



Contents lists available at ScienceDirect

## Current Problems in Cancer

journal homepage: [www.elsevier.com/locate/cpcancer](http://www.elsevier.com/locate/cpcancer)

## Fibrolamellar carcinoma: An entity all its own

Allison F. O'Neill, MD<sup>a,\*</sup>, Alanna J. Church, MD<sup>b</sup>,  
Antonio R. Perez-Atayde, MD<sup>b</sup>, Raja Shaikh, MD<sup>c</sup>,  
Karen J. Marcus, MD<sup>d</sup>, Khashayar Vakili, MD<sup>e</sup>

<sup>a</sup> Department of Pediatric Oncology, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston MA

<sup>b</sup> Department of Pathology, Boston Children's Hospital, Boston MA

<sup>c</sup> Department of Radiology, Boston Children's Hospital, Boston MA

<sup>d</sup> Department of Radiation Oncology, Brigham and Women's Hospital and Boston Children's Hospital, Boston MA

<sup>e</sup> Department of Surgery, Boston Children's Hospital, Boston MA

### ABSTRACT

Fibrolamellar carcinoma (FLC) is a rare malignant entity arising from the liver and primarily affecting patients in late adolescence and young adulthood. FLC tumors are characterized by their unique histologic features and an only recently discovered genomic alteration: a chimeric fusion protein found in nearly all tumors. The rarity of these tumors coupled with the only recent acknowledgement of this genomic abnormality has likely led to disease under-recognition and de-prioritization of collaborative efforts aimed at establishing an evidence-guided standard of care. Surgical resection undoubtedly remains a mainstay of therapy and a necessity for cure but given the incidence of metastatic disease at diagnosis and high rates of distant relapse, systemic therapies remain a key component of disease control. There are few systemic therapies that have demonstrated proven benefit. Recent efforts have galvanized around single-institute or small consortia-based studies specifically focused on the enrollment of patients with FLC or use of agents with biologic rationale. This review will outline the current state of FLC epidemiology, histology, biology and trialed therapies derived from available published literature.

© 2021 Published by Elsevier Inc.

### ARTICLE INFO

**Keywords:** Fibrolamellar; Carcinoma; DNAJB1-PRKACA; Hepatocellular; Therapy; Surgery

\* Correspondence to: Allison O'Neill, MD Department of Pediatric Oncology, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston MA.

E-mail address: [allison\\_oneill@dfci.harvard.edu](mailto:allison_oneill@dfci.harvard.edu) (A.F. O'Neill).

<https://doi.org/10.1016/j.currproblcancer.2021.100770>

0147-0272/© 2021 Published by Elsevier Inc.

## Introduction

Fibrolamellar carcinoma (FLC), also referred to as fibrolamellar hepatocellular carcinoma (FL-HCC), is a rare tumor arising from the liver affecting approximately 0.02 patients per 100,000 people per year in the US.<sup>1-3</sup> The average age of presentation is 25 years, thereby FLC disproportionately occurs in the adolescent and young adult populations with a smaller peak incidence in the 7th decade of life.<sup>1-3</sup> Patients traditionally present with chronic gastrointestinal symptoms, abdominal pain or a palpable mass, occasional abdominal distension from ascites, pain from metastases, in some circumstances gynecomastia due to associated high levels of aromatase expression, and in rare instances mental status change secondary to hyperammonemia and acquired ornithine transcarboxylase deficiency.<sup>4-8</sup> While disease arises within the liver, it has the propensity to spread to the intra-abdominal cavity (lymph nodes, peritoneum), lung, and in rare cases brain.<sup>9,10</sup> For patients with surgically resectable disease, outcomes have been reported as high as 80% at 5-years.<sup>11,12</sup> However for patients with disseminated disease at diagnosis, outcomes are unfortunately dismal with a less than 10%-20% 5-year overall survival.<sup>12-15</sup> While it was originally thought that patients with FLC have a superior prognosis to patients with conventional HCC, this is now unfounded.<sup>15</sup>

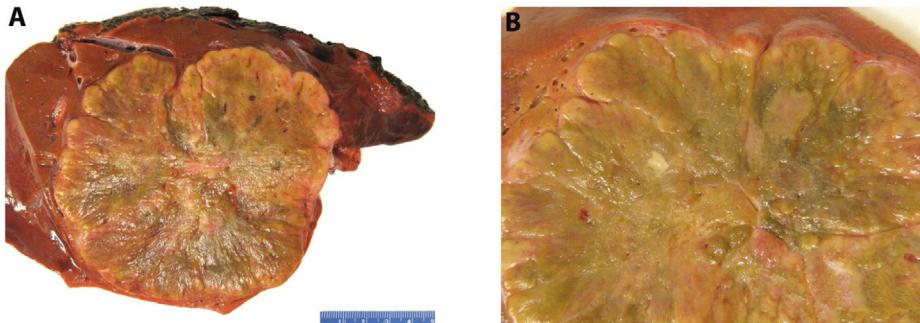
Historically, FLC was categorized as a subset of hepatocellular carcinoma, however FLC is emerging as an entity unique from "conventional" HCC given its histologic appearance, its origin from a structurally and functionally normal liver, and its association with normal levels of alfa-feto protein (AFP). FLC tumors, unlike conventional HCC tumors, have been associated with elevated aromatase levels, B12 binding protein levels, and neurotensin; while possibly linked to pathophysiology, none of these markers has been deemed prognostic, they are not traditionally tracked throughout the course of therapy, nor are they therapeutically targetable.<sup>4,16-18</sup> In 2014 the unique *DNAJB1-PRKACA* chimeric fusion protein was identified consistently in FLC cases; work has since demonstrated that this fusion is likely a driver of disease (see Biology section).<sup>19</sup> This chimera has also since been reported in tumors of pancreaticobiliary origin calling into question the primary stem cell of FLC tumors and their relation to other gastrointestinal tumors.<sup>20,21</sup> Prior to the discovery of the *DNAJB1-PRKACA* fusion, FLC tumors may have been mistakenly categorized as conventional HCC thereby underestimating the population affected. The rarity of this tumor, paired with the only recent revelation of its unique biology, contributes to the lack of a uniform approach to diagnosis and clinical management.

Given that FLC bridges both the pediatric and adult patient populations, therapeutic approaches have evolved separately depending upon whether patients are seen by pediatric vs. adult oncologists. Only in the last decade have clinical trials, organized in small consortia or at a single center, aimed to study FLC prospectively and enroll both pediatric and adult patients. What has emerged as a consistent thread, both in the pediatric and adult space, is the absolute necessity of complete surgical resection to achieve cure.<sup>11</sup> This review will serve as a high-level overview of the best-available evidence guiding existing therapies in the treatment of this rare and difficult-to-cure disease.

## Pathology

FLC, first recognized by Peters in 1982, is a hepatocellular tumor with a distinct morphology and arises in liver without chronic disease or cirrhosis.<sup>22</sup> Craig et al., were first to describe its distinct histopathology and the striking predilection for adolescents and young adults; they also were the first to coin the term FLC.<sup>23</sup>

FLC usually presents as a large, well circumscribed, unencapsulated, solitary mass within a background of normal hepatic parenchyma (Fig 1). In contrast to conventional HCC, FLC is localized more commonly in the left lobe of the liver rather than the right. Macroscopically, the tumor is lobulated with a firm light gray/tan cut surface often displaying a central scar. Areas



**Fig. 1.** (A) Well circumscribed, large hepatic mass surrounded by normal appearing nonneoplastic liver parenchyma. Stellate scarring is seen at the center of the mass. (B) The lobulated, unencapsulated mass has pushing borders compressing the surrounding hepatic parenchyma. The mass on cut surface is firm and fleshy and has a gray/tan color as well as green cholestatic areas.

of green cholestatic discoloration, necrosis or hemorrhage might be present. Satellite nodules of tumor may occur in the vicinity of the mass.

