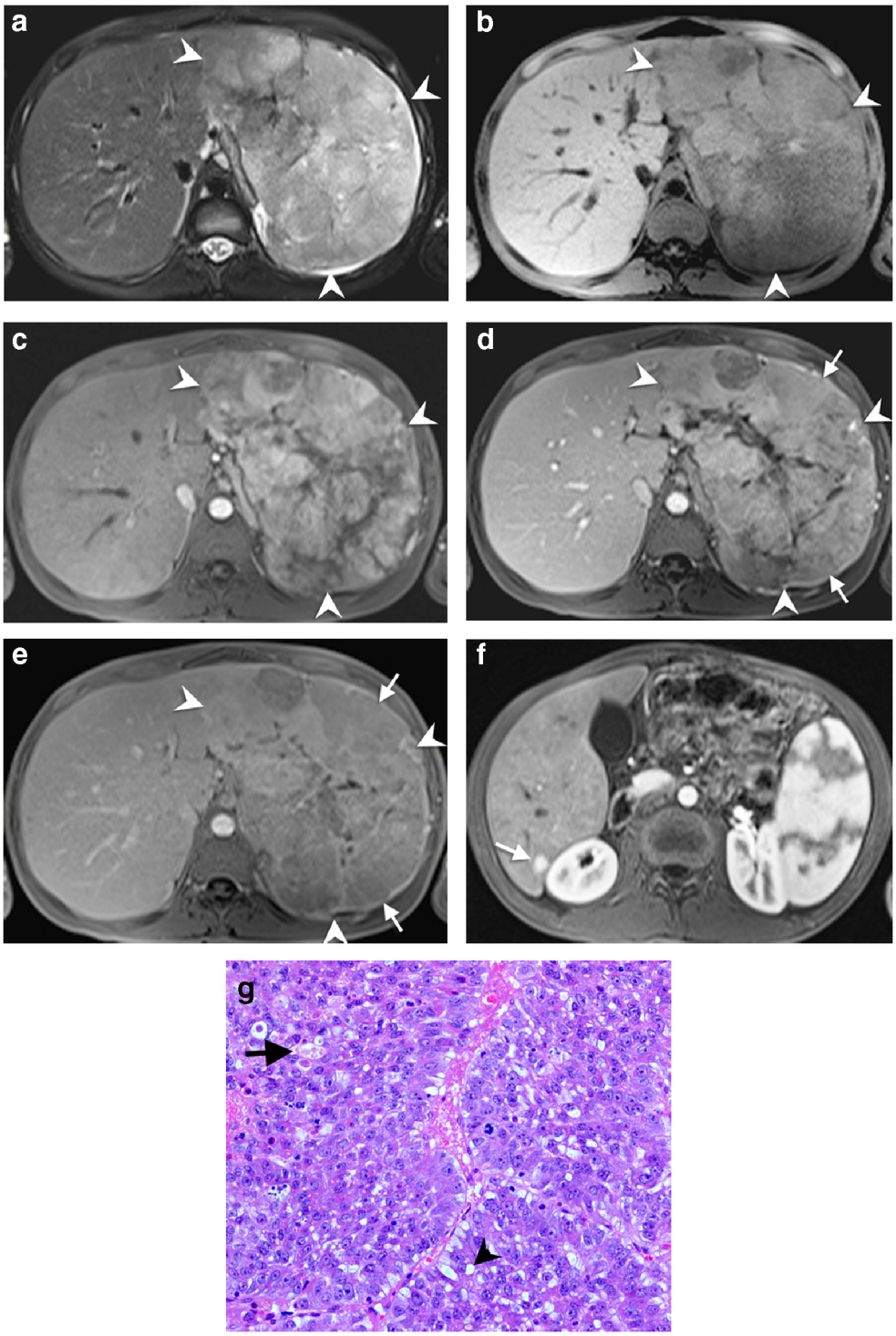

Fig. 1 Hepatocellular carcinoma. **a**–**f** A 17-year-old boy. The large left liver lobe mass (*arrowheads*) is heterogeneously hyperintense on axial T2-weighted fast spin-echo (**a**) and heterogeneously iso- to hypointense on pre-contrast axial T1-weighted volumetric interpolated breath-hold examination (VIBE) image (**b**). The mass (*arrowheads*) shows avid heterogeneous enhancement on arterial-phase axial image (**c**) and heterogeneous washout in some areas on portal-venous-phase (**d**) and equilibrium-phase axial T1-weighted VIBE (**e**) images. **f** An arterial-phase axial T1-weighted VIBE image at a lower level shows another small lesion (*arrow*) in segment 6, suggesting multifocality. **g** Microscopic image of poorly differentiated hepatocellular carcinoma in a different boy, 9 years old, demonstrates trabeculae of pleomorphic tall polygonal cells, up to 20 cells in thickness. Tumor cells are large, with abundant amphophilic granular cytoplasm. Focal bile pigment is also noted (*arrow*). Some cells contain large clear lipid vacuoles (*arrowhead*). Numerous atypical mitoses are noted (hematoxylin and eosin, magnification ×400)

Fibrolamellar hepatocellular carcinoma

Fibrolamellar variant of HCC (fibrolamellar HCC) is typically seen in adolescents and young adults without gender predilection [4]. It accounts for almost one-third of HCC seen in those younger than 20 years and occurs without cirrhosis or underlying liver disease [2]. Serum AFP is not elevated in fibrolamellar HCC but some cases show gynecomastia. Children often present with a palpable abdominal mass associated with pain, malaise, nausea and weight loss. Nodal involvement or distant metastases, usually to the lungs, are detected in approximately 50% of patients at diagnosis [25].

Pathology

Pathologically, fibrolamellar HCC appears as a well-circumscribed, firm (in comparison to conventional HCCs, which are soft), lobulated and extensively fibrous lesion with central fibrous scar in almost 70% of cases [4, 26]. Calcification is seen in almost half of cases and is limited to the central scar. Microscopically, fibrolamellar HCC shows clusters and sheets of large polygonal cells with abundant coarsely granular eosinophilic cytoplasm and large nuclei with prominent nucleoli, separated by hyalinized collagen bundles of varied thickness arranged in lamellar pattern [4]. Bile and mucin production might be present. Both Mallory hyaline and periodic acid Schiff (PAS)-positive cytoplasmic hyaline inclusions can be seen. Immunohistochemistry shows expression of cytokeratin 7 (diffuse membranous staining pattern) and CD68, with high specificity for anterior gradient-2 (AGR-2) [27]. Recent molecular advances have discovered a novel kinase fusion between DnaJ heat shock protein family member B1 (*DNAJB1*) and protein kinase cAMP-activated catalytic subunit alpha (*DNAJB1-PRKACA*) generated by a chromosomal deletion that appears unique to fibrolamellar HCC, but its role in fibrolamellar HCC oncogenesis remains unclear [25, 28]. A *PRKACA FISH* break-apart probe has been designed to detect this gene rearrangement [28].

Imaging

Fibrolamellar HCC is typically a solitary well-defined mass that is heterogeneously iso- or hyperechoic with hyperechoic central scar on ultrasound images. On unenhanced CT images, it is seen as a well-defined lobulated hypodense mass with central scar showing calcification in some cases. Fibrolamellar HCC is slightly hypointense on T1-weighted MR images and slightly hyperintense on T2-weighted MR images. On dynamic imaging with CT or MRI, fibrolamellar HCC shows avid enhancement on arterial-phase images, which could be heterogeneous [26]. It shows variable attenuation on portal-venous- or equilibrium-phase images including washout in some, but most tend to be isoattenuating on equilibrium phase [26]. Fibrolamellar HCC is typically hypointense to surrounding hepatic parenchyma on hepatobiliary-phase images with injection of hepatocyte-specific contrast media [29]. The central scar of fibrolamellar HCC is typically hypointense on all sequences including T2-weighted and post-contrast T1-weighted MR images (Fig. 2). This helps to differentiate it from focal nodular hyperplasia (FNH), in which the central scar is hyperintense on T2-weighted images and shows enhancement on delayed images.

