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HEPATIC CANCER (A SINGAL AND A MUFTI, SECTION EDITORS)

Primary Liver Tumors Other than Hepatocellular Carcinoma: Clinical and Molecular Pearls

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Abstract

Purpose of Review Liver tumors, excluding hepatocellular carcinoma and metastatic disease, are rare. However, it is important to understand how to distinguish these lesions from hepatocellular carcinoma. They run the spectrum of benign to malignant, some aggressive with relatively few therapeutic options. The goal of this paper is to review the most recent literature to provide current insights into diagnosis, treatment, and pathogenesis of these tumor types.

Recent Findings Recent literature has focused on oncogenomics and putative targets for therapeutic intervention. Several ongoing studies are elucidating molecular pathways and evaluating novel therapies in these rare tumors and we focus on these findings, particularly in intrahepatic cholangiocarcinoma and fibrolamellar HCC. While these advances are promising, surgical resection continues to be associated with the greatest survival benefit for rare malignant tumors of the liver.

Summary Clinicians must be aware of rare liver tumors to distinguish them from hepatocellular carcinoma and to develop a differential diagnosis in complicated or atypical presentations. In these rare tumors, advances in understanding tumor biology hold the promise of expanding diagnostic and therapeutic possibilities.

Keywords Hepatocellular carcinoma · Intrahepatic cholangiocarcinoma · Fibrolamellar hepatocellular carcinoma · Hepatic epithelioid hemangioendothelioma · Hepatic angiosarcoma, hepatic adenoma

Introduction

Liver tumors, excluding hepatocellular carcinoma (HCC) and metastatic disease, account for roughly 10% of primary liver cancers [1]. While HCC is the most prevalent primary hepatic malignancy, it is important to be knowledgeable about entities such as intrahepatic cholangiocarcinoma, fibrolamellar HCC, hepatic epithelioid hemangioendothelioma, angiosarcoma, and hepatic adenoma, especially in patients with atypical presentations. Mixed hepatocellular cholangiocarcinoma will not be covered in this review, as it is addressed in a separate paper by Yang and Roberts in this issue. Likewise, common benign lesions, such as focal nodular hyperplasia and hemangioma, are beyond the scope of this review.

Oncogenomics has revealed several important pathways in cholangiocarcinoma and fibrolamellar HCC that have improved our understanding of tumor biology and provide insight into potential therapeutic targets. Combining careful histologic characterization with genomic data has led to phenotypic characterization of hepatic adenomas that allows for a more rational approach to management of these tumors with variable malignant potential. Despite emerging studies that promise more personalized medicine in the future, surgical resection for these malignancies, and even certain adenomas with malignant potential, remains the mainstay of therapy.

In this review, the topic of non-HCC primary liver tumors was approached from the lens of tumors that may be encountered by a hepatologist in the context of a liver tumor board

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(clinical presentation and radiographic findings) and divided into several subtypes based on malignancy potential. For each entity, we describe epidemiology, diagnosis, and management as well as selected insights into molecular pathogenesis, and novel treatments/clinical trials, where applicable. Because these are rare entities, the objective is to impart to the reader a sense of when to think of these tumors, how to manage them and where to look for emerging therapies based on advances in understanding tumor biology.

Malignant Lesions

Intrahepatic Cholangiocarcinoma (iCCA)

Epidemiology, Diagnosis, and Management

Intrahepatic cholangiocarcinoma (iCCA), also termed intrahepatic bile duct cancer, accounts for at least 10% of primary malignant liver lesions, second only to HCC [1, 2]. Because the incidence of iCCA has significantly increased over the past decade in the USA [3••], by as much as sevenfold in the past two decades [4], and worldwide [1, 5], we chose to highlight this to the exclusion of perihilar (pCCA) and distal cholangiocarcinoma (dCCA). Recognizing iCCA as a distinct cancer, the International Liver Cancer Association developed practice guidelines published in 2014 [6]. The authors address the difficulty in understanding trends in iCCA in the setting of unclear nomenclature and provide suggestions concordant with the modifications of the American Joint Committee on Cancer (AJCC) Staging Manual 7th edition that delineates an independent staging system for intrahepatic cholangiocarcinoma [7]. Commonly cited risk factors for iCCA include fluke infestation (the etiology most common in Asia), primary sclerosing cholangitis, biliary duct cysts, and hepatolithiasis [6]. However, many risk factors for iCCA, particularly those that develop in a cirrhotic liver, mimic those for HCC, including viral hepatitis, alcohol, cirrhosis, obesity, diabetes mellitus, and smoking [8, 9•, 10, 11••]. Increasingly, we are identifying iCCA during routine HCC surveillance of patients with cirrhosis.

