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## **Fibrolamellar Hepatocellular Carcinoma: A rare but unpleasant event**

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### **Abstract**

Fibrolamellar carcinoma (FLC) is a rare variant of hepatocellular carcinoma (HCC), comprising 1%–9% of all HCCs. FLC is a poorly understood malignancy, which seems to be more prevalent in young patients with no underlying liver diseases. The term “fibrolamellar” is derived from thick fibrous collagen bands surrounding the tumor cells. Unlike HCC, cirrhosis and viral hepatitis infection are not predisposing to FLC, and it is not associated with elevations in serum alpha-fetoprotein (AFP). FLC patients often present with vague abdominal pain, nausea, malaise, and weight loss. Most cases present are at an advanced stage at the time of initial diagnosis. However, curative treatment options can still be offered to up to 70% of patients. Surgery (resection/Liver transplantation) is the mainstay of treatment and the only potentially curative option. FLCs have been less chemo-responsive than the conventional HCC, however, in advanced cases, multimodality treatments can be effective. Recent advances in molecular studies of FLC have found a unique DNAJB1-PRKACA fusion transcript in most of the cases studied. The review aims to describe clinical characteristics, diagnostic methods, and therapeutic modalities for this rare tumor to raise awareness among clinicians and surgeons.

**Key Words:** Fibrolamellar carcinoma; Hepatocellular carcinoma; Hepatitis; Cirrhosis.

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**Core Tip:** Fibrolamellar carcinoma (FLC) is a rare liver cancer that displays unique features in behavior and clinical findings from conventional hepatocellular carcinoma (HCC). No certain underlying trigger is detected in FLC. Alpha-fetoprotein levels are normal, unlike in traditional HCC. Surgery (resection/Liver transplantation) is the current mainstay of treatment and remains the only curative option. FLCs have been less chemo-responsive than the conventional HCC. Controlled trials evaluating checkpoint inhibitors in FLC are lacking. In this review, we collect and summarize current evidence and clinical experience of conversion therapy, highlight remaining problems and challenges for further research.

## **INTRODUCTION**

Fibrolamellar carcinoma (FLC) is an uncommon liver cancer with behaviour and clinical findings that vary significantly from ordinary hepatocellular carcinoma (HCC)<sup>[1]</sup>. It comprises 1%–9% of all HCCs, according to the Surveillance, Epidemiology, and End Results SEER database<sup>[2]</sup>. Edmonson first described FLC in 1956 as an adult type of liver cancer in a 14-year-old female without a background of liver affection<sup>[3]</sup>. FLC receives its name from the histologically distinct intra tumoral lamellar collagen bands observed between large polygonal cells with abundant eosinophilic cytoplasm, large vesiculated nuclei, and large nucleoli<sup>[4]</sup>. The majority of FLC patients are in their second or third decade<sup>[5, 6]</sup>. It often affects patients between (10–35 years of age) with no primary liver disease<sup>[6, 7]</sup>. No certain underlying trigger is detected in FLC. Less than 10% of patients with FLC have cirrhotic liver morphology<sup>[8]</sup>. Unlike HCC, cirrhosis and viral hepatitis infection are not predisposing to FLC, and it is typically not associated with elevations in serum alpha-fetoprotein (AFP)<sup>[9, 10]</sup>. More than half of patients with FLC are Caucasians, while more than 80% of HCC patients are Caucasians<sup>[6]</sup>. Tumour markers are increased in less than 10% of affected patient and have no role in the assessment or diagnosis of FLC. <sup>[11, 12]</sup>.

Most cases with FLC cases are advanced at the time of diagnosis; however, up to 70% of patients may still be treated with curative therapy. The current cornerstone therapy (resection/liver transplantation) is still the sole possibly curative approach<sup>[13]</sup>. Chemotherapy was utilized as a complimentary treatment before and after postoperative resection. However, because of the low frequency of FLC, no randomized controlled trial (RCT) has explained the most successful regimens<sup>[14]</sup>. Still, no neo-adjuvant/adjuvant systemic therapies have been reported to improve survival in patients with resected FLC<sup>[14]</sup>. Therefore, chemotherapeutic agents like gemcitabine, cisplatin, 5-fluorouracil, interferon, and oxaliplatin have been tried and have demonstrated various degrees of response <sup>[15, 16]</sup>.

## **EPIDEMIOLOGICAL FACTS**

Due to the rarity of this tumor, exact estimates of its occurrence across nations are difficult to come by. FLCs account for less than 1% of primary liver tumors in the United States and 5.8% of liver tumors in Mexico<sup>[17]</sup>. Incidence rates, on the other hand, are very consistent over the world<sup>[6, 18]</sup>. FLC affects a younger group, with a median age of 21 years, compared to HCC, affecting people between the ages of 14 and 33. The vast majority of cases (64%) are discovered before the age of 40<sup>[6]</sup>. A bimodal age distribution has been described, with incidence peaks between the ages of 10 and 30, and a second peak between the ages of 60 and 69 years<sup>[20]</sup>. Most research show that both sexes are equally affected, however a few have shown a slight male predominance (Male: Female = 1.7:1)<sup>[6, 18]</sup>.