Management and prognosis

The primary treatment of fibrolamellar HCC is surgical resection, and the most important prognostic factor is surgical resectability, along with lymph node status. Children with fibrolamellar HCC might also be candidates for liver transplantation and local interventions such as TACE [30]. Chemotherapy and radiation provide minimal benefit. The recurrence rate remains extremely high, estimated at >50% within 3 years [25]. Loco-regional lymphadenectomy is deemed important for better clinical outcomes and to reduce recurrence rates [31, 32]. The pediatric literature, including the SIOPEL [33] and COG [34] experiences, reports similar unfavorable event-free survival and overall survival rates for fibrolamellar HCC and classic HCC. A reduced 5-year overall survival after transplant was seen with fibrolamellar HCC compared with classic HCC (48% versus 68%), which might reflect more advanced disease for fibrolamellar HCC preceding transplant [35].

Hepatocellular malignant neoplasm, not otherwise specified (NOS)

Some malignant hepatocellular tumors demonstrate histological features of both hepatoblastoma and HCC in the same tumor, thereby precluding a specific classification. These tumors were previously called “transitional cell liver tumors” but the International Pediatric Liver Tumors Consensus Classification (2014) has placed them in the provisional category of “hepatocellular malignant neoplasm, NOS” [2]. These tumors are aggressive in nature and are associated with very high serum alpha-fetoprotein levels. They have overlapping morphological features of hepatoblastoma and focal HCC-like histology, accompanied by mixed immunophenotype. It has been proposed that the TERT promoter mutation might be involved with this entity [36]. On imaging, these tumors tend to be very large and multifocal at presentation (usually PRETEXT III/IV) with aggressive features such as vascular invasion [36]. Response is sometimes achievable with hepatoblastoma-type chemotherapy, including cisplatin, doxorubicin and complete resection.

Undifferentiated embryonal sarcoma

Undifferentiated embryonal sarcoma is the most common sarcoma in the pediatric liver, representing 5–15% of all liver tumors [37], and typically presents in children ages 6–10 years [2]. Children present with abdominal pain and systemic symptoms including nausea, vomiting, anorexia and weight loss. It is an aggressive tumor with often normal AFP level. Undifferentiated embryonal sarcoma metastasizes in up to 15% of children, usually to lungs, pleura and peritoneum [38].

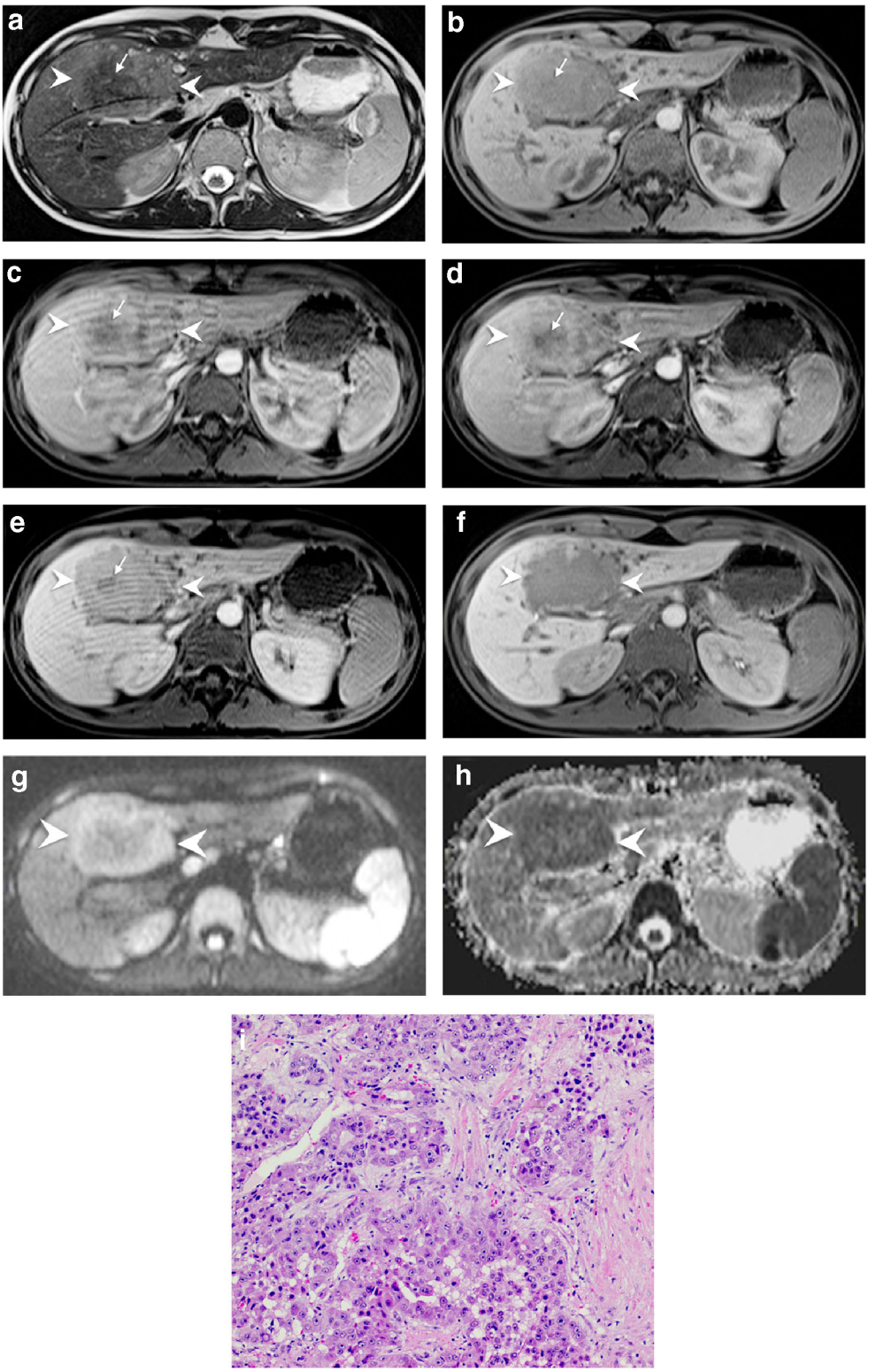

Fig. 2 Fibrolamellar hepatocellular carcinoma (HCC). **a–h** A 13-year-old girl. The lesion (*arrowheads*) is slightly hyperintense with hypointense central scar (*arrow*) on axial T2-weighted fast spin-echo (**a**) and hypointense on pre-contrast axial T1-weighted volumetric interpolated breath-hold examination (VIBE; **b**) images. Mass shows heterogeneous prompt enhancement on arterial-phase (**c**) and becomes isointense on portal-venous-phase (**d**) images. **e** The lesion shows complete washout on equilibrium-phase T1-weighted VIBE image. **f** The lesion is hypointense on 20-min hepatobiliary-phase axial T1-weighted VIBE image. **g, h** It shows diffusion restriction on axial diffusion-weighted (b value 800) image (**g**) and apparent diffusion coefficient (ADC) map (**h**). **i** Microscopic image of fibrolamellar HCC in a different child, a 16-year-old boy, demonstrates tumor arranged in nests, ribbons and trabeculae, and occasional pseudo-gland formation. The tumor cells are surrounded by a prominent fibrous stroma, which in places has a lamellar appearance (hematoxylin and eosin, magnification ×200)