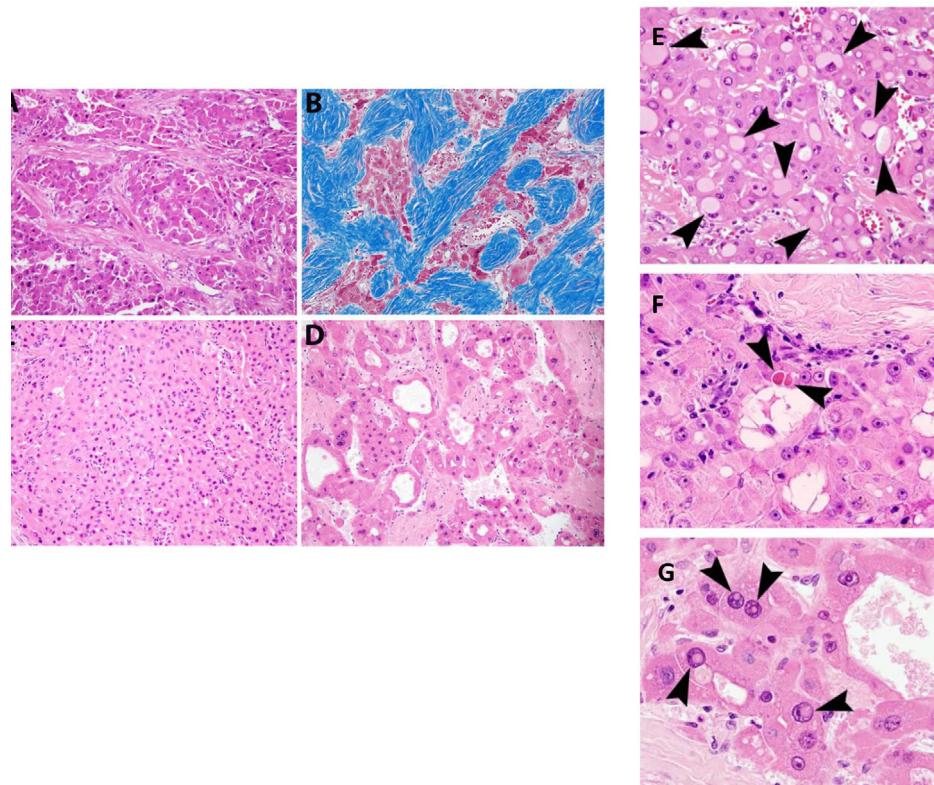
Microscopically, FLC is made up of large polygonal hepatoid cells usually immersed in characteristic platelike stacks of lamellar collagen (Fig 2A-D). The neoplastic cells are arranged in cords, nests, pseudoacinar structures or sheets and have abundant eosinophilic granular cytoplasm rich in lysosomes and mitochondria that impart an oncocytic appearance.<sup>23-25</sup> Scattered throughout the tumor, two types of cytoplasmic inclusions are observed, namely, well-defined pale gray cytoplasmic bodies and eosinophilic PAS positive, diastase resistant, hyaline globules (Fig 2E-G). Cytoplasmic or canalicular bile plugs are also frequently observed. The nuclei are round with open chromatin, a single prominent nucleolus and occasional pseudoinclusions of invaginated cytoplasm (Fig 2G). At the center of the mass, the bands of collagen may coalesce constricting and replacing the neoplastic cells with broad stellate scar(s), mimicking focal nodular hyperplasia.<sup>26,27</sup>

Although the H&E histopathology is very characteristic of this tumor, by itself it is not entirely specific; on occasion, conventional HCC tumors focally have the appearance of FLC and vice versa.<sup>11,28,29</sup> The immunohistochemical profile of the tumor cells reveals a dual hepatocytic and biliary phenotype with expression of the hepatocytic markers HepPar1 and CK8 and the biliary marker CK7 (Fig 3). Diffuse and strong immunohistochemical expression for CK7 and CD68 are supportive of FLC and both stains should be performed together in all cases.<sup>30-33</sup> Expression of CD68 or CK7 may also occur in conventional HCC. Currently, the detection of the *DNAJB1-PRKACA* fusion in concert with histologic and immunohistochemical features are the best confirmatory tests for FLC.<sup>19,34</sup>

Ultrastructurally, the neoplastic cells have numerous mitochondria that occupy most of the cytoplasm. Lysosomes and neurosecretory-type granules may also be present.<sup>24,35,36</sup> Intra- or intercellular canalicular structures of variable size are lined by well-developed surface microvilli (Fig 4).

## Biology

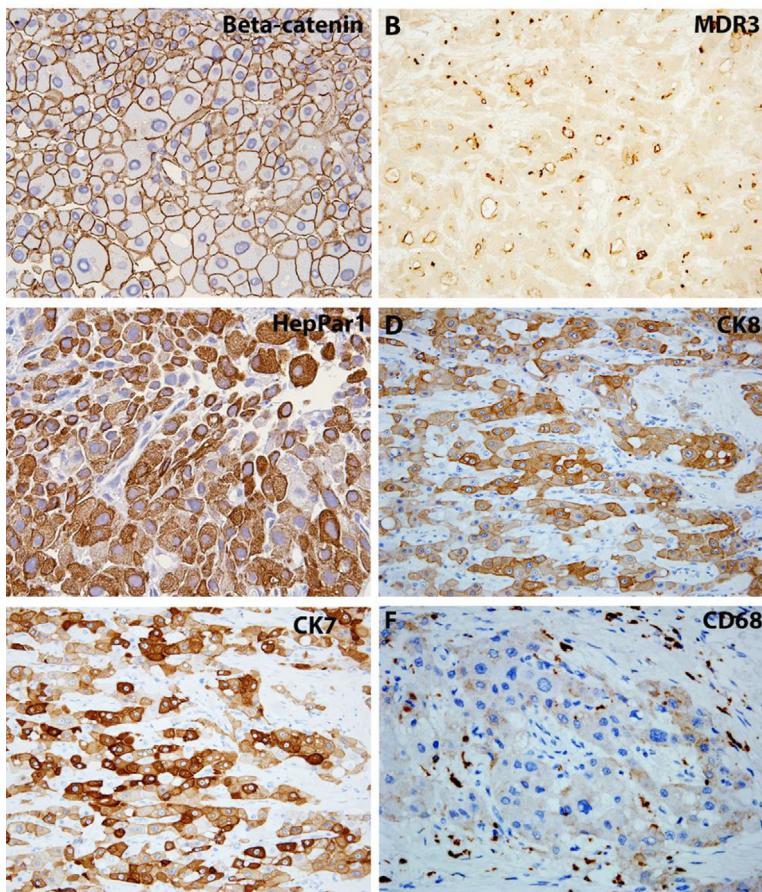
The unique tumor biology of FLC was first described in 2014 by Honeyman et al., with the support of the FLC patient community.<sup>19</sup> They described the presence of the *DNAJB1-PRKACA* fusion in all available cases ( $n = 15$ ) of FLC, and not in adjacent hepatocytes. The fusion connects the *DNAJB1* and *PRKACA* genes, both on chromosome 19 (Fig 5), following an intergenic deletion of ~400 kilobases. Given the relatively small size of the deletion, it was not previously identifiable using conventional cytogenetic techniques, and was discov-



**Fig. 2.** By light microscopy, nests and cords of polygonal, oncocytic tumor cells are surrounded by characteristic stacks of lamellar collagen. (B) Mature collagen is bright blue on the Masson trichrome stain. Tumor cells are arranged in sheets. (D) Glandular or pseudoacinar growth of the tumor is observed. (E) Characteristic well-defined pale gray bodies distending the cytoplasm of tumor cells are numerous (arrowheads). (F) Eosinophilic hyaline cytoplasmic globules are indicated by arrowheads. (G) Nuclear cytoplasmic pseudoinclusions are often observed in tumor cells (arrowheads).

