Advances in Fibrolamellar Hepatocellular Carcinoma: A Review

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Abstract

Fibrolamellar hepatocellular carcinoma is a rare primary liver tumor that often arises in the absence of cirrhosis or viral hepatitis. Compared with hepatocellular carcinoma, patients are typically younger with less comorbidities. Diagnosis is often multimodal and requires a high level of suspicion, as traditional liver pathology markers, such as serum α fetoprotein and transaminases, are often normal. Overall, patients respond well to surgical resection but recurrences are frequent, and alternative therapies, such as chemotherapy and radiation, are not well studied. Currently, there are no established chemotherapy regimens; there are only limited case reports of select agents, such as 5-fluorouracil with interferon-α and gemcitabine with oxaliplatin, used with varying degrees of success. Because little is known about this rare tumor, the development of serum markers and alternative therapies continues to be a challenge. A major advancement in the understanding of this rare disease is the discovery of a functional chimeric transcript incorporating *DNAJB1* and *PRKACA*. This finding may finally provide the basis for specific diagnostic markers and chemotherapies that patients with this disease have long needed. Here, we present advances in the surgical treatment of fibrolamellar hepatocellular carcinoma, as well as recent data on its tumor biology and pathogenesis.

Keywords
- ► liver tumors
- ► fibrolamellar hepatocellular carcinoma
- ► liver resection

Introduction

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a rare primary liver tumor that was first described by Edmondson in 1956.[1] Microscopically, FL-HCC is characterized by large polygonal, well-differentiated tumor cells with an eosinophilic cytoplasm interspersed with lamellar bands of collagen fibers[2,3] (►Fig. 1). Initially thought to be a variant of hepatocellular carcinoma (HCC), FL-HCC is now considered an entirely different entity: it is associated with fewer chromosomal changes and genomic heterogeneity in comparison to HCC, as well as the absence of mutations in key genes such as p53, and low levels of promoter methylation.[4] It occurs in the absence of underlying cirrhosis or viral hepatitis. Moreover, markers such as liver enzymes and serum α fetoprotein (AFP) that are typically elevated in conventional HCC are within normal limits or only mildly elevated in FL-HCC.[5]

Accounting for less than 1% of all primary liver cancer cases,[6] FL-HCC is seen largely as a pediatric and adolescent disease.[2,7] Recent studies, however, have found two age-specific incidence peaks from 10 to 30 years and 70 to 79 years of age.[8] Incidence rates were found to be homogeneous across racial and ethnic groups, compared with conventional HCC, with male-to-female ratio of 1.7:1 (compared with 3.2:1 in HCC).[8] While FL-HCC is more likely to be diagnosed at advanced stages with larger tumor sizes,[9] patients are more likely to receive potentially curative therapy.[8,10]
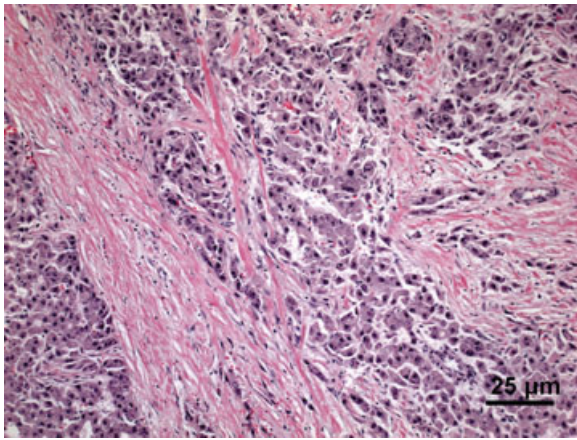
Fig. 1 Collagen bands are seen interspersed between large nests of oncocytic tumor cells in this hematoxylin and eosin stain image.