Pathology

Undifferentiated embryonal sarcomas are large, predominantly solid tumors of mesenchymal origin, typically located in the right lobe [4]. On microscopy, the tumor is variably cellular and consists of stellate, oval or spindle anaplastic cells with ill-defined borders arranged compactly or loosely in an abundant myxoid stroma [4]. Sometimes atypical tumor cells contain prominent eosinophilic cytoplasm and PAS+

(periodic acid-Schiff positive) diastase-resistant hyaline globules. Negative staining for myogenin and a dot-like staining in the cytoplasm with CD56 reactivity help to distinguish undifferentiated embryonal sarcoma from other hepatic sarcomas including rhabdomyosarcoma [2]. The association of undifferentiated embryonal sarcoma and cystic mesenchymal hamartoma has been debated in the literature. Some authors believe that undifferentiated embryonal sarcoma develops within a pre-existing mesenchymal hamartoma because both tumors have solid–cystic components, some common histological features and immunohistochemistry [39]. Undifferentiated embryonal sarcoma shares some translocation with mesenchymal hamartoma including 19q13.4 chromosomal rearrangement and t(11;19) translocation [2]. Some consider them a continuum of the same pathology [40].

Imaging

The characteristic feature of undifferentiated embryonal sarcoma is solid–cystic appearance. It appears predominantly solid on ultrasound but cystic on CT images because of the high water content of the myxoid stroma. This is considered a distinct feature of this tumor [4]. On ultrasound, most tumors are solid and hyperechoic, with some showing cystic spaces separated by septa [41]. The tumor is hypoattenuating on CT images, with some showing solid enhancing components and progressively enhancing septa on delayed images [41]. A peripheral rim enhancement is seen corresponding to pseudocapsule around the tumor, which is dark on T1- and T2-weighted MR images. Most of these tumors demonstrate fluid signal intensity on T1- and T2-weighted images. The internal details of the tumor are better appreciated on MR images including solid components, septa that show progressive enhancement on delayed images, and intratumoral hemorrhage with hypointensity on T2-W images and fluid-fluid levels (Fig. 3). The solid enhancing components in the tumor tend to show diffusion restriction. Spontaneous tumor rupture increases the risk of bleeding and peritoneal dissemination, better appreciated on MRI as compared to ultrasound and CT. Vascular invasion is usually not seen in undifferentiated embryonal sarcoma [41].

Management and prognosis

With a multimodal approach to treatment including chemotherapy, resection and transplantation, the prognosis of undifferentiated embryonal sarcoma has improved in recent years, with the 5-year overall survival of 80–100% [38, 42, 43]. Most undifferentiated embryonal sarcomas respond to neoadjuvant chemotherapy before surgical resection, which is the mainstay of cure. Interestingly, margin status has been found not to significantly affect survival [38]. Multi-agent chemotherapy regimens are variable and usually contain an alkylator and anthracycline backbone such as vincristine/actinomycin-D/cyclophosphamide, or vincristine/doxorubicin/cyclophosphamide and ifosfamide/etoposide.

Biliary rhabdomyosarcoma

Biliary rhabdomyosarcoma is an extremely rare tumor seen most often in the central biliary tree and porta hepatis of children younger than 5 years and remains the most common cause of neoplastic biliary obstruction in children [4, 44]. The most common clinical features are jaundice along with abdominal distension, abdominal pain and associated vomiting and fever.

Pathology

These are polypoid myxoid masses arising within the wall of the bile duct and extending into the lumen. They usually display a polypoid grape-like (botryoid) and small cystic growth pattern in the bile duct. The botryoid subtype has a better prognosis and macroscopically resembles sarcoma botryoids commonly seen in rhabdomyosarcoma of the vagina and bladder. It most commonly arises in extrahepatic ducts and grows into the intrahepatic ducts. Extension into the duodenum can occur. Histologically, the rhabdomyosarcoma in the biliary tract typically displays features of embryonal type with small poorly differentiated spindle cells containing hyperchromatic nuclei and eosinophilic cytoplasm with rare cross striations, surrounded by myxoid stroma. The tumor cells demonstrate a densely packed cambium layer beneath the bile duct epithelium and lose this density elsewhere. They often show skeletal muscle differentiation and are positive for myogenin on immunohistochemistry.

Imaging

On ultrasound, the tumor is typically seen as a hypo- or isoechoic intraductal soft-tissue mass with some vascularity filling the extrahepatic ducts. The polypoidal or grape-like tumor can be variable in density on CT images. It is typically hypointense on T1-weighted and hyperintense on T2-weighted MR

images. It shows variable enhancement but typically hyperenhancement in most cases. It can show small cystic areas on all imaging modalities (Fig. 4). There is dilatation of the intrahepatic ducts. Historically, the tumor was often misdiagnosed as choledochal cyst when tumors had central necrosis [44], but with advances in all imaging modalities and improvement in image resolution this is unlikely to happen in current practice.

Management and prognosis

The treatment and prognosis depend on extent of the tumor within the liver, and regional and distant metastases. The COG considers biliary tract rhabdomyosarcoma as a favorable site and localized disease is considered stage 1 (low risk). Metastases are seen in up to 30% of cases and extrahepatic disease has a poor prognosis [4]. The role of surgery has moved from aggressive surgery with internal and external