ered using RNA sequencing. Since the initial report, other groups have reinforced that the *DNAJB1-PRKACA* fusion is the key driver of FLC oncogenesis.<sup>34,37,38</sup> While initially thought to be unique to FLC, *DNAJB1-PRKACA* fusions have been recently described in pancreaticobiliary neoplasms.<sup>20</sup>

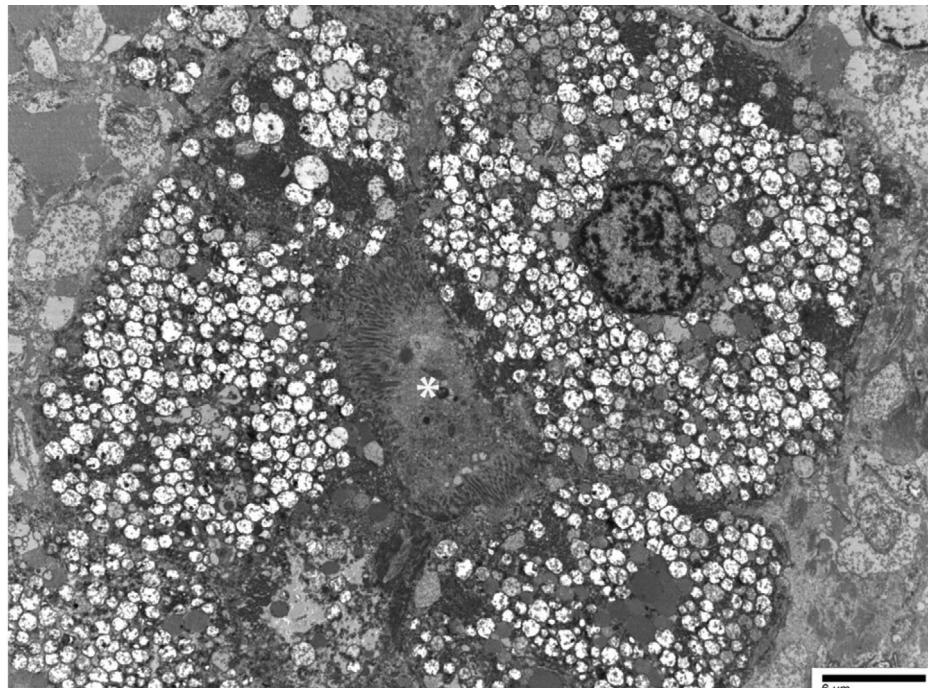
*DNAJB1* encodes a member of the DnaJ or Hsp40 (heat shock protein 40 kD) family of proteins. It acts as a molecular chaperone that stimulates the ATPase activity of Hsp70 heat-shock proteins in order to promote protein folding and prevent misfolded protein aggregation.<sup>39</sup> *PRKACA* encodes one of the catalytic subunits of protein kinase A. cAMP-dependent phosphorylation of proteins by protein kinase A is important to many cellular processes, including differentiation, proliferation, and apoptosis. Constitutive activation of *PRKACA* caused either by somatic mutations, or genomic duplications of regions that include this gene, have been associated with hyperplasias and adenomas of the adrenal cortex and are linked to corticotropin-independent Cushing's syndrome.<sup>40</sup> The in-frame chimeric protein product of the *DNAJB1-PRKACA* fusion connects exon 1 of *DNAJB1* to exons 2–10 of *PRKACA*, maintaining the N-terminal of the DnaJ heat-shock protein and most of the kinase domain of *PRKACA*.<sup>19,41,42</sup> *DNAJB1-PRKACA* fusions can be identified by targeted RNA fusion panel sequencing or by *PRKACA* break apart FISH at the time of diagnosis.<sup>20,43</sup>



**Fig. 3.** Immunohistochemistry Negative nuclear b-catenin expression, (B) Canalicular MDR3, Diffuse, strong cytoplasmic HepPar1, (D) Hepatocytic marker CK8, Biliary marker CK7, and (F) Cytoplasmic CD68.

CRISPR-Cas9 models demonstrate that expression of the *DNAJB1-PRKACA* fusion gene can induce tumor formation in hepatocytes.<sup>44,45</sup> In an animal model, the *DNAJB1-PRKACA* fusion introduced into hepatocytes induces hepatomegaly, increased hepatocyte size, and an innate immune inflammatory response.<sup>46</sup> Notably, overexpression of *PRKACA* alone is not sufficient for oncogenic transformation, supporting that the presence of the DnaJ domain supplied by *DNAJB1* is critical.<sup>45</sup> An alternative related genetic driver of FLC is *PRKAR1A*, which encodes a regulatory subunit of protein kinase A. Germline alterations of *PRKAR1A* are associated with Carney complex, and FLCs without *DNAJB1-PRKACA* fusions have been rarely reported in affected patients.<sup>47</sup> Downstream targets of the *DNAJB1-PRKACA* hybrid protein include miR-375 and YAP1.<sup>48,49</sup> *DNAJB1-PRKACA* may also interact with the Wnt signaling pathway, which is known to be important in the oncogenesis of other hepatocellular tumors.<sup>45</sup>

FLCs do not harbor the genetic alterations typically associated with other pediatric and adult hepatocellular tumors including hepatoblastomas and conventional hepatocellular carcinomas supporting the assertion that these tumors represent a distinct biologic and diagnostic entity.<sup>37,38,50</sup>



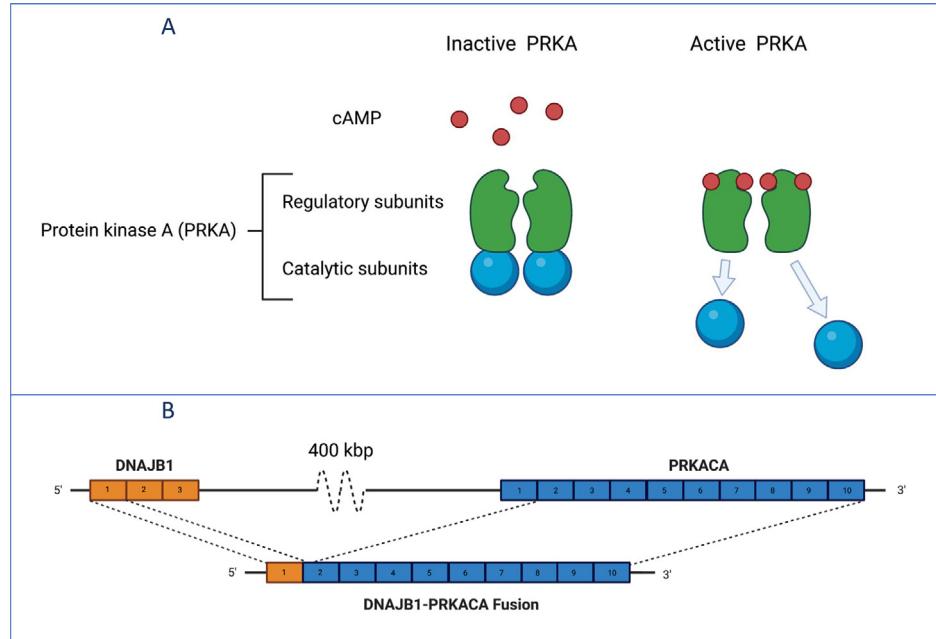
**Fig. 4.** Electron microscopy. A group of tumor cells packed with numerous mitochondria surround a central canalicular structure (\*) with surface, well-developed microvilli.