This strategy may be due in part to the younger age of the patients, as well as the lack of cirrhosis and other comorbidities. The perception that this tumor has an indolent clinical course, and that there is little proven alternative effective therapy, has encouraged an aggressive surgical approach including both resection and transplantation.[4] As treatment approaches for FL-HCC remain largely surgical, this review will focus on the recent advances in surgical treatments and understanding the biology of the disease.

Pathogenesis

From its first description in 1956,[1] FL-HCC and its pathogenesis have yet to be definitively determined. Histologically, FL-HCC tumor cells appear to be hepatocytes and immunohistochemical studies confirm hepatocyte differentiation by staining positive for heppar-1 and glypican-3.[11] FL-HCC tumor cells were also found to have markers of biliary differentiation such as CK19 and EpCAM.[11,12] Recent transcriptional profiling of FL-HCC, however, has questioned its presumed hepatocyte origin. Malouf et al found overexpression of the neuroendocrine genes prohormone convertase 1, neurotensin and calcitonin, suggesting a different origin entirely.[13] Indeed, high aromatase activity and elevated estradiol levels have been noted in case reports,[14] but with limited evidence to the contrary, FL-HCC is still considered to be derived from hepatocytes.

Multiple studies have attempted to explain the pathogenesis of FL-HCC. Sulaiman et al describe a patient presenting with recurrent nonhepatic hyperammonemic encephalopathy, suggesting that FL-HCC can mimic ornithine transcarbamylase deficiency.[15] Riehle et al have studied the role of mammalian target of rapamycin complex 1 (mTORC1) and fibroblast growth factor receptor 1 (FGFR1) signaling in the setting of FL-HCC.[16] mTORC1 activation and FGFR1 overexpression have been found in the subset of FL-HCC studied, implicating a potential role of the mTORC1 pathway in the pathogenesis of the disease.[16] Advances in whole genome sequencing have revealed what may be the closest explanation for the pathogenesis of FL-HCC. In all 15 patient samples, a functional chimera of the first exon of *DNAJB1*, encoding a member of the heat-shock 40 protein family and *PRKACA*, the gene encoding the cAMP-dependent protein kinase A catalytic subunit α, was found in all tumor tissues, and absent in normal tissues.[17] This chimera (►Fig. 2) appears to be responsible for both increased activity and levels of *PRKACA* in tissue (►Fig. 3). Subsequent analysis by other groups show the same chimera in additional FL-HCC samples.[18] Preliminary data suggest that the chimera plays a transformative role,[18] though much remains to be investigated.

Without a clear mechanism of the disease, the development of serum markers for early detection of primary, or even recurrent, FL-HCC is difficult. Nonetheless, studies have shown promising candidates such as vitamin B12, high serum vitamin B12-binding capacity, and neurotensin.[19–21] Elevations in these markers have been described, but not consistently.[5,21] AFP serum elevations, commonly observed in conventional HCC, are not typically seen in FL-HCC.[5,22] Alternatively, FL-HCC has been associated with higher levels of expression of epidermal growth factor receptor (EGFR) compared with conventional HCC.[23] Currently, definitive diagnosis is limited to the tumor's distinct appearance on microscopy, specifically the large nests of oncocytic tumor cells within fibrous lamellar collagen bands (►Fig. 1).

Clinical Presentation, Work-up, and Prognosis

Clinical presentation of FL-HCC is usually nonspecific and may present with abdominal pain, malaise, and weight loss.[4,24] Thus, imaging studies are an integral part of diagnosis. Multimodal imaging is utilized, particularly in the pediatric population, beginning with abdominal ultrasound followed by abdominal magnetic resonance imaging (MRI) or computed tomography (CT) scan. CT and MRI are the preferred methodologies for tumor, nodal, and systemic metastasis (TNM) staging.[25] On imaging, FL-HCC tends to present as a large, heterogeneous enhancing mass (►Figs. 4 and 5) that may contain a central scar and/or calcifications.[24,26,27] The value of positron emission tomography (PET) scan for conventional HCC is limited because the sensitivity of PET imaging is not sufficiently high.[28] However, case reports have described unequivocal tracer uptake in FL-HCC, and further study of its role in assisting diagnosis primary or recurrent FL-HCC may be warranted.[29]