When caught early, it may be difficult to distinguish iCCA from HCC on imaging. This is particularly important in patients with cirrhosis. On CT or MRI, the accumulation and retention of contrast in the delayed phase and a thick rim of enhancement help to distinguish iCCA from HCC [12] (Table 1). The diagnosis of iCCA is confirmed by biopsy. When it presents at advanced stages, with multiple liver masses, a biliary origin as the primary site is often only confirmed after correlation with immunostains and exclusion of a pancreatic source. Early

Table 1 Magnetic resonance imaging characteristics of non-HCC primary liver tumors

Tumor type	Common appearance		Distinguishing Features	Benign mimics
	Arterial phase	Portal and equilibrium phase		
Intrahepatic cholangiocarcinoma (iCCA)	Peripheral enhancement with progressive central enhancement	Progressive or persistent enhancement, often with a thick rim	Capsular retraction	Inflammatory pseudotumor Sclerosed hemangioma
Fibrolamellar HCC (FL-HCC)	Diffuse and heterogeneous enhancement	Persistent enhancement	Central scar	Focal nodular hyperplasia
Hepatic epithelioid hemangioendothelioma (HEHE)	Progressive, peripheral target-like or rim enhancement Often a confluence of multiple masses	Progressive enhancement	Peripheral location Targetoid appearance Capsular retraction Can bridge fissures	Hemangioma
Hepatic angiosarcoma (HAS)	Progressive, heterogeneous and often incomplete enhancement which can follow the blood pool Multifocal or single, dominant mass	Progressive, centripetal nodular enhancement	Intratumoral hemorrhage Splenic metastasis	Hemangioma
Hepatic adenoma (HCA)	Homogeneous mild enhancement	Isointense to hypointense	Intratumoral fat Intratumoral hemorrhage Hypointense on hepatobiliary phase	Focal nodular hyperplasia (especially in inflammatory HCA)

surgical intervention remains potentially curative for iCCA. However, due to its aggressive nature and limited mechanisms for screening at risk individuals, nearly 70–90% of patients are not considered surgical candidates at diagnosis [6]. Even when diagnosed early, 5-year survival after resection is less than 40% and recurrence is seen in 50% of patients within 12 months [6, 13]. For those with inoperable or advanced metastatic disease, median survival is less than 15 months and 5-year survival is less than 10% [6, 14]. Chemotherapy (gemcitabine-based) has proven purely palliative for patients with inoperable and advanced iCCA, achieving only limited improvement in survival [15].

While liver transplant may be performed for perihilar cholangiocarcinoma meeting very strict criteria, it is not offered to patients with iCCA due to the high risk of metastasis and early recurrence. However, a retrospective study assessing survival after liver transplant in patients with well-differentiated, very early iCCA (< 2 cm) at explant has shown 1-, 3-, and 5-year survival of up to 93%, 84%, and 65%, respectively [16]. A recent small prospective case series reports an 83.3% 5-year survival in six patients with locally advanced iCCA who underwent transplantation after achieving stability on neoadjuvant gemcitabine-based therapies; however, three of six patients developed recurrent disease [17•]. A systematic review on selective internal radiation therapy [18] and a meta-analysis of TACE [19] for local palliation have shown benefits in progression-free survival and overall survival. These studies are of significant clinical relevance for patients with cirrhosis who cannot be safely resected or who may not tolerate systemic chemotherapy due to liver dysfunction. Locoregional modalities are being studied in prospective clinical trials, the results of which may impact clinical practice.

Molecular Pathogenesis

There have been many recent advances in our understanding of the molecular pathogenesis of iCCA. Hepatic progenitor cells can differentiate into mature hepatocytes or mature cholangiocytes. While adult cholangiocytes can only give rise to iCCA, hepatocytes are capable of dedifferentiating into precursor cells or transdifferentiating into biliary-like cells that can ultimately give rise to iCCA. Sia and colleagues [11••] delineate the many animal studies that have assessed cell of origin in iCCA and HCC. The authors underscore the poor prognosis of liver cancers with stem cell features, the need for further studies to determine drivers of oncogenesis in mature and progenitor cells, and how the tumor microenvironment, specifically the chronic inflammation often accompanying iCCA (and HCC), contributes to liver carcinogenesis [11••]. Despite significant developments in characterizing the mutational landscape of iCCA, no targeted molecular therapy has shown significant improvement in overall survival in iCCA [20•, 21••].

Studying iCCA as a distinct phenotypic entity has led to a better understanding of the molecular classification of this disease into two subtypes: proliferation and inflammation as defined by genetic mutations and clinical phenotypic observations [11••, 22, 23]. The inflammatory subclass is characterized by activation of STAT3 or cytokine associated pathways [21••], while the proliferative subclass is characterized by interaction with tyrosine kinase (TK) receptors by oncogenes inducing activation of the TK signaling pathway. However, mutations in chromatin remodeling genes and TP53 and FGFR2 translocations affect both classes.