## Local control

### Surgery

Complete surgical resection of FLC traditionally provides the only chance at cure, with only few exceptions of an extraordinary response to systemic therapy. Surgically resectable tumors are those in which all gross tumor can be removed with tumor-free margins while maintaining sufficient remnant liver mass to support adequate hepatic function for the body. Median tumor diameter is commonly reported to be around 10–12 cm and vascular invasion is present in 20%–30% of cases.<sup>51,52</sup> FLC generally presents as advanced disease with regional lymph node involvement in 30%–50% and distant metastasis in 30–40% of patients.<sup>51,53</sup> The majority of the current surgical literature on FLC is based on the adult population, however, the findings are likely applicable to the pediatric population. A study using the Surveillance, Epidemiology, and End Result (SEER) database from 1973 to 2011 identified 62 pediatric patients with FLC.<sup>53</sup> In this cohort, the extent of disease at presentation was localized in 28%, regional in 39%, and distant in 33%. The advanced pattern of disease presentation of FLC creates significant surgical challenges. Therefore, determination of the presence of extrahepatic disease with cross-sectional imaging (CT, MRI) is critical in the overall surgical decision-making and approach.

Unifocal tumors confined to the liver should be resected in a standard fashion with the aim of obtaining an R0 resection. Patients with involvement of regional or distant lymph nodes may benefit from lymph node dissection since an aggressive approach to decrease overall tumor burden may have survival benefit.<sup>54</sup> In several series, despite an aggressive surgical approach, a high rate of tumor recurrence has been reported at 50%–100%.<sup>51,55–57</sup> Poor five-year survival rates following surgery (ranging from 10%–60%) correlate strongly with the presence of extrahepatic dis-



**Fig. 5.** (A) The protein kinase A (PKA) protein is composed of 2 regulatory subunits (encoded by genes PRKACA, PRKACB and PRKACG), and two catalytic subunits (subunit type I is encoded by genes PRKAR1A and PRKAR1B, subunit type II is encoded by genes PRKAR2A and PRKA2B). When activated by cyclic adenosine monophosphate (cAMP), the catalytic subunits of PKA separate, free to phosphorylate downstream targets. (B) The key oncogenic driver of fibromamellar carcinoma (FLC) is the fusion of two genes on chr19, DNAJB1 and PRKACA. The fusion product connects exon 1 of DNAJB1, which encodes the N-terminal of the Dnaj heat-shock domain to exons 2-10 of PRKACA, which encode most of the kinase domain and the C-terminus. Expression of the chimeric DNAJB1-PRKACA protein product induces tumor formation in functional studies. FLC is also rarely associated with alterations in the PRKAR1A gene (not pictured). Images created with biorender image software.

ease.<sup>3,53,58</sup> Due to the indolent nature of FLC in some patients, surgical resection of recurrent disease may provide some benefit and extend overall survival.<sup>59</sup>

The decision to resect recurrent disease should be based on technical feasibility with an acceptable surgical risk-to-benefit ratio. Common sites of recurrence include liver, lung, lymph nodes, and peritoneal surfaces. Several studies on the surgical outcomes for FLC have reported on resection of recurrent disease in 18–61% of patients.<sup>11,52,56</sup> Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) has yielded a complete response in one patient case report (follow-up 1 year).<sup>60</sup>

Patients with unresectable primary tumors may be considered for total hepatectomy and liver transplantation in the absence of extra-hepatic disease. Evaluation at a transplant center is necessary to determine appropriate candidacy of the individual for liver transplantation. An analysis using the United Network for Organ Sharing database between 1988 and 2013, reviewed 63 patients who underwent liver transplantation for FLC at a mean age of 30 years and found, in this cohort, a 1-, 3-, and 5-year overall survival of 96%, 80%, and 48%, respectively.<sup>61</sup> Multi-visceral transplantation (liver, stomach, pancreas, small bowel, spleen) for FLC in the setting of direct tumor extension into the porto-mesenteric vasculature has been reported with satisfactory long-term survival and may be considered in select patients.<sup>62</sup>

In summary, the role of surgery as intent-for-cure is critical in patients with resectable disease, though likely non-curative in patients with extrahepatic disease. However, resection of extrahepatic disease at the time of initial presentation as well as resection of recurrent disease ap-

pear to provide long-term benefit. Due to the indolent nature of FLC, long-term surgical follow-up with surveillance scans are important to monitor for recurrent disease and resection when appropriate.

### *Radiotherapy*

If the primary FLC is not resectable and the patient is not a transplant candidate, alternative treatments can be considered. One such approach employed regularly in adults is liver-directed radiotherapy. Radiotherapeutic approaches include stereotactic body radiotherapy or SBRT. SBRT has been shown to be a safe, well-tolerated and effective for the treatment of hepatocellular malignancies.<sup>63</sup>

Liver-directed RT, including SBRT, depends on accurate target identification, precise and reproducible patient immobilization, and assessment of target and organ motion. Fiducial markers are placed to provide proper target localization and ensure accurate treatment delivery. SBRT has shown efficacy as a local control measure for small inoperable hepatocellular carcinomas.<sup>64</sup> SBRT can be delivered safely even after previous liver-directed therapies. Additionally, other liver therapies can be given following treatment with SBRT. In an adult experience, although 32% of patients experienced grade 3 toxicities, these changes were mainly transient with minimal clinical impact.<sup>64</sup> Typically doses of 24-60 Gy in 3 to 5 fractions are administered. Literature specific to radiotherapy aimed at metastatic sites of FLC is limited, however, case reports have demonstrated response.<sup>59,65</sup>

### *Interventional Radiology*

The use of interventional oncologic (IO) procedures such as transarterial chemoembolization or percutaneous thermal ablation are slowly gaining traction for the management of pediatric liver cancers. As surgical local control approaches are not always an option for large FLC tumors at the time of diagnosis, IO procedures can be entertained either as a definitive local control or a bridge to surgical resection.

*Transcatheter arterial chemoembolization (TACE)* can increase intra-tumoral concentration of chemotherapeutic medications by 10-25-fold with the embolization aspect increasing the dwell time of the medication inside the target tissue while reducing the amount of drug entering the systemic circulation. TACE is performed by carefully selecting the feeding arteries to the tumor and injecting an emulsion of the chemotherapeutic with an oil-based contrast medium such as ethiodized oil (conventional TACE) followed by embolization. Alternatively, chemotherapy impregnated drug-eluting micro beads (DEB-TACE) can be injected for the same effect. Treatment of a solitary FLC patient with TACE was included in a recent case series of 8 patients (4-17 years) with unresectable histologically proven HCC. While there was change in tumor volume reported for the entire cohort of patients, the FLC patient's tumor did not change in size nor did the patient achieve a long-term survival.<sup>66</sup>

*Trans arterial radio embolization (TARE)* involves selective catheter directed implantation of yttrium-90 (<sup>90</sup>Y) radioisotope, which is  $\beta$  radiation (0.97mEv)-emitting, directly into the tumor-feeding arteries by means of glass or resin microspheres. This provides targeted brachytherapy without the systemic side effects of radiation. As noted above, FLC has been described to be radiosensitive<sup>59,65</sup>. This treatment modality could be considered in patients who do not have a chemotherapy-sensitive tumor or when toxicity limits have been reached from previous chemotherapy. Selective internal radiation therapy (SIRT) using Yttrium 90-coated glass spheres injected in the hepatic artery followed by successful resection has also been reported.<sup>67</sup> Hawkins *et al.* treated a 17-year-old FLC patient with TARE who then survived 20 months after the initial treatment.<sup>68,69</sup> An older patient (52-year-old female) with a 9.5-cm FLC, considered unsuitable for surgical resection, underwent TACE followed by TARE with Yttrium-90 to downsize the tu-

mor. The tumor decreased in volume from 350 to 20 cm<sup>3</sup> allowing curative (R0) resection with an extended left hepatectomy and reconstruction of the IVC.<sup>67</sup>

### Percutaneous ablation techniques

Percutaneous thermal ablation techniques such as radiofrequency ablation (RFA) and microwave ablation (MWA) are minimally invasive procedures associated with few complications that can be performed repeatedly for small sites unamenable to surgical resection. These techniques can be paired with either TACE or TARE but lack FLC-specific evidence.