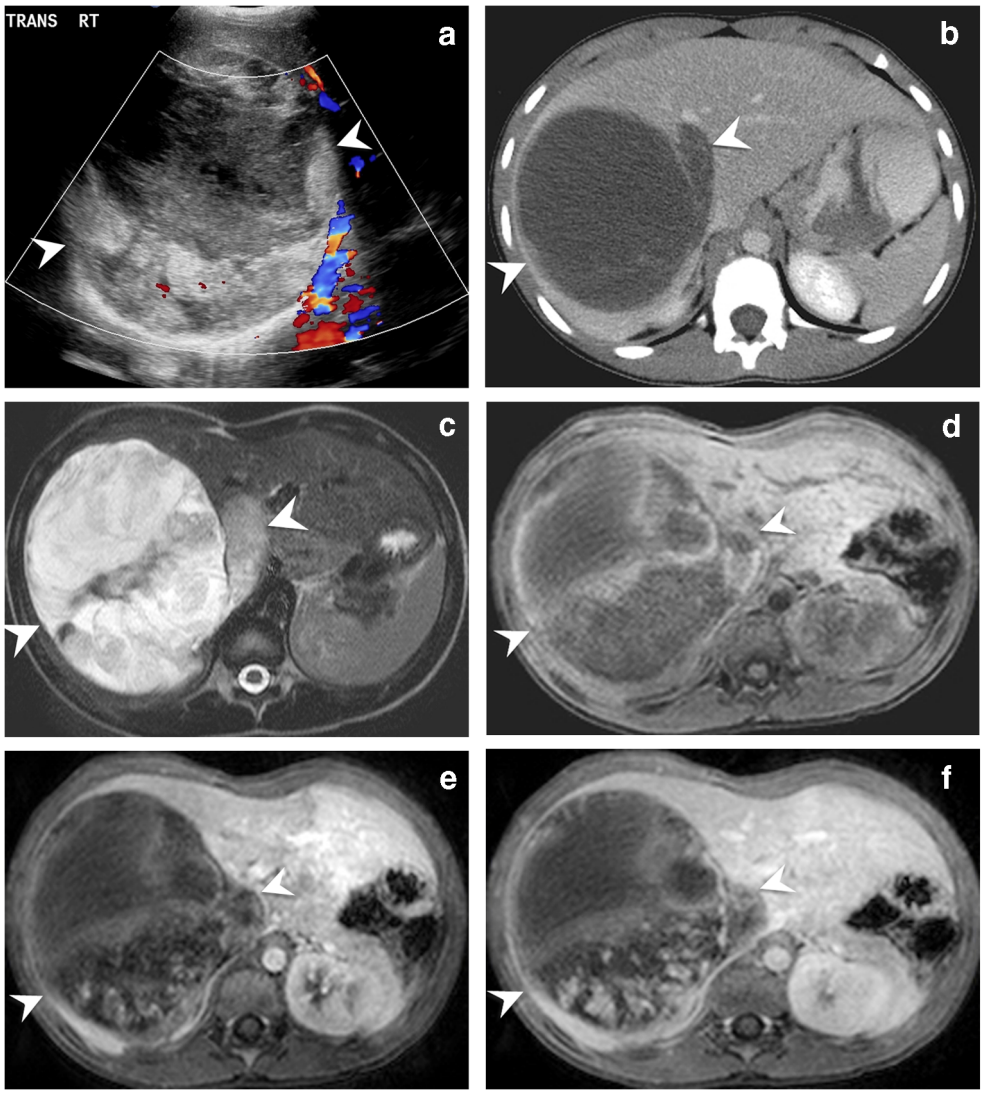

Fig. 3 Undifferentiated embryonal sarcoma of liver in a 9-year-old boy. **a** Transverse ultrasound image of the liver shows a well-circumscribed mixed echogenic solid mass (*arrowheads*). **b** The mass is apparently cystic because of its myxoid stroma on post-contrast axial CT image. **c, d** The lesion (*arrowheads*) is hyperintense with some hypointense content on T2-weighted fast spin-echo (**c**) and hypointense on pre-contrast T1-weighted VIBE (**d**) axial MR images. **e–g** Post-contrast axial T1-weighted volumetric interpolated breath-hold examination (VIBE) images in (**e**) arterial phase, (**f**) portal venous phase and (**g**) equilibrium phase at 5 min demonstrate progressive enhancement of some peripheral solid components in the posterior aspect of the tumor. **h** Gross specimen post-resection shows variegated pale tan tumor (*arrowheads*) with central necrosis, surrounded by a rim of unremarkable liver parenchyma. **i, j** Microscopic images (hematoxylin and eosin, magnification ×200) demonstrate a hypercellular region of atypical spindle cells (**i**) and a hypocellular region of myxoid stroma containing malignant stellate to spindle-shape cells with enlarged atypical nuclei and bizarre mitotic figure (*arrowhead* in **j**). **k** Image shows anaplastic cells with atypical enlarged nuclei containing cytoplasmic hyaline globules (hematoxylin and eosin stain, magnification ×400). **l** Image demonstrates these globules to be diastase-resistant on periodic acid Schiff stain (magnification ×400). Immunohistochemistry staining (not shown) was negative for actin and myogenin

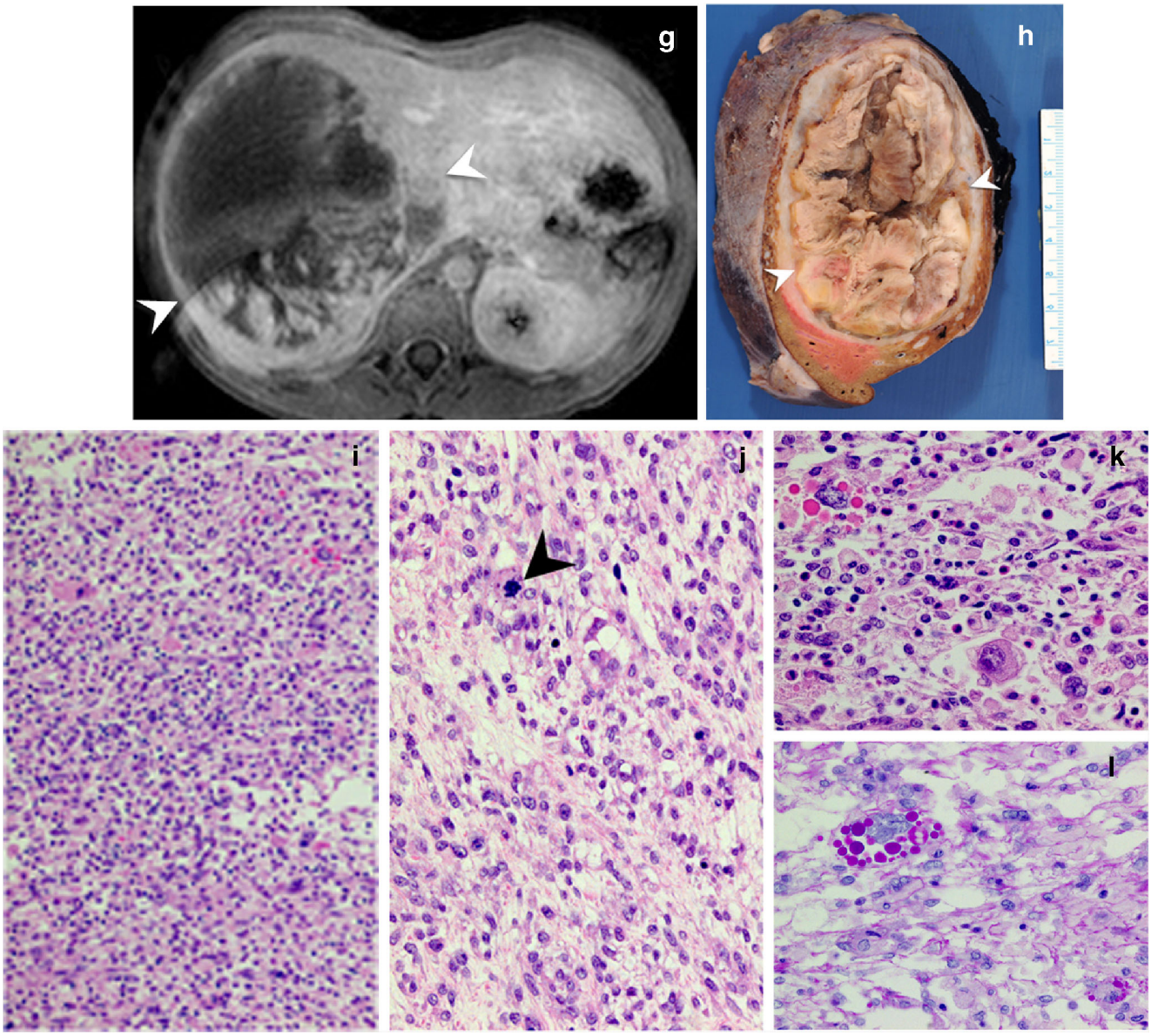

Fig. 3 (continued)

drainage to a primary role in diagnosis and staging. Neoadjuvant chemotherapy usually relieves the biliary obstruction with less morbidity, and multimodality therapy might include delayed resection and radiation. In recent years the prognosis has improved, with estimated 5-year survival up to 66% [45].