The most commonly identified mutations in iCCA are TP53, KRAS/NRAS, and IDH, and these mutations are also seen in perihilar and distal cholangiocarcinoma [24–27, 28••, 29, 30, 31•]. Mutations in KRAS/NRAS, TP53, and mutation or epigenetic silencing causing loss of PTEN are associated with a poor prognosis in iCCA [32, 33]. Whole genome sequencing identified mutations in the chromatin remodeling genes PBRM1, BAP1, and ARID1A more frequently in iCCA than perihilar or distal CCA [24, 25, 34]. FGFR2 fusions and mutations in IDH 1/2 have been identified in iCCA but are rarely seen in HCC or perihilar or distal CCA [21••] (Table 2). IDH 1/2 mutations have been identified as precursors for cholangiocarcinogenesis through regression in differentiation of hepatocytes [35]. A recent study of 38 CCAs in The Cancer Genome Atlas (TCGA) highlighted distinctions in IDH-mutant CCAs, and the authors report the complete lack of IDH mutations in otherwise standard HCC from the TCGA set [36••]. Studies like this aim to improve the molecular classification of cholangiocarcinoma, a heterogeneous cancer without a predominant oncogenic pathway [36]. Genomic studies in carefully selected populations (in this case non-fluke associated, non-viral associated cholangiocarcinoma) are necessary to elucidate specific pathways for further study.

Novel Treatments/Clinical Trials

There are several active clinical trials underway, especially in advanced iCCA. While not an exhaustive list, the studies that follow highlight a variety of approaches. Several studies are focused on the safety and efficacy of transarterial therapies, such as yttrium 90 selective internal radiation therapy or transarterial chemoembolization in the treatment of iCCA before or with cisplatin and gemcitabine (CIS-GEM) in patients with inoperable iCCA (NCT02512692, NCT02807181, NCT02994251, NCT01648023). The National Cancer Institute is conducting a phase 3 randomized trial evaluating the effectiveness of radiation therapy with CIS-GEM (NCT02200042). Another study is assessing the effect of high dose intrahepatic CIS-GEM (NCT03086993). New combination chemotherapies, such as floxuridine-dexamethasone and

Table 2 Tumor origin, population at risk, recent discoveries and their current application

Tumor type	Origin	Patient population	Recent discoveries in pathogenesis	Application of discovery
Intrahepatic cholangiocarcinoma (iCCA)	Biliary or hepatic progenitor	PSC increasing in prevalence in advanced fibrosis/cirrhosis (in the USA)	FGFR2 fusion IDH catalytic site mutations	Prognostic Potentially therapeutic (FGFR2 inhibitors)
Fibrolamellar HCC (FL-HCC)	Hepatic	Young, no underlying liver disease (ages 10–40)	DNAJB1-PRKACA fusion	Diagnostic
Hepatic epithelioid hemangioendothelioma (HEHE)	Vascular endothelial (low grade)	Young, no underlying liver disease (ages 30–40)	WWTR1(TAZ)-CAMTA1 fusion YAP1-TFE3 fusion	Diagnostic
Hepatic angiosarcoma (HAS)	Vascular endothelial (high-grade)	Older, more commonly males (ages 60–70), discrete environmental exposures	Alternative lengthening of telomeres (ALT)	Diagnostic, potentially therapeutic (ATR kinase inhibitors)
Hepatic adenoma (HCA)	Hepatic	Young, more commonly female (ages 35–40)	HNF1α inactivation JAK-STAT pathway activation β-catenin exon 3 mutation β-catenin exon 7,8 mutation Sonic Hedgehog activated	Diagnostic Prognostic

gemcitabine are also being studied in phase 1 and 2 trials (NCT01938729, NCT01862315).

Derazantinib, an oral tyrosine kinase inhibitor with specific activity against the FGFR family of kinases, is being studied as a second line agent in patients with inoperable or advanced iCCA with FGFR2 gene fusions (NCT03230318). Apatinib, an oral tyrosine kinase inhibitor with specific activity against VEGFR2 is also being studied as a second-line agent in advanced iCCA (NCT03251443).

Finally, a trial assessing the efficacy of liver transplantation for patients with cirrhosis diagnosed with very early iCCA ($\leq$ 2 cm) will begin enrolling in December 2018 (NCT02878473).