### Portal vein embolization for hepatic hypertrophy

Portal vein embolization for the induction of selective hepatic hypertrophy has been performed as a bridge to surgical resection, particularly in preparation for extreme resections.<sup>70</sup> This approach should be weighed carefully with the technical feasibility of each surgery and the surgical risk-to-benefit ratio.

## Systemic therapies

Prior to the advent of prospective clinical trials designed specifically for patients with FLC, physicians in both pediatric and medical oncology borrowed from chemotherapeutic regimens historically intended for either conventional HCC or, in pediatrics, hepatoblastoma. As small molecule inhibitors emerged on the scene, these agents alone or in combination with conventional chemotherapeutics gained momentum for use. Finally, in the era of immunotherapy, there is some evidence to suggest that the immune environment of FLC tumors can be therapeutically engaged. The following section will scrutinize published evidence for use of systemic agents in FLC as well as detail prospective clinical trials recently conducted or currently underway. Most reports are retrospective in nature and therefore subject to traditional reporting bias. It remains crucial to interpret the efficacy of reported agents in the context in which they were administered (ie, in the neoadjuvant vs adjuvant state) as well as the methodology used to designate disease response (i.e, RECIST vs time to progression, TTP) (Table 1). Given the small numbers of patients treated in each series and the variability in reporting, it is difficult to draw meaningful conclusions from the data or to establish a standard of care. Ongoing prospective clinical trials will serve as a valuable source to guide therapeutic management of these patients going forth.

### Conventional chemotherapeutics

Conventional chemotherapeutics utilized for patients with FLC, both adult and pediatric, have historically been extrapolated from regimens designed for other primary liver tumors. In the adult context, agents used to treat conventional HCC such as 5-FU/oxaliplatin (FOLFOX), gemcitabine/oxaliplatin (GEMOX), or rarely doxorubicin have been trialed in small series of FLC patients.<sup>13,59,71-74</sup> In pediatric patients, the treatment of FLC evolved from the treatment of hepatoblastoma, the most common primary liver tumor affecting children. The Children's Oncology Group and the European Société Internationale d'Oncologie Pédiatrique previously enrolled FLC patients on prospective trials intended to treat hepatoblastoma. Results to these trials demonstrated some efficacy for cisplatin/5-FU/vincristine, cisplatin/doxorubicin (PLADO), and carboplatin/doxorubicin/cisplatin.<sup>12,15</sup> GEMOX has likewise been trialed in pediatric patients with some success.<sup>75</sup> Generally, response rates to any of these combination therapies are reported at 20%-30% or less, are not typically durable, and do not facilitate surgical resection.

### Targeted agents

Small molecule inhibitors have been increasingly studied for conventional HCC alone or in combination with backbone chemotherapeutics and more recently, immunotherapeutics. While sorafenib was initially heralded a success in adult patients with conventional HCC, extending survival for months in comparison to placebo, and the second generation lenvatinib holds

**Table 1**

Published data for systemic therapies trialed in FLC and ongoing prospective trials.

Authors	Journal	Prospective	Regimen	# of patients	Neoadjuvant	Adjuvant	Follow-up	Comments
<b>Standard Chemotherapeutics</b>								
Bower et al. [71]	Clinical Oncol 1996	N	Cis/5FU/Epi	1	Y (n = 1)	Y (n = 1)	Alive (n = 1), 11 months	* Chemo administered pre- and post-surgery.
Katzenstein et al. [12]	Cancer 2003	Y	Cis/Dox vs. C5V	10	Y (n = 5)	Y (n = 10)	Alive (n = 4), median 9 years	* Patients who survived were all upfront surgical CRs. One of the 4 is alive with recurrent disease.
Maniaci et al. [59]	Eur J Surg Oncol 2009	N	Cis/5FU	3		Y (n = 3)	Alive (n = 1), 144 months	* Of these 5 patients, all underwent upfront surgery and received adjuvant chemotherapy. All recurred and only one was salvaged with receipt of more Cis/5FU.
Gras et al. [72]	Case Rep Oncol 2012	N	Cis Dox GEMOX	1 1	Y (n = 1) Y (n = 1)		CR, Alive (n = 1), 5 years	* Alive without surgical resection of disease.
Kaseb et al. [13]	Oncology 2013	N	PIAF	10	Y (n = 8)	Y (n = 2)	1MR, 6SD, 1PD	* Responses reported on patients receiving neoadjuvant therapy.
Weeda et al. [15]	Eur J Cancer 2013	Y	Carbo/Dox/Cis	13	Y (n = 13)	Y (n = 4)	4PR, 6SD, 1PD, 2 not available	* Responses reported on patients receiving neoadjuvant therapy.
Fonseca et al. [73]	World J Gastroint Surg 2014	N	GEMOX	1	Y (n = 1)		Alive (n = 1), 14 months	
O'Neill et al. [75]	Pediatr Blood Cancer 2014	N	GEMOX	14	Y (n = 14)		2PR, 7SD, 5PD	* Responses reported on patients receiving neoadjuvant therapy.
Tanaka et al. [74]	Intern Med 2018	N	FOLFOX	1	Y (n = 1)		1SD	* Responses reported on patients receiving neoadjuvant therapy.
<b>Targeted Agents</b>								
Fakih 2014 [79]	Am J Ther 2014	N	Bevacizumab/ Erlotinib	1	Y (n = 1)		Improved pain	
Abou-Alfa et al. [81]	The Oncologist 2020	Y	ENMD-2076	35	Y (n = 35)		1PR, 20SD, 10PD, 2 other	* Responses reported on patients receiving neoadjuvant therapy.

(continued on next page)

**Table 1 (continued)**

Authors	Journal	Prospective	Regimen	# of patients	Neoadjuvant	Adjuvant	Follow-up	Comments
El Dika et al. [82]	The Oncologist 2020	Y	everolimus, E2 deprivation, both	26	Y (n = 26)		9SD	*Responses reported on patients receiving neoadjuvant therapy. Early evaluation for efficacy, no CR/PR.
<b>Immunotherapeutics</b>								
Patt et al. [83]	JCO 2003	Y	5FU + IFN	8	Y (n = 8)		1CR, 4PR, 1SD, 1PD, 1 minor response	*Responses reported on patients receiving neoadjuvant therapy.
Kaseb et al. [13]	Oncology 2013	N	5FU + IFN	27	Y (n = 25)	Y (n = 2)	2CR, 6 PR, 2MR, 10SD, 5PD	*Responses reported on patients receiving neoadjuvant therapy.
(Patt et al.) Chakrabarti et al. [86]	J Gastr Oncol 2019	N	Xeloda + IFN Nivo	10 2	Y (n = 9) Y (n = 2)	Y (n = 1)	3MR, 3SD, 3PD 1CR (alive, 11 months), 1PD	*Responses reported on patients receiving neoadjuvant therapy.
Lamarca et al. [84]	Eur J Cancer 2020	N	5FU + IFN	8	Unable to assess	Unable to assess	Reported as TTF	
De Toni et al. [87]	Gut 2020	N	Nivo/Ipi	1	Y (n = 1)		1 near CR (Follow-up unknown)	*Responses reported on patients receiving neoadjuvant therapy.
Gottlieb et al. [85]	Oncology 2021	N	5FU/IFN/Nivo	22	Unable to assess	Unable to assess	Reported as PFS	
Al Zahrani et al. [80]	J or Medical Case Reports 2021	N	atezolizumab/ bevacizumab	2	Y (n = 2)		2PD	*Responses reported on patients receiving neoadjuvant therapy.
<b>Current open trials</b>								
Trial		ClinicalTrials.gov	Agents					
COG AHEP1531	NCT04478292	Y	Upfront resected: PLADO					
Dana-Farber Cancer Institute	NCT04134559	Y	Upfront unresectable: PLADO+S/Gemox+S Pembrolizumab					
MD Anderson Johns Hopkins	NCT04380545 NCT04248569	Y Y	5FU/IFN/Nivo DNAJB1-PRKACA Fusion Kinase Peptide Vaccine + Nivo/Ipi					