Another interesting study showed a that female gender was more prevalent in the FLC group than in the traditional HCC group (60 vs 37 percent) <sup>[6]</sup>. This was also seen in the SEER study, where the authors discovered that FLC had a larger percentage of females (51.5 vs 26.3 percent )<sup>[6]</sup>.

Furthermore, the United States, Mexico, Sweden, Saudi Arabia, Thailand, France, Canada, South Africa, Japan, Korea, India, Taiwan, and the United Kingdom have all reported a comparable incidence of FLC. This could exclude the strong association between race and ethnicity with FLC risk<sup>[21-24]</sup>.

### PATHOGENESIS OF FLC

The etiology of FLC remains uncertain. It typically occurs in normal livers without a clear background of liver fibrosis or cirrhosis<sup>[25]</sup>. Unlike HCC, which are usually found in the presence of cirrhosis or chronic hepatitis<sup>[26]</sup>, FLC has been reported to occur in association with focal nodular hyperplasia (FNH), a benign form of liver tumors<sup>[27, 28]</sup>. Pathologically, both have a central stellate scar which appears on imaging studies, and copper accumulation upon histological examination<sup>[28, 29]</sup>. Hepatitis B viral proteins or DNA have been found in FLC on rare occasions, although this seems to be by coincidence given the enormous global frequency of chronic hepatitis B infection, and there is no evidence to identify hepatitis B as an etiological agent<sup>[30-33]</sup>. Similarly, FLCs

have arisen in women who use oral contraceptives, although the link seems to be coincidental<sup>[34]</sup>.

### **PATHOLOGICAL PICTURE OF FLC**

FLC tumors are big, yellow/tan, hypervascular, well-circumscribed lumps in otherwise normal liver parenchyma with patches of necrosis<sup>[35]</sup>. A central stellate scar and conspicuous fibrous tissue may be seen in up to 75% of tumors<sup>[35]</sup>. Histological examination generally reveals well-differentiated big polygonal tumor cells with eosinophilic hyaline cytoplasmic particles. <sup>1</sup> Large polygonal or spindle-shaped tumor cells with highly eosinophilic cytoplasm due to numerous mitochondria and conspicuous nuclei grouped in cords surrounded by lamellated collagen fibres describe FLC microscopically<sup>[30, 36, 37]</sup>.

Usually, there is no cirrhosis in the surrounding liver parenchyma, although mononuclear cells and lymphocytes imply nonspecific inflammation<sup>[37]</sup>. Electron microscopy often reveals an increase in mitochondrial number, a pathogenic characteristic unique to FLC<sup>[30]</sup>. FLC immunohistochemistry has several characteristics with HCC, such as staining positive for hepatocyte paraffin<sup>[38]</sup>. Unlike HCC, however, FLC stains are negative for alpha-fetoprotein and significantly positive for CK7 and epithelial membrane antigen, both of which are indicators of biliary differentiation (CK19 and Ep CAM)<sup>[39, 40]</sup>. Additionally, FLC exhibits the stem cell markers CD133 and CD44<sup>[41]</sup>. FLC also stains for epithelial growth factor receptor and transforming growth factor-beta more often and diffusely than classic HCC<sup>[40, 42]</sup>. FLC may be distinguished from normal liver parenchyma and HCC thanks to genetic differences revealed. Honeyman and his colleagues found that a 400-kb deletion on chromosome 19 leads in a functional DNAJB1-PRKACA chimeric transcript in 100 percent of FLC tumors examined, further identifying FLC as a distinct entity<sup>[43, 44]</sup>.

### **DIAGNOSTIC APPROACH TO FLC**

#### **Clinical presentation**

Patients frequently report with a variety of symptoms and signs, ranging from discomfort to a liver tumour discovered during a clinical examination for another indication<sup>[11, 45]</sup>. Symptoms commonly seen with the conventional HCC are not seen in FLC<sup>[24, 46]</sup>. FLC patients often complain of nonspecific abdominal pain, nausea, abdominal fullness, malaise, and weight loss<sup>[30]</sup>. A palpable abdominal mass or hepatomegaly with or without right upper quadrant pain and jaundice due to biliary obstruction<sup>[47-49]</sup>, male gynecomastia<sup>[50]</sup>, fulminant liver failure<sup>[7, 51-53]</sup>, recurrent deep venous thrombosis<sup>[54]</sup>, encephalopathy<sup>[55]</sup>, lower limb thrombophlebitis<sup>[56]</sup>, anemia<sup>[57]</sup>, ascites<sup>[58]</sup>, and hypoglycemia<sup>[59]</sup>. Hepatic transaminases and alkaline phosphatase levels are usually normal or slightly elevated<sup>[30, 60, 61]</sup>. Common characteristics of FLC upon presentation are featured in figure 1.