Fibrolamellar Hepatocellular Carcinoma (FL-HCC)

Epidemiology, Diagnosis, and Management

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a rare primary liver cancer with an estimated age adjusted incidence rate of 0.02 per 100,000 in the United States [37, 38]. FL-HCC often presents in asymptomatic young patients (usually between the ages of 10–40) without existing liver disease as a single large hepatic mass. While FL-HCC is slightly more common in women, no known risk factor has been identified [39, 40]. The characteristic clinical presentation of FL-HCC in a young patient with a single large liver lesion in the setting of no known underlying liver disease should help most in differentiating this entity from HCC. On CT and MRI, FL-HCC demonstrates heterogeneous hyperattenuation on arterial phase and variable appearance on subsequent phases, which helps to distinguish it radiographically from HCC [41•]. Intratumoral fat has not been reported in FL-HCC, a common finding in HCC, and the presence of a central scar is commonly seen in FL-HCC, but is not the norm in HCC. However, when HCC arises in a non-cirrhotic liver, it may be difficult to differentiate from FL-HCC by imaging characteristics alone [42] (Table 1). Focal nodular hyperplasia, a benign liver tumor, is often associated with a central scar and is considered a radiographic mimic of FL-HCC. Diagnosis is made by biopsy. Histological features on biopsy include clusters or sheets of large tumor cells with prominent nuclei and granular eosinophilic cytoplasm surrounded by dense fibrotic bands (lamellae). However, the heterogeneous histological findings of FL-HCC may make it difficult to differentiate from conventional HCC and positive cytokeratin (CK) 7 and CD 68 immunostains may aid in diagnostic accuracy [43, 44].

Over half of all patients diagnosed with FL-HCC are diagnosed at an advanced stage with distant metastasis [40, 45]. The standard of care remains surgical resection that also includes regional lymph node resection and many times resection of distant metastases [46–51]. It is important to note that patients deemed inoperable often do not survive 1 year from the time of diagnosis [51, 52]. Despite surgical resection for curative intent, recurrence rates are high, often presenting as distant metastasis, most commonly extra-hepatic [39, 45, 53]. Throughout the course of the disease patients often undergo multiple resections. Ultimately, the 5-year survival rate in patients diagnosed with FL-HCC is less than 50% [40].

In 63 patients with inoperable tumor burden confined solely to the liver, orthotopic liver transplant (OLT) had similar survival rates to those reported in HCC. Overall 1, 3, and 5-year survival rates of patients with FL-HCC who underwent OLT were 96%, 80%, and 40%, respectively, as compared to 1, 3, and 5-year survival rates of 89%, 77% and 68%, respectively, for patients with HCC [54•].

Molecular Pathogenesis

Distinct molecular characteristics differentiate FL-HCC from HCC [55•]. In 2014, Honeyman and colleagues described the discovery of a fusion protein, DNAJB1-PRKACA, the result of a ~ 400-kilobase deletion on chromosome 19 (Table 2). The fusion of DNAJB1 (heat shock protein 40) with PRKACA (a subunit of protein kinase A) results in an enzymatically active chimeric protein [56]. This somatic mutation has not been described as an inheritable genetic disease, and it has not been associated with the development of other cancers [57]. Expression of this chimeric protein in humans and in mouse studies is associated with the development of FL-HCC [55•, 56, 58, 59•, 60], but expression of PRKACA alone is not adequate for oncogenesis [59•, 61•]. The constitutive activation of protein kinase A caused by fusion alters the transcriptome and proteome of cells, and further evaluation of associated pathways is an important area of additional study to accelerate development of therapeutic interventions, such as a novel small molecule inhibitor targeted at the region of fusion [57, 60, 61•].

DNAJB1-PRKACA kinase inhibition has been an area of intense focus especially over the past 1–2 years. As this fusion protein is specific to FL-HCC and does not appear in normal cells, it is ideal for targeted therapy (inhibition) with limited off-target effects. However, the constitutively active kinase pocket mimics the normal kinase, making it difficult to create a selective inhibitor without affecting normal cellular function.

It is unclear whether a "second hit" may be required for the development of FL-HCC in the presence of the chimeric fusion protein. However, it is known that expression of DNAJB1-PRKACA is closely linked to development of FL-HCC suggesting that the mutation is necessary, but not independently sufficient [57]. It has also been postulated that up-regulated non-coding RNAs in FL-HCC relative to normal liver or HCC may play a role in development of FL-HCC [62•]. There are conflicting data on whether hypomethylation and loss of differentiation can distinguish FL-HCC from HCC [63–66].

Novel Treatments/Clinical Trials

There have been mixed results in clinical trials for FL-HCC. For example, aromatase inhibition showed little effect in FL-HCC [67]. The use of everolimus resulted in significant reduction in tumor mass and increased quality of life in an isolated case [68]. A randomized phase 2 trial is currently comparing three arms; everolimus alone, estrogen deprivation therapy (EDT) with leuprolide plus letrozole, and everolimus plus EDT in patients with inoperable FL-HCC (NCT01642186). The primary outcome measure will be progression-free survival at 6 months; this trial is scheduled to conclude in late 2018. Another multicenter trial is studying ENMD-2076 (a multi-tyrosine kinase inhibitor) in patients with advanced FL-HCC (NCT02234986).