The prognosis for FL-HCC has traditionally been shown to be better than conventional HCC. In a recent Surveillance, Epidemiology and End Results (SEER) study encompassing the largest group of FL-HCC patients in the United States,[8] FL-HCC patients between ages 0 and 39 years presented with larger tumors than patients with conventional HCC of the same ages, but 5-year relative survival rates were higher in patients with FL-HCC (40.3% vs. 25%). Overall 5-year survival rates irrespective of tumor size or age were similarly more favorable for FL-HCC patients compared with conventional
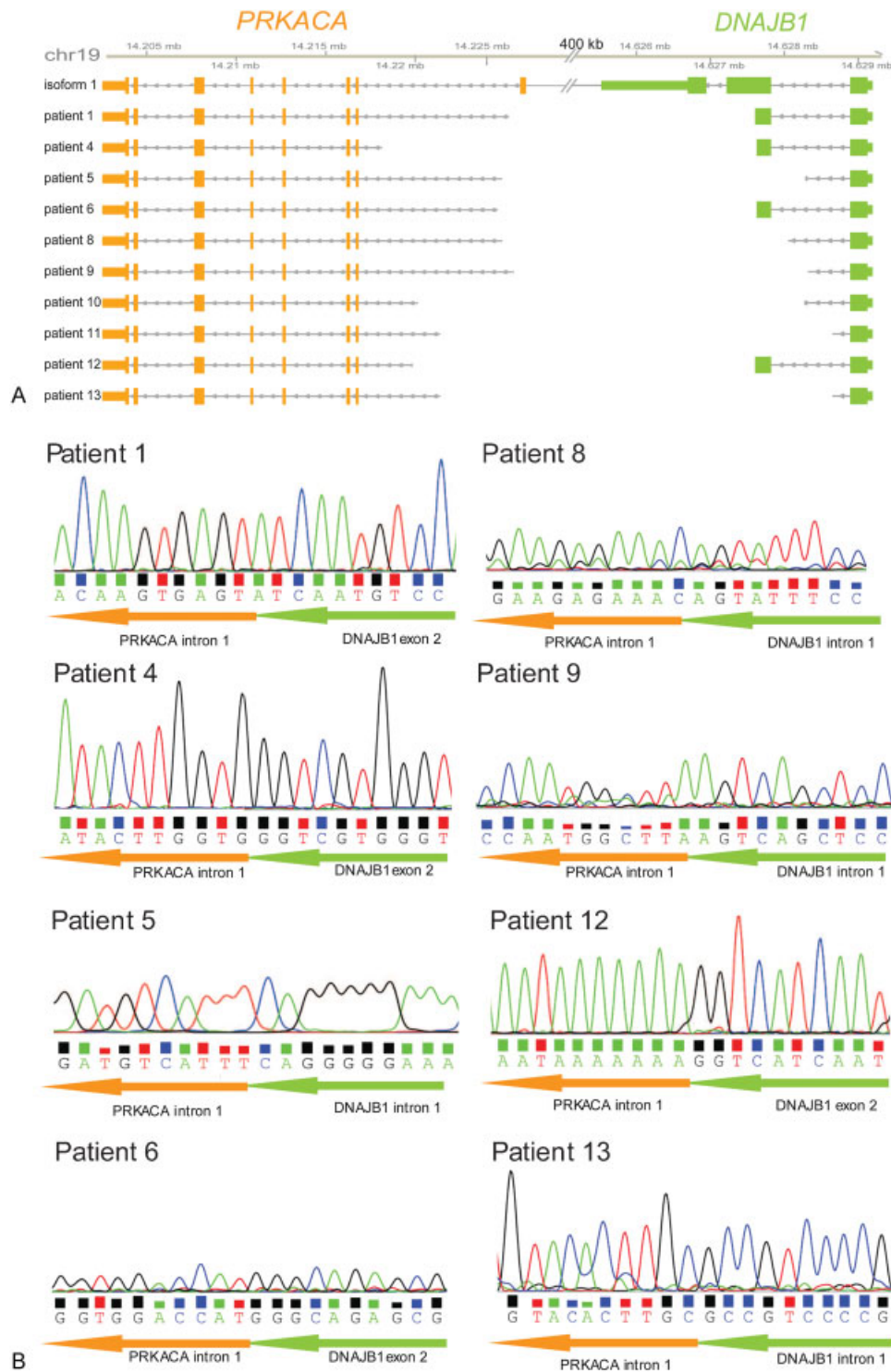
Fig. 2 DNA sequence analysis mapping the size and location of breaks in DNA between *DNAJB1* and *PRKACA* genes to form a DNAJB1–PRKACA chimera.[17] Originally published in: Honeyman JN et al. Detection of a recurrent DNAJB1-PRKACA chimeric transcript in fibrolamellar hepatocellular carcinoma. *Science* 2014; 343:1011. © 2014 American Association for the Advancement of Science. Reprinted with permission.