Cholangiocarcinoma

Cholangiocarcinoma, primarily a highly malignant tumor of adults, is extremely rare in children. It is typically seen in children associated with underlying primary sclerosing cholangitis, congenital malformation of the biliary tract, primary immune deficiency, human immunodeficiency virus (HIV) infection, inflammatory bowel disease, post radiation and secondary to a choledochal cyst [46]. The median age at diagnosis is usually 15–18 years and the tumor is slightly more common in boys [47].

Pathology

Most of these tumors arise from epithelial cells in intrahepatic ducts, mostly central ducts. The lesion could be mass-forming intrahepatic, periductal infiltrating intrahepatic or intraductal. Microscopically, cholangiocarcinoma can be well to poorly differentiated adenocarcinoma and might resemble any adenocarcinoma of extrahepatic origin. Therefore a definitive diagnosis depends primarily on the exclusion of other potential

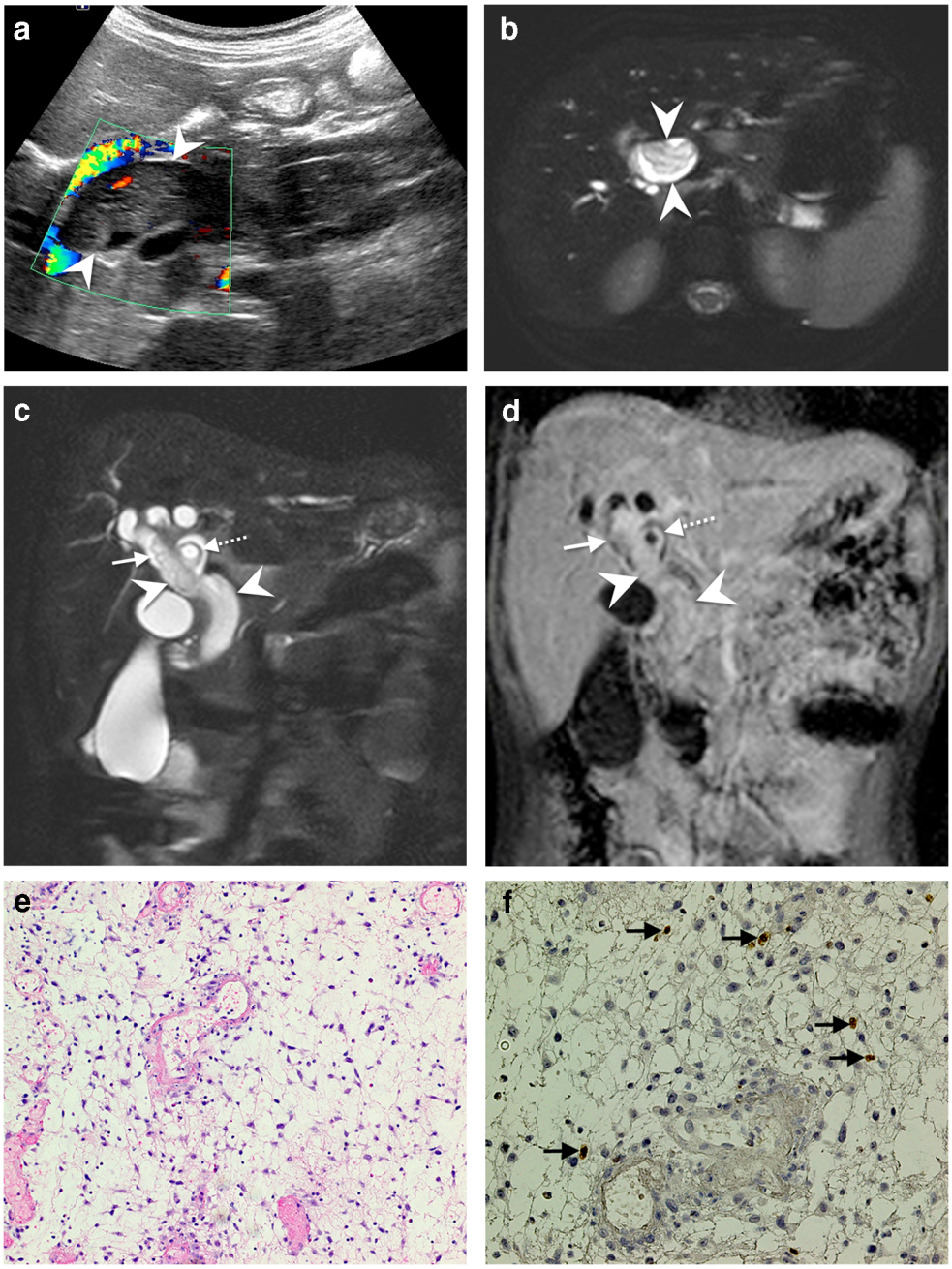

Fig. 4 Biliary rhabdomyosarcoma in a 5-year-old boy. **a** Transverse ultrasound image shows iso- to hypoechoic soft-tissue lesion with vascularity (*arrowheads*) filling the extrahepatic bile duct. **b–d** The lesion (*arrowheads*) is hyperintense on axial (**b**) and coronal (**c**) T2-weighted fast spin-echo MR images and enhances on coronal post-contrast T1-weighted high-resolution isotropic volume examination (THRIVE) image (**d**). The lesion shows frond-like growth (*solid arrow* in **c** and **d**) and a cystic area (*dashed arrow* in **c** and **d**). **e** Microscopic image shows variably cellular loose stroma with an edematous and mildly inflammatory background. The stromal cells are spindled and ovoid, containing scant cytoplasm, some with nuclear enlargement and cytoplasmic extensions (hematoxylin and eosin, magnification ×200). **f** Immunohistochemistry for myogenin shows nuclear positivity (*arrows*; magnification ×200)

primary sites. The tumor cells are most often arranged in tubules and glands, with variable differentiation, typically dispersed in a fibrous stroma. In cases of poorly differentiated cholangiocarcinoma, immunohistochemistry for CK7 and CK19 might help to distinguish it from other liver tumors such as HCC and hepatoblastoma. Rarely, cholangiocarcinoma is poorly differentiated and shows mixed cholangiocarcinoma–HCC histology. These cases account for <1% of hepatocellular tumors and usually have a worse prognosis (Fig. 5) [48].

Imaging

The lesions can be seen as hypo- to isoechoic soft tissue on ultrasound and are usually hypodense on unenhanced CT images. They are slightly hypointense on T1-weighted and slightly hyperintense on T2-weighted MR images [49]. The enhancement is variable on CT and MRI, with most showing only mild enhancement on delayed images (Fig. 5). The peripheral lesions show hepatic capsular retraction.