Despite the current paucity of treatments for FL-HCC, the last several years have seen great leaps in discovery in FL-HCC that may translate to targeted therapies and to a better understanding of the molecular pathogenesis of this cancer and what sets it apart from HCC.

Hepatic Epithelioid Hemangioendothelioma (HEHE)

Epidemiology/Diagnosis/Management

Epithelioid hemangioendotheliomas (EHE) can arise in multiple tissue types. Histologically, EHE is characterized by predominantly epithelioid- and histiocytic-like cells in a fibrotic stroma. Hepatic epithelioid hemangioendothelioma (HEHE) is a rare, low grade vascular endothelial tumor of the liver that often presents as an incidental finding on imaging or in patients with non-specific abdominal symptoms. The disease is slightly more common in women, and average age at presentation is 30–40 years [69]. Various reports suggest associations with infectious or inflammatory processes; but HEHE is most often diagnosed in patients without underlying liver disease. No clear risk factors have been identified [70]. Contrast enhanced CT or MRI is helpful in the diagnosis of HEHE when characteristic findings are seen, such as coalescing multifocal subcapsular tumors [41•, 71] (Table 1).

HEHE may be mistaken for HCC, angiosarcoma, or even cholangiocarcinoma, delaying diagnosis. Immunostains for endothelial markers are essential to confirm the diagnosis. CD34 and CD31 are positive in 94% and 86% of cases, respectively [71]. Factor VIII-related antigen is positive, albeit variable, in nearly 100% of HEHEs [71, 72], and podoplanin may be positive in HEHE, but not in other liver angiomatous lesions [73]. More recently, cytogenetic discoveries have improved diagnostic accuracy in EHE. Immunostaining with an antibody to the C-terminus of calmodulin-binding transcription activator 1 (CAMTA1) was positive in 86% of patients [74].

Surgical resection remains the therapy of choice in local, single lobe disease; liver transplant is reserved for bi-lobar variants. In patients deemed inoperable, several chemotherapeutic agents have been attempted with mixed results. Interestingly, while patients with multifocal tumors have a poorer prognosis, increased mortality is not associated with extra hepatic infiltration [75]. This was corroborated by a study of long-term follow-up (100 months) of patients after surgical resection [76]. A model for a prognostic score based on the analysis of the European Liver Transplant Registry has been proposed and ultimately reported that patients are doing quite well post-transplant, even when metastatic disease was present [77•].

Molecular Pathogenesis

Like FL-HCC, the pathogenesis of EHE is also related to fusion proteins. The translocation of CAMTA1 (usually expressed in the brain) and WWTR1 (a transcriptional coactivator, highly expressed in endothelial cells) was identified in EHE from bone, soft tissue, liver, and lung; this translocation was not present in any of the control samples [78–80]. Because the fusion gene is under the transcriptional control of the WWTR1 promoter, CAMTA1 expression is activated inappropriately, and the result is a chimeric oncogene [80] (Table 2). This fusion gene inhibits the Hippo tumor suppressor pathway [81••].

A second translocation has also been described, initially discovered in a case of pulmonary EHE that tested negative for the CAMTA1-WWTR1 fusion but was found to be positive for transcription factor E3 (TFE3). In 80% of WWTR1(TAZ)-CAMTA1 negative cases, there was development of a YAP1-TFE3 rearrangement [82] (Table 2). On a follow-up study, WWTR1(TAZ)-CAMTA1 and YAP1-TFE3 fusions were present in 94% and 6% of cases, respectively, on florescence in situ hybridization (FISH) analysis [83]. The recent discoveries in the pathogenesis of EHE are not only promising for improving diagnostic accuracy and developing targeted therapies for this malignancy but also for unraveling the biology of tumor pathways implicated in multiple different types of tumors.

Novel Treatments/Clinical Trials

Currently, therapy for advanced EHE is focused on inhibition of vascular endothelial growth factor (VEGF). Because the disease is rare, the literature is composed primarily of case reports/case series. One such report shows promising results with the use of sorafenib in EHE [84]. Other studies are aimed at both EHE and angiosarcoma. A phase 2 trial assessing eribulin (a mitotic inhibitor derived from the sea sponge) as a possible therapy for angiosarcoma or EHE is ongoing (NCT03331250). The National Cancer Institute is conducting a phase 2 trial evaluating the efficacy of trametinib, a MEK inhibitor, in treating patients with metastatic, inoperable EHE (NCT03148275). While these trials are more specific to EHE, multiple therapeutic trials are ongoing to assess the efficacy of multiple agents in treating EHE combined with other types of advanced sarcomas.