HCC (33.6% vs. 16.1%).[8] Long-term overall survival between FL-HCC and HCC, however, was found to be similar in two separate studies.[30,31] This discrepancy may be attributable to the inclusion of adult patients in the SEER data, while the studies showing similarity in survival rates were limited to the pediatric and adolescent population. Relative survival rates may be longer in FL-HCC compared with HCC due to late recurrences that are common in FL-HCC.[30] Regardless, poorer outcomes and decreased survival rates have consistently been described in patients with extrahepatic disease, such as positive regional lymph nodes and distant metastatic disease.[32]
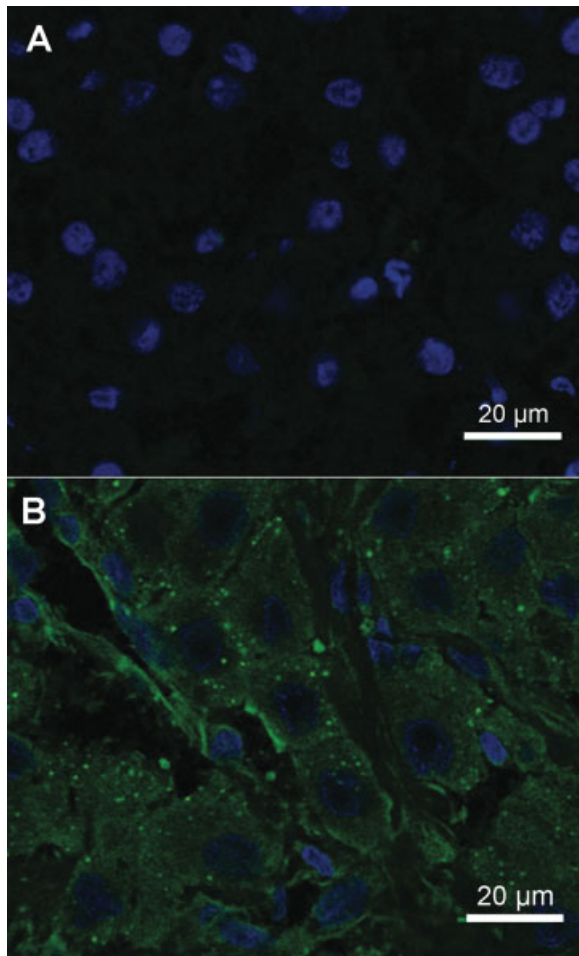
Fig. 3 Comparison of levels of PRKACA (green) in normal tissue (A) and FL-HCC tumor tissue (B) under confocal microscopy (nuclei are stained in blue).[17] Originally published in: Honeyman JN et al. Detection of a recurrent DNAJB1-PRKACA chimeric transcript in fibrolamellar hepatocellular carcinoma. *Science* 2014; 343:1011. © 2014 American Association for the Advancement of Science. Reprinted with permission.