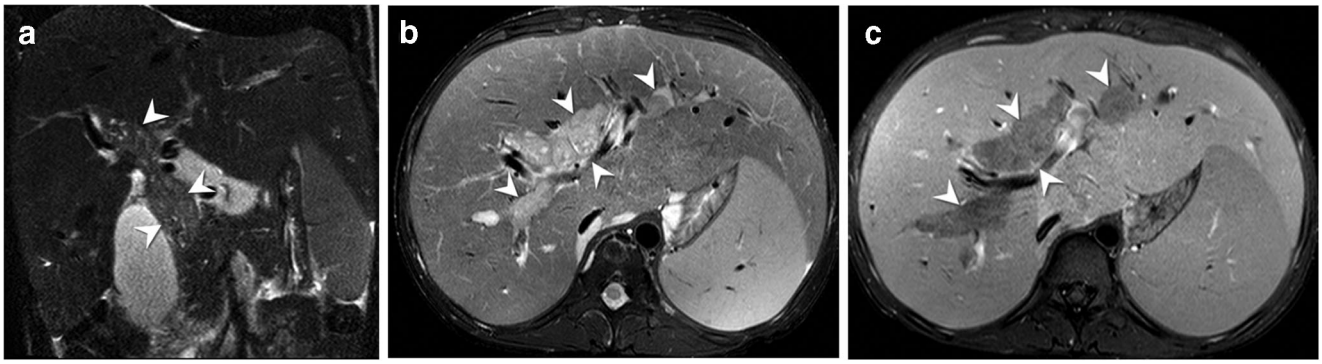

Fig. 5 Combined cholangiocarcinoma and hepatocellular carcinoma in a 16-year-old boy with longstanding primary sclerosing cholangitis. **a, b** Coronal (**a**) and axial (**b**) T2-weighted MR images demonstrate mildly hyperintense heterogeneous soft tissue at the porta and extending along central portal tracts (*arrowheads*). **c** The lesion (*arrowheads*) shows only minimal enhancement, significantly less as compared to surrounding parenchyma on post-contrast axial T1-weighted image

Management and prognosis

Survival and prognosis are dismal if the cholangiocarcinoma is not resectable, with a 3-year overall survival of approximately 35% [47].

Epithelioid hemangioendothelioma

Epithelioid hemangioendothelioma is a rare malignant vascular neoplasm [50]. Usually it is a multifocal multisystem tumor, most commonly involving liver, lung and bones [51]. In the liver it most frequently demonstrates diffuse nodularity, predominantly with peripheral nodular masses but occasionally solitary [4]. Clinical symptoms are nonspecific, with right upper quadrant pain, weight loss and hepatomegaly.

Pathology

Macroscopically, they are usually firm, ill-defined and sometimes focally confluent nodules with infiltrative borders. Microscopically, the tumor produces an abundant fibromyxoid stromal matrix surrounding small groups of tumor cells scattered throughout, infiltrating the sinusoids and disrupting the liver cell plates. The tumor cells tend to form small lumina within individual cells and between cells, mimicking glands of an adenocarcinoma and sometimes signet-ring cells. Mucin stains are negative. The tumor consists of a mixture of dendritic and epithelioid cells with vascular differentiation; the cells contain intracytoplasmic vacuoles and are arranged in strands, or short cords [4, 52]. The center of the tumor is avascular and hypocellular with predominant stroma while the periphery is hypercellular with growing neoplastic cells. A thin avascular zone can be seen in and around the tumor from vascular invasion. Immunohistochemistry shows expression of ERG, FLI1, factor VIII, CD34 and CD31 [52]. Reciprocal translocations have been found consistently with this vascular tumor, t(1;3)(p36;q25) corresponding to fusion gene *WWTR1-CAMTA1* and, less commonly, t(11;X) (q13;p11), an alternative gene fusion protein YAP1-TFE3, is detected [52].

Imaging

On imaging, multiple predominantly peripheral nodules are seen in the early stage that can coalesce to form larger masses in later stages. Individual nodules can appear hypoechoic on ultrasound and hypodense on CT but multiple nodules and coalescing masses can give a nonspecific heterogeneous appearance to liver parenchyma. The lesion commonly shows a target-like appearance on MRI and post-contrast CT images, reflecting the zonal architecture of cellularity seen on pathology. It is hypointense on T1-weighted images and shows a hyperintense center and relatively less hyperintense periphery on T2-weighted images (Fig. 6). On dynamic imaging with CT and MRI, the lesions show avid peripheral arterial-phase enhancement and centripetal filling on delayed phase, similar to infantile hemangioma [6, 53]. The lesions are hypointense to liver parenchyma on hepatobiliary phase after injection of hepatocyte-specific contrast media, with some showing a more hypointense well-circumscribed center, termed “core pattern” [53, 54]. The hypercellular thick peripheral rim that shows avid arterial-phase enhancement also shows diffusion restriction. Capsular retraction is a characteristic finding in 75% of cases [53]. Target appearance, centripetal enhancement and capsular retraction are characteristic imaging features of epithelioid hemangioendothelioma and help to differentiate it from metastases that are common imaging differentials.

Management and prognosis

The evolution of epithelioid hemangioendothelioma is highly variable and unpredictable, with unclear long-term prognosis [55]; 5-year patient overall survival was reported as 41% for any type of treatment or observation [56]. The natural history ranges from spontaneous regression and long-term stability to rapid decline and death, and as such, treatment also varies from surveillance to liver resection, chemotherapy, anti-angiogenic agents (sorafenib, pazopanib), monoclonal antibodies (bevacizumab), immunomodulatory agents (lenalidomide) and liver transplant [55, 56]. Chemotherapy has limited effect and surgical resection is the mainstay of treatment for localized disease. Liver transplant is considered for unresectable disease. Metastatic disease at diagnosis does not equate to a reduction in survival [57]. Pleural effusion and ascites, hemoptysis and involvement of more than three bones have been shown to reduce survival [55, 57]. Prognosis of epithelioid hemangioendothelioma in children is worse than in adults; however it is less aggressive than other primary liver tumors such as angiosarcoma [4].