Angiosarcoma

Epidemiology/Diagnosis/Prognosis

Primary hepatic angiosarcoma (HAS) comprises approximately 2% of primary hepatic tumors; it is the most common primary sarcoma of the liver [85, 86]. There are several known environmental risk factors associated with HAS including exposure to vinyl chloride, arsenic, radiation, and thorium dioxide (Thorotrast) [85]. These exposures are now exceedingly rare in developed countries. Average age at diagnosis is 60–70 years and it most commonly occurs in males (4:1 ratio). While HAS has been described in patients with hemochromatosis and neurofibromatosis, most lesions encountered in clinical practice have no clear etiology [85]. In one large series, 40% of patients with HAS had underlying fibrosis or cirrhosis [87]. Limited symptomatology leads to delayed diagnosis and often symptoms are nondescript. Most HAS are inoperable, as these high-grade vascular endothelial tumors are usually multifocal at diagnosis. HAS are highly vascular and invasive tumors, and spontaneous hemorrhage is a common complication for which embolization has been effective for control of bleeding [88]. CT and MRI remain the gold standard for radiographic evaluation. Where available, contrast enhanced ultrasound (CEU) demonstrates arterial phase nodular enhancement without the necessity of CT scan or MRI [89] and some studies suggest that pathognomonic findings on CEU may be sufficient to diagnose HAS [90–92]. On CT or MRI, increased peripheral arterial phase enhancement without significant portal venous phase hypointensity can help differentiate between a solitary HAS and HCC. Displacement of hepatic arteries, and a blush and "puddling" during the middle of the arterial phase has been described [41•, 93] (Table 1). Differentiating HAS from benign hemangioma can be challenging on MRI, and CT may be helpful in differentiating one from the other [94].

Due to concerns for bleeding, there is variable opinion regarding the safety of liver biopsy (fine needle aspiration cytology versus open biopsy), but pathological diagnosis remains the gold standard. Angiosarcomas histologically are composed of malignant spindle cells of endothelial cell differentiation that coalesce to form poorly organized vessels and sinusoids. Tumors can be mass-like or can grow linearly along pre-existing vessels. Cavernous tumors can form when liver cell plates atrophy [85]. Like EHE, the diagnosis of HAS requires immunostains for confirmation. Transcription factor ERG expression has been reported as 100% positive in HAS versus CD31 (79% positive) or CD34 (87.5% positive) making it the marker of choice [95].

Zheng and colleagues reviewed 25 papers detailing 64 HAS cases. Median survival was 5 months, and resection alone or combined with adjuvant therapy was optimal, with a median survival time of 17 months [88]. The cause of death is usually related to hemorrhage or liver failure [88]. Radical tumor resection remains the most effective therapy with improved survival times over that of liver transplant and studies have suggested that liver transplant should not be pursued as a viable intervention in the

management of HAS due to its highly aggressive nature [88, 96•]. Chemotherapy and radiation offer alternatives where surgical intervention is precluded, but survival benefits are limited [97]. Palliative chemotherapy may be considered in cases of advanced or metastatic disease [98]. Palliative transarterial chemoembolization (TACE) has also been shown to improve survival [88, 90].

Molecular Pathogenesis

Most genetic studies in HAS have focused on environmentally associated mutations in oncogenes. However, several recent papers have reported HAS arising in dyskeratosis congenita, a short telomere syndrome [99, 100]. Interestingly, cancer cells are known to maintain telomere length through telomerase expression and alternative lengthening of telomeres (ALT) [101]. Mutations in the promoter of the telomerase reverse transcriptase (TERT) gene activate telomerase expression; TERT mutations are a common occurrence in HCC [102]. A minority of cancers (10–15%) maintain telomeres by ALT, a process dependent upon homologous recombination. ALT positive cells have a phenotype characterized by heterogeneity of telomere lengths and extrachromosomal telomere repeats [103, 104]. In pancreatic neuroendocrine tumors, inactivation of either death domain-associated (DAXX) protein or α-thalassemia/mental retardation syndrome X-linked (ATRX) protein correlated with ALT, suggesting that these proteins played crucial roles in the ALT phenotype [105, 106]. In a study assessing 119 malignant vascular tumors, Liau and colleagues reported that hepatic angiosarcomas had the highest rate of loss of ATRX expression (8/13; 62%), and loss of ATRX expression was seen more frequently in hepatic than non-hepatic tumors [107••] (Table 2). Recently, ALT-positive tumor cells have been sensitive to treatment with ataxia telangiectasia and Rad3-related (ATR) kinase inhibitors [108•].