Surgical Treatment

Complete surgical resection remains the cornerstone of the treatment of FL-HCC. While small peripheral lesions may be treated with nonanatomic wedge resections with adequate margins, this may not be feasible as FL-HCC uncommonly presents in this manner. Many cases are diagnosed at advanced stages with larger tumors,[8,9] and a major anatomic resection such as a right hepatectomy is often necessary. The extent of resection is based on a multitude of factors, including tumor location and proximity to vascular and ductal structures. Imaging, in the form of triple-phase CT or abdominal MRI, are imperative for preoperative planning as they provide crucial information on vascular and ductal anatomy. Notably, up to 85% of the liver parenchyma may be removed, as complete regeneration is often seen, even with postoperative chemotherapy.

Following a bilateral subcostal (or a right subcostal for patients with narrow costal margins) incision, the liver is mobilized by division of the right triangular and coronary

Fig. 4 Appearance of FL-HCC on CT scan. A heterogeneous, pedunculated mass is seen arising from the right lobe of the liver.

ligaments to the falciform ligament anteriorly and the inferior vena cava posteriorly. A combination of palpation and intraoperative ultrasound should be performed to identify multifocal disease. Once resectability is confirmed, the hepatoduodenal ligament is isolated with a looped vascular tape for subsequent Pringle maneuver. Vascular structures are controlled, either by extrahepatic vascular control or by hepatic pedicle ligation, prior to parenchymal division. Intraoperative management with anesthesia is key as maintenance of a lower central venous pressure minimizes blood loss during liver parenchymal transection. In rare cases, FL-HCC tumors may be focal lesions isolated to one segment that can be resected using anatomic segmentectomies. Preoperative, as well as intraoperative, imaging will aid in the dissection for control of arterial and portal inflow.

FL-HCC is associated with more favorable outcomes compared with conventional HCC when treated with surgical
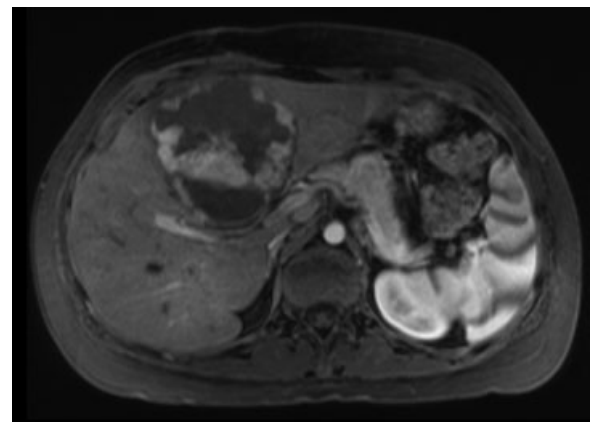
Fig. 5 Appearance of FL-HCC on MRI. This T1-weighted image shows a heterogeneously enhancing mass in segment IV.

resection, with 5-year survival rates ranging from 58 to 82%.[8,33] Resection of larger or even ruptured tumors[34] is attempted more often for FL-HCC than for HCC[8] due to its more favorable response to surgery. In fact, patients with complete resection are twice as likely to survive as those without successful surgical resection.[30] Moreover, recurrence-free survival increases with R0 resection such that recurrence-free survival to 4 years may be predictive of disease-free survival.[22] Recurrences, however, are common, with median recurrence-free survival rates ranging from 20 to 48 months.[22,35] Common sites of recurrence include liver, regional lymph nodes, peritoneum, bones and lungs, with lymph nodes being the most frequent site of metachronous metastatic spread.[36] Resection of these recurrences is thus becoming increasingly important, especially when they recur in the liver.[22] In such cases, an anatomic segmentectomy may be appropriate.