Carbo, carboplatin; capecitabine; PLADO, cisplatin/dox; Cis, cisplatin; CR, complete response; C5V, cisplatin/5FU/vincristine; Dox, doxorubicin; Epi, epirubicin; 5FU, 5-fluorouracil; GEMOX, gemcitabine/oxaliplatin; IFN, recombinant interferon -a-2B; Xeloda; MR, mixed response; PD, progressive disease; PR, partial response; PFS, progression free survival; PIAF, cisplatin/IFN/doxorubicin/5FU; FOLFOX, 5FU/oxaliplatin; S, sorafenib; SD, stable disease; TTP, time to progression.

promise, there are limited published FLC-specific data for either of these agents despite consistent use in the community.<sup>76,77</sup> A pediatric pilot study demonstrated tolerance and partial efficacy of PLADO chemotherapy in concert with sorafenib for conventional pediatric HCC.<sup>78</sup> On the basis of this work, PLADO as adjuvant therapy following upfront resection, or PLADO plus sorafenib alternating with GEMOX plus sorafenib for patients with upfront unresectable disease is now under prospective study in the open, enrolling COG AHEP1531 trial (NCT04478292) for pediatric patients with both conventional HCC and FLC.<sup>78</sup> There are only limited case reports detailing use of anti-angiogenic agents, specifically bevacizumab, which demonstrate limited efficacy.<sup>79,80</sup> There have been two studies conducted in succession studying targeted agents posited specific to FLC: (1) an aurora kinase inhibitor (ENMD-2076) selected given the association of the *DNAJB1-PRKACA* fusion transcript with overexpression of aurora kinase A (AURKA), and (2) an mTor inhibitor (everolimus), estrogen deprivation therapy, or the combination given overexpression of mTor and aromatase in FLC tumors.<sup>81,82</sup> Unfortunately neither trial yielded substantive response. A third trial studying neratinib (an EGFR inhibitor) for a broad list of indications opened an FLC-specific arm; enrollments on this arm were prematurely terminated.

### Immunotherapeutics

Early evidence that engagement of the immune system may be therapeutic for FLC came from prospective pilot data suggesting a single, robust response for the use of recombinant interferon alpha 2b-like protein and 5-fluorouracil.<sup>13,83,84</sup> A follow-up retrospective article confirmed this success but there has been little published on the combination in the last decade.<sup>13</sup> These agents were recently revisited in a retrospective report describing use of interferon alpha, 5-fluorouracil and nivolumab.<sup>13</sup> There is not convincing evidence in this report to suggest that the addition of nivolumab adds benefit to the two-drug combination.<sup>85</sup> A recently launched trial seeks prospectively to study the safety and efficacy of triple therapy in FLC patients (NCT04380545). There is parallel interest in the study of checkpoint inhibition for the treatment of FLC patients. Limited adult and pediatric pilot data has prompted an open and enrolling trial to assess the safety and efficacy of single-agent pembrolizumab in relapsed or refractory HCC in patients under 30 years of age, FLC included, allowing concomitant radiotherapy or interventional radiology procedures to study a synergistic abscopal effect (NCT04134559).<sup>86</sup> The combination of nivolumab and ipilimumab has demonstrated promise in a solitary case report.<sup>41</sup> Finally, a novel vaccine trial is underway targeting the *DNAJB1-PRKACA* fusion kinase in combination with nivolumab and ipilimumab in patients with unresectable or metastatic FLC (NCT04248569). Each of these trials will include correlative studies assessing patient immune response and changes to the tumor immune environment over the course of therapy.

### Future

To conclude, FLC is a rare entity, unique from conventional HCC, that warrants dedicated trials interrogating biologic or immune regulatory pathways unique to this tumor. While conventional chemotherapeutics have been disappointing in the past, it is plausible that use of a chemotherapeutic backbone in combination with novel agents will repurpose traditional agents to yield improved outcomes. The medical community, at present, remains fragmented in its approach to the treatment of this vulnerable patient population. However, a recent surge in data scrutiny and preclinical and translational endeavors geared towards understanding tumor biology, *in vivo* modeling, and the tumor microenvironment lends promise to forthcoming collaborative endeavors dedicated to the identification of more efficacious therapies. The treatment of FLC requires seamless multidisciplinary care with providers from each of the above-described disciplines well versed in FLC as well as an *a priori*, well-defined treatment plan balancing risk and relying upon existing data or enrollment on open clinical trials. The academic community must prioritize the study of reliable surgical endpoints and definitions of "success," must design future trials aimed at efficient study of novel therapies for both pediatric patients (>12 years

of age) and adults and unite to study FLC prospectively assuring the collection of reliable data and meaningful conclusions. We can and must capitalize on a growing momentum specifically geared towards FLC-related discoveries and dedicated to improving outcomes for this difficult-to-treat population.