Novel Treatments/Clinical Trials

Multiple studies are assessing angiosarcomas (primary, secondary, and of multiple sites). A very interesting recent case report described decreased tumor size and stabilization of metastatic lesions at 15 months in a patient with HAS treated with local radiofrequency ablation followed by pazopanib (a VEGF inhibitor), pembrolizumab (a PD-1 inhibitor), and allogeneic RetroNectin-activated killer cells (RAK cells), a new kind of cytokine induced killer cells [109]. See above for discussion of eribulin which is being evaluated for use in HAS (NCT03331250).

Lesions with Malignant Potential

Hepatocellular Adenoma (HCA)

Epidemiology/Diagnosis/Management

Hepatocellular adenoma (HCA) encompasses several types of benign hepatocellular proliferations. Unlike other benign liver lesions, certain variants of HCA carry a significant risk of malignant transformation and other complications such as hemorrhage. HCA is most commonly seen in women ages 35–40 and has been strongly associated with high estrogen states. There is a significant (nearly 40-fold) increase in the incidence of HCA in women on long-standing oral contraceptive medications [110, 111]. HCA has also been reported in males using anabolic steroids and in patients with excess endogenous androgen production. Several studies have observed an increase in the incidence of HCA and hypothesized an association with the increasing prevalence of obesity and diabetes in the population [112–116]. Interestingly, hepatic adenomatosis (> 10 HCAs) is associated with inherited diseases of glucose metabolism: maturity onset diabetes of the young type 3 (MODY3) [117] and glycogen storage disease (GSD), most commonly type I [118] and rarely type III [119].

Imaging characteristics are variable for HCA. On MRI, adenomas most often show early arterial enhancement and become nearly isointense to the liver on delayed images. If there is hemorrhage, blood products may lead to significant heterogeneity in signal on all sequences [120] (Table 1). Like HCC, adenomas can contain intratumoral fat. A hepatocyte-specific MRI contrast agent, gadoxetate disodium (Eovist), can be used to help distinguish adenoma from FNH with improved sensitivity over conventional MRI. Hepatocyte-specific imaging helps determine both hepatocyte function and biliary excretion. HCAs have no or few bile ducts and the hepatocytes within HCA do not function normally, hence the contrast agent does not accumulate avidly in HCA. Hepatocytes within FNH are functional, often with septal ductular reaction, resulting in increased accumulation of the contrast agent [121].

Adenomas may be difficult to distinguish from well-differentiated HCC on needle biopsy; it may even be difficult to distinguish adenoma from FNH on biopsy. A proliferation of pleomorphic hepatocytes without normal lobular architecture defines HCA, but there can be significant heterogeneity. There should be little or no cytologic atypia. Many of the immunostains used to subtype hepatic adenomas are frequently positive in hepatocellular carcinomas [122•].

Molecular Pathogenesis

Several subtypes of HCA have been discussed with variable malignant progression [123•]. In general, HCA has a

relatively low malignant transformation rate, but in the setting of activating mutations in β-catenin, the risk of malignancy is higher. Progression from a benign to malignant lesion is much more common in males compared to females; therefore, resection is advised for HCA arising in males. Based on extensive correlation of morphologic phenotypes with genetic analysis, Zucman-Rossi and colleagues have characterized HCA into six main molecular subgroups: HNF1α-inactivated HCA (HHCA), inflammatory HCA (IHCA), β-catenin exon 3 mutated HCA (βex3HCA), β-catenin exon 7/8 mutated HCA (βex7,8 HCA), Sonic Hedgehog activated HCA (shHCA), and unclassified HCA (UHCA) [102, 124, 125] (Table 2).

HHCA comprises 40–50% of all HCAs and is defined by the biallelic inactivation of HNF1α, a transcription factor that is responsible for hepatocyte metabolism and differentiation [126, 127]. Multifocal hepatic adenomas are seen in MODY3, a germline mutation of HNF1α. A unique feature of HHCA is the absence of expression of liver fatty acid-binding protein (LFABP) that is present in unaffected hepatocytes [126, 128]. This is likely why marked steatosis is especially apparent in HNF1α mutated tumors.

IHCA represents a large heterogeneous group (35–40% of HCAs) with various gene mutations associated with activation of the JAK STAT pathway [129]. Although many mutations have been identified interestingly they are all mutually exclusive in IHCA. The most common of these gene mutations is gp130 (interleukin-6 signal transducer). Multiple other factors have been linked to IHCA including obesity, diabetes, and high alcohol consumption. IHCA, like HHCA, can display varying degrees of steatosis and can also show mutations in β-catenin.

Mutations in β-catenin are seen in 5–10% of HCAs and are divided into βex3HCA and βex7,8 HCA. Mutations in exon 3 of CTNNB1 (the gene encoding β-catenin) lead to strong activation of the WNT/β-catenin pathway and a high risk of malignant transformation, whereas mutations in exons 7 and 8 lead to weak activation of the pathway and do not increase the risk of malignant transformation [130••]. βex3HCA and βex7,8 mutations are mutually exclusive.