In multiple studies, the presence of extrahepatic disease is a consistent, independent predictor of overall and recurrence-free survival.[20,22,32] In particular, spread to regional lymph nodes is more common in FL-HCC than in conventional HCC. In a study by Mayo et al, the incidence of regional disease among patients with FL-HCC was more than 42.2% compared with 22.1% in conventional HCC.[37] In one study, of 28 FL-HCC patients, 100% 5-year survival was seen in lymph node-negative patients compared with 45% 5-year survival in lymph node-positive patients.[35] Patients undergoing resection for FL-HCC may benefit from concomitant regional lymphadenectomy, as a recent study by the US National Cancer Institute's SEER Program reported superior survival rates in patients who underwent lymphadenectomy compared with those who did not (70% vs. 57%).[38]

Transplantation for the treatment of HCC has long been a subject of debate, and guidelines such as the Milan criteria[39] have been established. Specifically, orthotopic liver transplantation is employed as an alternative treatment when partial hepatectomy is otherwise contraindicated.[40] Given its rare nature, FL-HCC infrequently requires transplantation and, thus, patients are not prioritized among those awaiting transplant.[40] Of those few FL-HCC patients for whom transplantation is considered, the clinician must take into account the high rates of early lymph node metastasis, which may result in recurrence soon after liver transplant.[41]

Nonoperative Management

Various nonoperative modalities have been described as either adjuncts to surgery, or as down-staging mechanisms for patients with locally advanced, or metastatic disease with unresectable tumors. As patients with FL-HCC generally do not have a background history of cirrhosis or liver disease, they are thought to have the ability to tolerate higher doses of chemotherapy compared with conventional HCC patients.[2,3]

As a rare hepatic malignancy, FL-HCC currently has no standardized systemic drug treatments. Case reports and subgroup analyses of studies of liver cancers suggest possible activity for platinum-based agents, fluoropyrimidines and interferon-α (INF-α); however, particular combinations of chemotherapeutic agents are not seen as standardized treatments throughout the literature.[2,42] While there is no overall consensus in the chemotherapeutic management of FL-HCC, many case reports describe the use of gemcitabine/oxaliplatin (GEMOX) or 5-fluorouracil (5-FU) with INF-α and folinic acid/5-FU/oxaliplatin (FOLFOX) with varying degrees of success in patients.[2,42,43] Radiation therapy is not typically used in primary management of FL-HCC, but has been described with recurrent and metastatic disease.[4,27,42] A recent retrospective study has reported the use of intraoperative radiation therapy for distant nodal disease, which also warrants further research.[32] With the new advances toward understanding the pathogenesis of FL-HCC, multi-institutional randomized clinical trials are ongoing, with one examining the role of estrogen suppression and mTOR inhibition and its potential therapeutic effects on FL-HCC (ClinicalTrials.gov Identifier: NCT01642186)*.

Conclusion

Liver cancers are uncommon in children and FL-HCC represents only a fraction of this population. As a rare tumor with limited established adjunctive therapies to surgical resection, further investigation is clearly warranted. Until then, surgery remains the only definitive treatment for this disease. Investigations in the tumor biology of FL-HCC, as well as research in improved methods of diagnosis and response to adjunctive therapies, will hopefully result in the development of effective nonoperative treatments to complement surgical resection.

Conflict of Interest
None.

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* *This clinical trial (ClinicalTrials.gov Identifier: NCT01642186) is sponsored by Memorial Sloan Kettering Cancer Center in collaboration with: The Fibrolamellar Cancer Foundation; Dana-Farber Cancer Institute/Brigham and Women's Cancer Center and Massachusetts General Hospital Cancer Center; Johns Hopkins University; University of California, San Francisco; Abbott Laboratories; and Novartis Pharmaceuticals.*

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