## References

- El-Serag HB, Davila JA. Is fibrolamellar carcinoma different from hepatocellular carcinoma? A US population-based study. *Hepatology*. 2004;39:798–803.
- Eggert T, McGlynn KA, Duffy A, et al. Epidemiology of fibrolamellar hepatocellular carcinoma in the USA, 2000–10. *Gut*. 2013;62:1667–1668.
- Eggert T, McGlynn KA, Duffy A, et al. Fibrolamellar hepatocellular carcinoma in the USA, 2000–2010: a detailed report on frequency, treatment and outcome based on the surveillance, epidemiology, and end results database. *United European Gastroenterol J*. 2013;1:351–357.
- Agarwal VR, Takayama K, Van Wyk JJ, et al. Molecular basis of severe gynecomastia associated with aromatase expression in a fibrolamellar hepatocellular carcinoma. *J Clin Endocrinol Metab*. 1998;83:1797–1800.
- McCloskey JJ, Germain-Lee EL, Perman JA, et al. Gynecomastia as a presenting sign of fibrolamellar carcinoma of the liver. *Pediatrics*. 1988;82:379–382.
- Lee JS, Jin HY, Ko JM, et al. Hyperammonemic encephalopathy mimicking ornithine transcarbamylase deficiency in fibrolamellar hepatocellular carcinoma: successful treatment with continuous venovenous hemofiltration and ammonia scavengers. *Cancer Res Treat*. 2021;53:283–288.
- Bartlett AL, Leslie ND, Gupta A, et al. Acquired ornithine transcarbamylase deficiency in pediatric and adolescent patients with fibrolamellar hepatocellular carcinoma. *Pediatr Blood Cancer*. 2018;65:e27392.
- Surjan RC, Dos Santos ES, Basseres T, et al. A proposed physiopathological pathway to hyperammonemic encephalopathy in a non-cirrhotic patient with fibrolamellar hepatocellular carcinoma without ornithine transcarbamylase (OTC) mutation. *Am J Case Rep*. 2017;18:234–241.
- Darcy DG, Malek MM, Kobos R, et al. Prognostic factors in fibrolamellar hepatocellular carcinoma in young people. *J Pediatr Surg*. 2015;50:153–156.
- Hammond WJ, Lazar G, Saltsman JA, et al. Intracranial metastasis in fibrolamellar hepatocellular carcinoma. *Pediatr Blood Cancer*. 2018;65.
- Stipa F, Yoon SS, Liu KH, et al. Outcome of patients with fibrolamellar hepatocellular carcinoma. *Cancer*. 2006;106:1331–1338.
- Katzenstein HM, Kralio MD, Malogolowkin MH, et al. Fibrolamellar hepatocellular carcinoma in children and adolescents. *Cancer*. 2003;97:2006–2012.
- Kaseb AO, Shama M, Sahin IH, et al. Prognostic indicators and treatment outcome in 94 cases of fibrolamellar hepatocellular carcinoma. *Oncology*. 2013;85:197–203.
- Katzenstein HM, Kralio MD, Malogolowkin MH, et al. Hepatocellular carcinoma in children and adolescents: results from the Pediatric Oncology Group and the Children's Cancer Group intergroup study. *J Clin Oncol*. 2002;20:2789–2797.
- Weeda VB, Murawski M, McCabe AJ, et al. Fibrolamellar variant of hepatocellular carcinoma does not have a better survival than conventional hepatocellular carcinoma—results and treatment recommendations from the Childhood Liver Tumour Strategy Group (SIOPEL) experience. *Eur J Cancer*. 2013;49:2698–2704.
- Kanai T, Takabayashi T, Kawano Y, et al. A case of postoperative recurrence of fibrolamellar hepatocellular carcinoma with increased vitamin B12 binding capacity in a young Japanese female. *Jpn J Clin Oncol*. 2004;34:346–351.
- Simonsen K, Rode A, Nicoll A, et al. Vitamin B(1)(2) and its binding proteins in hepatocellular carcinoma and chronic liver diseases. *Scand J Gastroenterol*. 2014;49:1096–1102.
- Riehle KJ, Kenerson HL, Riggle KM, et al. Neurotensin as a source of cyclic AMP and co-mitogen in fibrolamellar hepatocellular carcinoma. *Oncotarget*. 2019;10:5092–5102.
- Honeyman JN, Simon EP, Robine N, et al. Detection of a recurrent DNAJB1-PRKACA chimeric transcript in fibrolamellar hepatocellular carcinoma. *Science*. 2014;343:1010–1014.
- Vyas M, Hechtman JF, Zhang Y, et al. DNAJB1-PRKACA fusions occur in oncocytic pancreatic and biliary neoplasms and are not specific for fibrolamellar hepatocellular carcinoma. *Mod Pathol*. 2020;33:648–656.
- Oikawa T, Wauthier E, Dinh TA, et al. Model of fibrolamellar hepatocellular carcinomas reveals striking enrichment in cancer stem cells. *Nat Commun*. 2015;6:8070.
- Peters RL. Pathology of hepatocellular carcinoma. In: O'kuda KPRL, ed. *Hepatocellular carcinoma*. New York: Wiley; 1975:107–168.
- Craig JR, Peters RL, Edmondson HA, et al. Fibrolamellar carcinoma of the liver: a tumor of adolescents and young adults with distinctive clinico-pathologic features. *Cancer*. 1980;46:372–379.
- Farhi DC, Shikes RH, Silverberg SG. Ultrastructure of fibrolamellar oncocytic hepatoma. *Cancer*. 1982;50:702–709.
- Kakar S, Burgart LJ, Batts KP, et al. Clinicopathologic features and survival in fibrolamellar carcinoma: comparison with conventional hepatocellular carcinoma with and without cirrhosis. *Mod Pathol*. 2005;18:1417–1423.
- Altmann HW. Some histological remarks on the fibrolamellar carcinoma of the liver. *Pathol Res Pract*. 1990;186:63–69.
- Vecchio FM, Fabiano A, Ghirlanda G, et al. Fibrolamellar carcinoma of the liver: the malignant counterpart of focal nodular hyperplasia with oncocytic change. *Am J Clin Pathol*. 1984;81:521–526.
- Malouf G, Falissard B, Azoulay D, et al. Is histological diagnosis of primary liver carcinomas with fibrous stroma reproducible among experts? *J Clin Pathol*. 2009;62:519–524.
- Torbenzon M: Fibrolamellar carcinoma: 2012 update. *Scientifica (Cairo)* 2012;743790, 2012

30. Van Eyken P, Sciot R, Brock P, et al. Abundant expression of cytokeratin 7 in fibrolamellar carcinoma of the liver. *Histopathology*. 1990;17:101–107.
31. Abdul-Al HM, Wang G, Makhlof HR, et al. Fibrolamellar hepatocellular carcinoma: an immunohistochemical comparison with conventional hepatocellular carcinoma. *Int J Surg Pathol*. 2010;18:313–318.
32. Ross HM, Daniel HD, Vivekanandan P, et al. Fibrolamellar carcinomas are positive for CD68. *Mod Pathol*. 2011;24:390–395.
33. Ward SC, Huang J, Tickoo SK, et al. Fibrolamellar carcinoma of the liver exhibits immunohistochemical evidence of both hepatocyte and bile duct differentiation. *Mod Pathol*. 2010;23:1180–1190.
34. Graham RP, Jin L, Knutson DL, et al. DNAJB1-PRKACA is specific for fibrolamellar carcinoma. *Mod Pathol*. 2015;28:822–829.
35. Lloreta J, Vadell C, Fabregat X, et al. Fibrolamellar hepatic tumor with neurosecretory features and systemic deposition of AA amyloid. *Ultrastruct Pathol*. 1994;18:287–292.
36. Payne CM, Nagle RB, Papapanou SH, et al. Fibrolamellar carcinoma of liver: a primary malignant oncocytic carcinoid? *Ultrastruct Pathol*. 1986;10:539–552.
37. Cornella H, Alsinet C, Sayols S, et al. Unique genomic profile of fibrolamellar hepatocellular carcinoma. *Gastroenterology*. 2015;148:806–818 e10.
38. Darcy DG, Chiaroni-Clarke R, Murphy JM, et al. The genomic landscape of fibrolamellar hepatocellular carcinoma: whole genome sequencing of ten patients. *Oncotarget*. 2015;6:755–770.
39. Gene N. *DNAJB1 Dnaj Heat Shock Protein Family (Hsp40) Member B1*. NCBI Gene: [Homo sapiens (human)]; 2021.
40. gene N. *PRKACA Protein Kinase cAMP-Activated Catalytic Subunit Alpha*. NCBI Gene: [Homo sapiens (human)]; 2021.
41. Tomasini MD, Wang Y, Karamafrooz A, et al. Conformational Landscape of the PRKACA-DNAJB1 Chimeric Kinase, the Driver for Fibrolamellar Hepatocellular Carcinoma. *Sci Rep*. 2018;8:720. www.uniprot.org.
42. Graham RP, Yeh MM, Lam-Himlin D, et al. Molecular testing for the clinical diagnosis of fibrolamellar carcinoma. *Mod Pathol*. 2018;31:141–149.
43. Engelholm LH, Riaz A, Serra D, et al. CRISPR/Cas9 engineering of adult mouse liver demonstrates that the Dnajb1-Prkaca gene fusion is sufficient to induce tumors resembling fibrolamellar hepatocellular carcinoma. *Gastroenterology*. 2017;153:1–21 e10.
44. Kastenhuber ER, Lalazar G, Houlihan SL, et al. DNAJB1-PRKACA fusion kinase interacts with beta-catenin and the liver regenerative response to drive fibrolamellar hepatocellular carcinoma. *Proc Natl Acad Sci U S A*. 2017;114:13076–13084.
45. de Oliveira S, Houseright RA, Korte BG, et al. Dnaj-PKAc fusion induces liver inflammation in a zebrafish model of fibrolamellar carcinoma. *Dis Model Mech*. 2020;13.
46. Graham RP, Lackner C, Terracciano L, et al. Fibrolamellar carcinoma in the Carney complex: PRKAR1A loss instead of the classic DNAJB1-PRKACA fusion. *Hepatology*. 2018;68:1441–1447.
47. Dinh TA, Jewell ML, Kanke M, et al. MicroRNA-375 suppresses the growth and invasion of fibrolamellar carcinoma. *Cell Mol Gastroenterol Hepatol*. 2019;7:803–817.
48. Jewell ML, Gibson JR, Guy CD, et al. Single-Cell RNA sequencing identifies yes-associated protein 1-dependent hepatic mesothelial progenitors in fibrolamellar carcinoma. *Am J Pathol*. 2020;190:93–107.
49. Xu L, Hazard FK, Zmoos AF, et al. Genomic analysis of fibrolamellar hepatocellular carcinoma. *Hum Mol Genet*. 2015;24:50–63.
50. Ang CS, Kelley RK, Choti MA, et al. Clinicopathologic characteristics and survival outcomes of patients with fibrolamellar carcinoma: data from the fibrolamellar carcinoma consortium. *Gastrointest Cancer Res*. 2013;6:3–9.
51. Wahab MA, El Hanafy E, El Nakeeb A, et al. Clinicopathological features and surgical outcome of patients with fibrolamellar hepatocellular carcinoma (experience with 22 patients over a 15-year period). *World J Gastrointest Surg*. 2017;9:61–67.
52. Lau CS, Mahendaraj K, Chamberlain RS. Hepatocellular carcinoma in the pediatric population: a population based clinical outcomes study involving 257 patients from the surveillance, epidemiology, and end result (SEER) database (1973–2011). *HPB Surg*. 2015 2015.
53. McAtee JP, Goldin AB, Healey PJ, et al. Surgical treatment of primary liver tumors in children: outcomes analysis of resection and transplantation in the SEER database. *Pediatr Transplant*. 2013;17:744–750.
54. Pinna AD, Iwatsuki S, Lee RG, et al. Treatment of fibrolamellar hepatoma with subtotal hepatectomy or transplantation. *Hepatology*. 1997;26:877–883.
55. Hemming AW, Langer B, Sheiner P, et al. Aggressive surgical management of fibrolamellar hepatocellular carcinoma. *J Gastrointest Surg*. 1997;1:342–346.
56. El-Gazzaz G, Wong W, El-Hadary MK, et al. Outcome of liver resection and transplantation for fibrolamellar hepatocellular carcinoma. *Transpl Int*. 2000;13:S406–S409 Suppl 1.
57. Allan BJ, Wang B, Davis JS, et al. A review of 218 pediatric cases of hepatocellular carcinoma. *J Pediatr Surg*. 2014;49:166–171 discussion 171.
58. Maniaci V, Davidson BR, Rolles K, et al. Fibrolamellar hepatocellular carcinoma: prolonged survival with multimodality therapy. *Eur J Surg Oncol*. 2009;35:617–621.
59. Kyziridis D, Kalakonas A, Zarambouka K, et al. cytoreductive surgery and HIPEC for recurrent fibrolamellar hepatocellular carcinoma with peritoneal carcinomatosis. *J Gastrointest Cancer*. 2020;51:300–303.
60. Atienza LG, Berger J, Mei X, et al. Liver transplantation for fibrolamellar hepatocellular carcinoma: a national perspective. *J Surg Oncol*. 2017;115:319–323.
61. Lee E, Hodgkinson N, Fawaz R, et al. Multivisceral transplantation for abdominal tumors in children: a single center experience and review of the literature. *Pediatr Transplant*. 2017;21.
62. Keane FK, Wo JY, Zhu AX, et al. Liver-directed radiotherapy for hepatocellular carcinoma. *Liver Cancer*. 2016;5:198–209.
63. Yeung R, Beaton L, Rackley T, et al. Stereotactic body radiotherapy for small unresectable hepatocellular carcinomas. *Clin Oncol (R Coll Radiol)*. 2019;31:365–373.