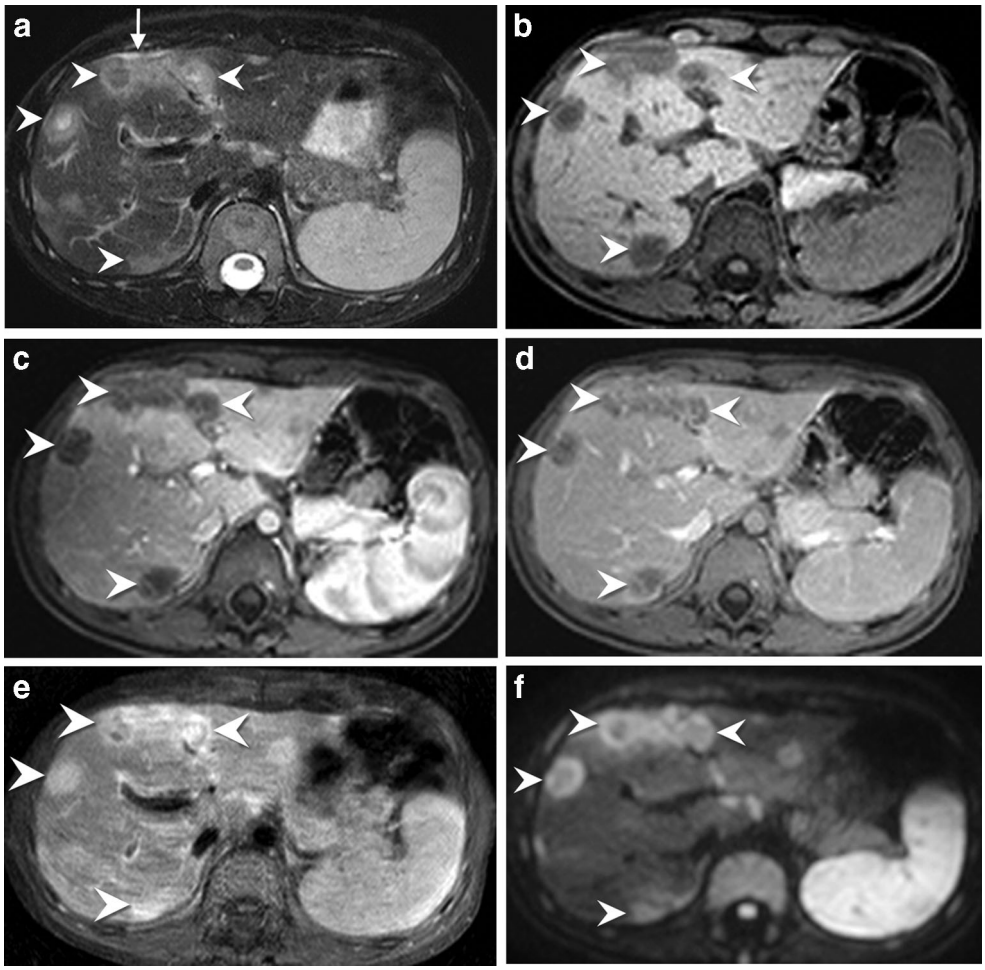

Fig. 6 Epithelioid hemangioendothelioma. **a–g** A 13-year-old girl. **a** Multiple lesions (*arrowheads*) are seen in the liver on axial T2-weighted fast spin-echo MR image; most of these lesions show central hyperintensity and peripheral less-hyperintense thick rim, giving a target appearance. There is capsular retraction associated with peripheral lesions (*arrow*). **b** The lesions are hypointense on axial pre-contrast T1-weighted high-resolution isotropic volume examination (THRIVE) MR image but maintain their target appearance. Axial post-contrast T1-weighted THRIVE MR images in (**c**) late arterial phase, (**d**) delayed venous phase and (**e**) equilibrium phase at 5 min demonstrate progressive centripetal enhancement of the lesions with complete filling. Axial diffusion-weighted (b value 600) MR image (**f**) and apparent diffusion coefficient map (**g**) demonstrate restriction of the thick peripheral rim of the target lesions. **h, i** Histology images in a 20-year-old woman. **h** Microscopy shows a mixture of dendritic and epithelioid tumor cells in a myxoid stroma, some cells with intracellular vascular lumina (hematoxylin and eosin, magnification ×200), resembling signet ring cells (*arrows,* magnification ×400). **i** Immunohistochemistry for CD31 diffusely staining the tumor cells (magnification ×200). (Histology images courtesy of Dr. Oyedele Adeyi, Toronto General Hospital, University of Toronto)

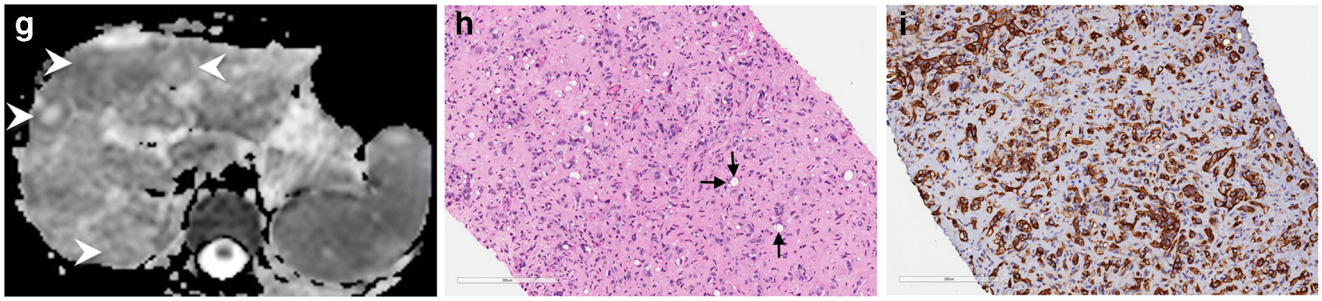

Fig. 6 (continued)

Angiosarcoma

Hepatic angiosarcoma is a rare but highly aggressive malignant vascular tumor that is commonly seen in elderly men but can also affect young children, typically girls, at a mean age of 3 years [4, 58]. Presenting symptoms include abdominal pain and distension from rapid liver enlargement. Complications such as consumptive coagulopathy, disseminated intravascular coagulation and congestive heart failure have been described with angiosarcoma, similar to infantile hepatic hemangioma or atypical hemangiomas [59, 60]. Malignant transformation from supposedly benign infantile hepatic hemangioma to hepatic angiosarcoma has been proposed in the literature [58, 59]. Occasionally, the tumor spontaneously ruptures and causes hemoperitoneum. Metastases, often to lung, are usually present at diagnosis.

Pathology

The tumor can present as a large solitary mass, multiple nodules or with a diffuse infiltrative pattern. On microscopy, the tumor consists of eosinophilic, spindle-shape or pleomorphic cells with high nuclear-to-cytoplasmic ratio, hyperchromatic nuclei and mitotic figures [4]. Malignant cells invade the preexisting vascular channels such as sinusoids and veins and create a variety of sinusoidal and cavernous vascular spaces. Hypercellular clusters or whorls of sarcomatous cells and spindle cells containing cytoplasmic eosinophilic globules, reported in pediatric angiosarcoma, distinguish it from typical histology in adult hepatic angiosarcoma [61]. There are shared morphological features among atypical hemangiomas, infantile hemangioma and hepatic angiosarcoma, thus clinical and biologic behavior plus imaging findings should be considered together with histology.

Imaging

Imaging features are variable, reflecting the pathological spectrum. Angiosarcoma is commonly confused with infantile hemangioma on imaging because it shows imaging features similar to those of infantile and other hemangiomas on CT and MRI, including peripheral nodular enhancement on arterial-phase and progressive centripetal filling. However, as compared to hemangiomas and epithelioid hemangioendothelioma, angiosarcoma shows marked heterogeneity on T2-weighted images and all phases of post-contrast images, and progressive filling could be bizarre instead of centripetal [54, 62] (Fig. 7). This could be related to the variety of vascular spaces formed and invaded by the tumor. Capsular retraction in the peripheral lesions and intratumoral hemorrhages are also common.

Management and prognosis

The prognosis is extremely poor; the majority of patients succumb to disease within 6–12 months. Treatment depends on the extent of disease; resection might be attempted, followed by chemotherapy with limited response. Varying treatments are described including embolization, radiation, liver transplant and targeted agents such as mTOR inhibitors, but they are rarely successful.

Conclusion

Malignant hepatic tumors other than hepatoblastoma are rare in children and in general are aggressive with poor prognosis. Some of them, such as epithelioid hemangioendothelioma and biliary rhabdomyosarcoma, have typical imaging features that can help in the diagnosis and expedite the workup, while others demonstrate largely nonspecific imaging features. A complete

MRI examination with hepatocyte-specific contrast media and diffusion-weighted imaging helps to better establish a definitive diagnosis. Rapid advancement within genomics has contributed to timely diagnosis, better understanding of tumor biology and knowledge of potential therapeutic targets. Complete staging to evaluate extent of the disease helps guide the management. Complete surgical resection remains an important