Sonic hedgehog pathway (shHCA) mutations were previously grouped under the unclassified category due to lack of characteristic features associated with the other primary subtypes. However, discovery of mutations activating the sonic hedgehog pathway led to this classification, accounting for 5% of HCAs. A somatic fusion between the inhibin beta E subunit (INHBE) and GLI family zinc finger (GLI1), a key transcription factor in the pathway, was discovered as the primary initiating step for activation of the sonic hedgehog pathway [102]. These adenomas have an increased risk of hemorrhage, and this fusion gene may represent a target for prevention of complications from bleeding in the future [102].

Unclassified HCA (UHCA) represents 7% of all HCA and does not display mutations in any of the aforementioned subgroups. No specific morphological features have been identified to date. Recently, argininosuccinate synthetase 1 (ASS1) was found to be a marker of UHCA and other HCAs with high bleeding risk [131•].

Unraveling the biology of HCAs has important corollaries to HCC, as many of these pathways have been implicated in HCC. This degree of molecular characterization is likely to lead better diagnostic and prognostic accuracy and possible advancements in therapeutic interventions.

Histologic subtyping and molecular analysis is not commonly performed in routine clinical practice. Radiographic subtyping is evolving as our understanding of the biology of HCAs has improved [132], however the accuracy of imaging is insufficient without histological/molecular correlation [122•]. Rather, size, imaging, and clinical findings inform treatment decisions. If the clinical scenario and imaging findings support the diagnosis of HCA, in tumors under 5 cm, biopsy is often not performed. Biopsies are reserved for atypical clinical or radiographic scenarios or significant change in tumor size or enhancement characteristics. The reader is directed to a recent excellent review by Torbenson on this topic [122•].

Treatment/Surveillance

HCA with significant growth over 5 cm or increase in diameter greater than 20% should be considered for surgical resection irrespective of subtype, as hemorrhage and malignant transformation are more commonly seen in larger adenomas [133, 134]. In cases of hemorrhage with hemodynamic instability, transcatheter bland embolization is the first line of therapy [135]. Males diagnosed with HCA should undergo surgical resection at any size, due to the strong association of malignant transformation in males [123•]. Based on data from small series, Agrawal et al. advise that radiofrequency ablation may be appropriate for patients who are not surgical candidates or in women who have hormone-sensitive tumors and wish to conceive, but this should be reserved for lesions less than 4 cm in diameter [136]. Special consideration must be made for HCA during pregnancy. Routine follow-up with interval ultrasound examination every 6–12 weeks is recommended to monitor the size of the lesion as evidence of enlargement is associated with risk of rupture [135, 137]. Women of childbearing age with large adenomas (> 5 cm) should strongly consider resection prior to conception.

More commonly, the clinical question is how to manage single or multiple adenomas smaller than 5 cm in females. For diagnosed or suspected HCAs in this size range, the American College of Gastroenterology advises surveillance CT or MRI at 6- to 12-month intervals. At our center, we prefer contrast enhanced MRI due to its improved sensitivity over CT. Currently, there are no data to support a specific timeline of surveillance. Chun and colleagues found that in women with

adenomas < 5 cm who discontinue estrogen, observation with contrast-enhanced MRI 6, 12, and 24 months after baseline imaging is a reasonable approach. They advise that if lesions remain stable or decrease in size, surveillance imaging may be discontinued [138]. The lack of published guidelines for the clinical management and surveillance of HCA is likely driven by the heterogeneity of this disease; a recent paper underscores the importance of developing guidelines and a multidisciplinary approach to management [123•].

Conclusion

Patients with non-HCC liver tumors comprise a relatively small population of individuals. However, in the routine surveillance of patients with risk factors for HCC, and with highly sensitive imaging techniques, atypical lesions are often found. The ability to make a reasoned differential diagnosis depends upon knowing about these rarer entities and the populations in which they arise. Increasingly, we are seeing iCCA in patients with cirrhosis. Hepatic adenoma is also increasingly more common in patients with obesity and fatty liver disease. Although FL-HCC, EHE, and HAS are rare, recent exciting advances in understanding their molecular pathogenesis have shed light on new pathways in tumor biology. The painstaking morphologic and genetic correlations that have led to the detailed classification of HCAs established an important paradigm that is currently unfolding in HCC and underscores the importance of multidisciplinary investigation to link clinical and morphological phenotypes to genetic mutational landscapes.

Compliance with Ethics Standard

Conflict of Interest Antonio Costantino, Jr and Tamar H. Taddei each declare no potential conflicts of interest.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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