64. GP J, AC J, RO K. Radiotherapy for metastatic fibrolamellar hepatocellular carcinoma. *Rare Tumors.* 2013;5:e28.
65. Weiss KE, Sze DY, Rangaswami AA, et al. Transarterial chemoembolization in children to treat unresectable hepatocellular carcinoma. *Pediatr Transplant.* 2018;22:e13187.
66. Mafeld S, French J, Tiniakos D, et al. Fibrolamellar hepatocellular carcinoma: treatment with yttrium-90 and subsequent surgical resection. *Cardiovasc Interv Radiol.* 2018;41:816–820.
67. Hawkins CM, Kukreja K, Geller JL, et al. Radioembolisation for treatment of pediatric hepatocellular carcinoma. *Pediatr Radiol.* 2013;43:876–881.
68. Aguado A, Ristagno R, Towbin AJ, et al. Transarterial radioembolization with yttrium-90 of unresectable primary hepatic malignancy in children. *Pediatr Blood Cancer.* 2019;66:e27510.
69. Li D, Madoff DC. Portal vein embolization for induction of selective hepatic hypertrophy prior to major hepatectomy: rationale, techniques, outcomes and future directions. *Cancer Biol Med.* 2016;13:426–442.
70. Bower M, Newlands ES, Habib N. Fibrolamellar hepatocellular carcinoma responsive to platinum-based combination chemotherapy. *Clin Oncol (R Coll Radiol).* 1996;8:331–333.
71. Gras P, Truant S, Boige V, et al. Prolonged complete response after GEMOX chemotherapy in a patient with advanced fibrolamellar hepatocellular carcinoma. *Case Rep Oncol.* 2012;5:169–172.
72. Fonseca GM, Varella AD, Coelho FF, et al. Downstaging and resection after neoadjuvant therapy for fibrolamellar hepatocellular carcinoma. *World J Gastrointest Surg.* 2014;6:107–111.
73. Tanaka H, Hijioka S, Iwaya H, et al. Fibrolamellar hepatocellular carcinoma with multiple lung metastases treated with multidisciplinary therapy. *Intern Med.* 2018;57:3537–3543.
74. O'Neill AF MM, Brugieres L, Casanova M, et al. Gemcitabine and oxaliplatin for the treatment of pediatric patients with hepatocellular carcinoma. *Pediatr Blood Cancer.* 2014;61:24.
75. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359:378–390.
76. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet.* 2018;391:1163–1173.
77. Schmid I, Haberle B, Albert MH, et al. Sorafenib and cisplatin/doxorubicin (PLADO) in pediatric hepatocellular carcinoma. *Pediatr Blood Cancer.* 2012;58:539–544.
78. Fakih M. A case of fibrolamellar cancer with a palliative response and minor radiographic regression with erlotinib and bevacizumab combination therapy. *Am J Ther.* 2014;21:e207–e210.
79. Al Zahrahi A, Alfakeeh A. Fibrolamellar hepatocellular carcinoma treated with atezolizumab and bevacizumab: two case reports. *J Med Case Rep.* 2021;15:132.
80. Abou-Alfa GK, Mayer RJ, Venook AP, et al. Phase II Multicenter, Open-Label Study of Oral ENMD-2076 for the Treatment of Patients with Advanced Fibrolamellar Carcinoma. *Oncologist.* 2020;25:e1837–e1845.
81. El Dika I, Mayer RJ, Venook AP, et al. A Multicenter Randomized Three-Arm Phase II Study of (1) Everolimus, (2) Estrogen Deprivation Therapy (EDT) with Leuprolide + Letrozole, and (3) Everolimus + EDT in Patients with Unresectable Fibrolamellar Carcinoma. *Oncologist.* 2020;25:925–e1603.
82. Patt YZ, Hassan MM, Lozano RD, et al. Phase II trial of systemic continuous fluorouracil and subcutaneous recombinant interferon Alfa-2b for treatment of hepatocellular carcinoma. *J Clin Oncol.* 2003;21:421–427.
83. Lamarca A, Frizziero M, Fulton A, et al. Fibrolamellar carcinoma: challenging the challenge. *Eur J Cancer.* 2020;137:144–147.
84. Gottlieb S, O'Grady C, Gliksberg A, et al. Early experiences with triple immunochemotherapy in adolescents and young adults with high-risk fibrolamellar carcinoma. *Oncology.* 2021;1–8.
85. Chakrabarti S, Tella SH, Kommalapati A, et al. Clinicopathological features and outcomes of fibrolamellar hepatocellular carcinoma. *J Gastrointest Oncol.* 2019;10:554–561.
86. De Toni EN, Roessler D. Using dual checkpoint blockade to treat fibrolamellar hepatocellular carcinoma. *Gut.* 2020;69:2056–2058.