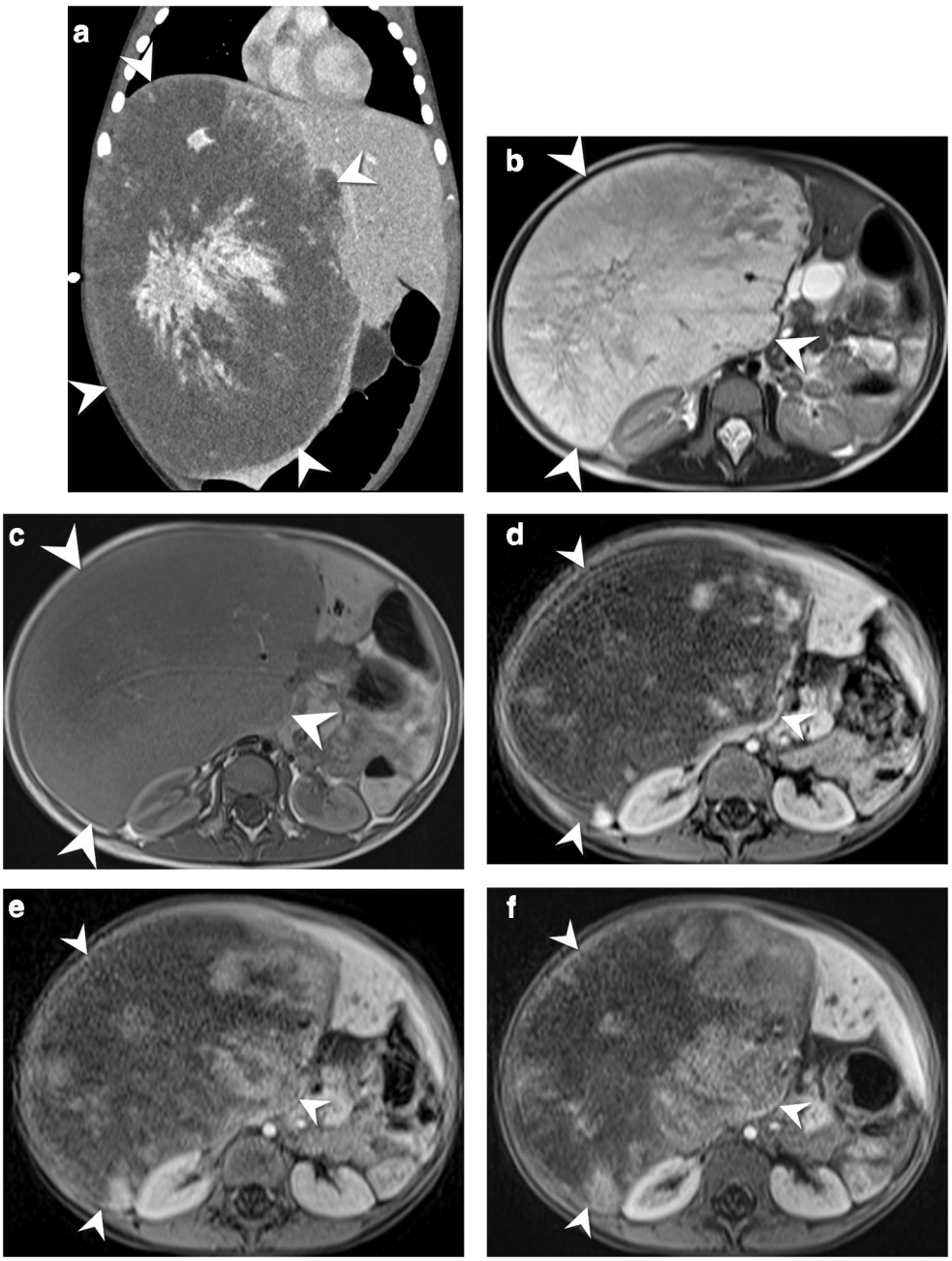

Fig. 7 Hepatic angiosarcoma in a 4-year-old girl. **a** Post-contrast coronal CT image demonstrates a well-circumscribed large mass (*arrowheads*) with an irregular central hyperdense area that could be combination of hemorrhage and enhancement. **b, c** The lesion (*arrowheads*) is heterogeneously hyperintense on T2-weighted fast spin-echo (**b**) and hypointense on pre-contrast T1-weighted (**c**) axial MR images. **d–g** Post-contrast T1-weighted volumetric interpolated breath-hold examination (VIBE) axial MR images in (**d**) arterial phase and at (**e**) 3 min, (**f**) 5 min and (**g**) 10 min post contrast administration demonstrate progressive enhancement of the lesion in the periphery. **h** Microscopy shows spindle-shape pleomorphic cells with high nuclear-to-cytoplasmic ratio and hyperchromatic nuclei invading the preexisting sinusoids (hematoxylin and eosin, magnification ×400). **i** Immunohistochemistry for CD34 shows diffuse positivity in tumor cells, showing endothelial origin (magnification ×200). **j** Immunohistochemistry for pan keratin shows entrapped hepatocytes (magnification ×200)

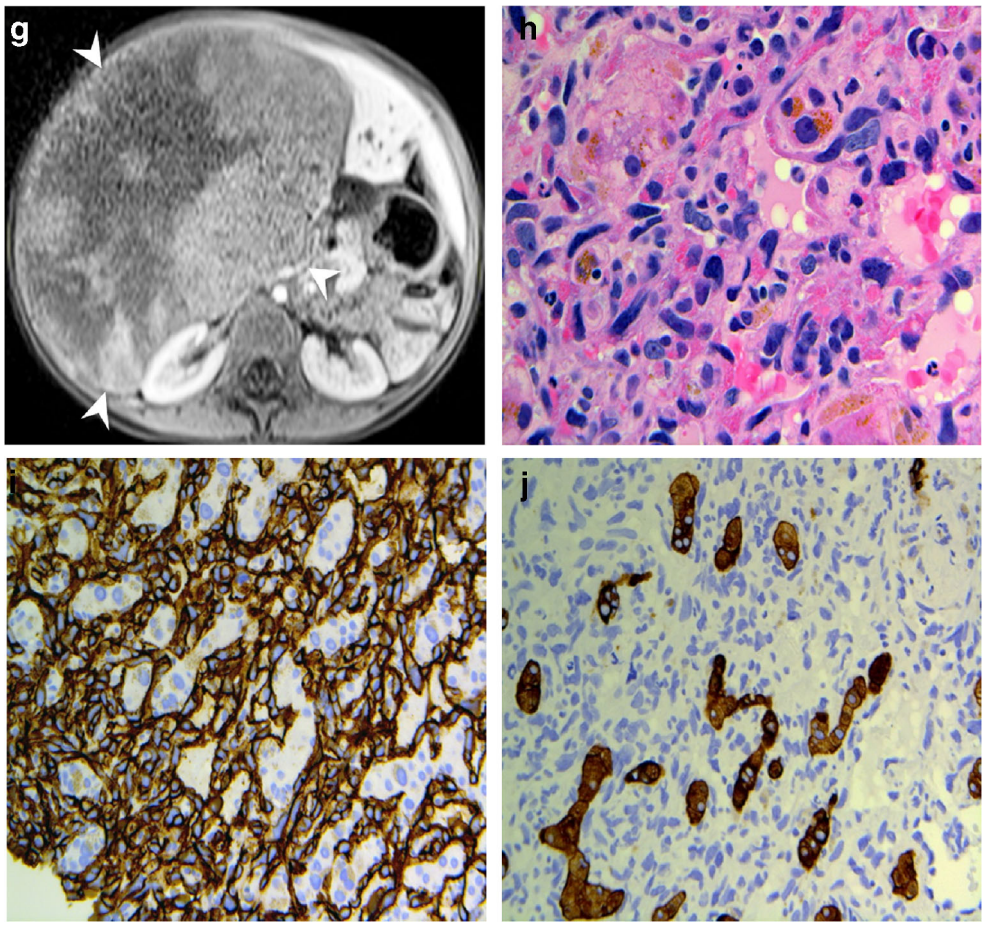

Fig. 7 (continued)

determining factor for long-term survival in rare liver tumors. The number of pediatric malignant liver tumors diagnosed outside of hepatoblastoma each year is extremely small and, as such, children should be included in future multicenter, multidisciplinary collaborative studies and trials to improve their clinical outcomes.

Compliance with ethical standards

Conflict of interest None

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