### **Tumor markers**

Alpha-fetoprotein levels are predominately normal, unlike in traditional HCC<sup>[62]</sup>. Several case reports have described increased levels of blood transcobalamin I (haptocorrin) and vitamin B12 binding capacity<sup>[63, 64]</sup>. To assess their diagnostic function, however, further research is needed. Although serum neurotensin levels have been reported to be high with FLC, this test was not enough sensitive or specific to be used for diagnosing FLC<sup>[25, 65, 66]</sup>. Des-gamma carboxy prothrombin is elevated in FLC and conventional HCC, which is less useful<sup>[66]</sup>.

### **Imaging**

#### **Ultrasound (US)**

FLCs exhibit a wide variety of sonographic characteristics and usually appear as well-defined masses with varying echogenicity<sup>[67]</sup>.

#### **Contrast-enhanced computed tomography (CECT)**

FLCs often appear on CT as large heterogeneous well-defined lesions (80%–100%) with a lobulated contour. Calcification and core stellate scarring, as well as tumour necrosis, are found in 65–70% of cases<sup>[39]</sup>. In the arterial phase, more than 80% of patients have increased contrast avidity, which reflects the tumors' primary blood supply. In the venous phase, half of these masses enhance similarly to the background liver, one-third

of these tumors show increased contrast avidity, and approximately two-thirds of these tumours enhance similarly to the background liver in the delayed phase, making differentiation difficult<sup>[5]</sup>. The hepatic hilum and hepatoduodenal ligament are the most prevalent sites for nodal metastatic lesions, accounting for up to 50% of cases<sup>[7, 35, 68]</sup>. On imaging, distant FLC metastasis, particularly to the lungs, peritoneum, and adrenal gland, has been recorded in 20%–30% of patients<sup>[6, 68]</sup>.

### **Magnetic Resonance Imaging (MRI)**

On MRI, FLC is hypointense on T1-weighted images and hyperintense on T2-weighted images with no intralesional fat. Unlike the FNH, the fibrous central scar is hypointense on both T1 and T2-weighted imaging<sup>[69]</sup>. When using Gadolinium as a contrast agent, the enhancement pattern is similar to that of a CT scan, with heterogeneous contrast enhancement on the arterial phase and isointense or hypointense contrast enhancement on the portal venous and delayed phases<sup>[70]</sup>.

### **Nuclear medicine**

Nuclear medicine imaging may help diagnose FLC in certain cases<sup>[71]</sup>. On delayed phase pictures, these tumors demonstrate enhanced absorption of 99 mTc-labeled RBCs during the arterial phase and washout. They also seem photopenic when 99 mTc-sulfur colloid scanning is performed<sup>[71]</sup>. Although the relevance of 18FDG PET/CT in FLC is unknown, it may be beneficial for primary staging and restaging in recurring cases<sup>[72]</sup>.

### **The role of biopsy**

Histologic appearances are the most objective and have widely accepted differences between FLC and HCC<sup>[73, 74]</sup>. So, histologic confirmation is needed to diagnose FLC with certainty<sup>[26]</sup>. Core biopsy is recommended over fine-needle aspiration for percutaneous biopsy because malignant hepatocytes may be aspirated without the distinctive fibrotic lamellae, resulting in a diagnosis of HCC rather than FLC<sup>[75]</sup>.

## **LINES OF TREATMENT**

### **Surgical resection**

Surgical resection is the ideal treatment option that could carry an advantageous prognosis<sup>[14]</sup>. Over 70% of patients need a major hepatectomy (i.e., semi hepatectomy or extended hepatectomy), with a median tumor size of 10.5 cm. Around 24% of patients undergo partial or minor hepatectomy<sup>[76-78]</sup>. When compared to older patients, young patients (under 40 years old) had a higher likelihood of resection<sup>[6]</sup>. Resected patients have 26%–76% postoperative survivals at five years with a median survival of 32–174 mo<sup>[7, 79-81]</sup>. Patients undergoing resection had an overall survival rate of 58.2 percent (44 percent –70 percent) according to a SEER database analysis<sup>[6]</sup>. Recurrence occurs in a large number of patients (more than two-thirds)<sup>[1]</sup>. Disease recurrence after complete surgical resection is high, ranging from 33 to 100%<sup>[19, 77, 81, 82]</sup>. The median time for recurrences to occur ranges between 10 and 33 months, which is obviously short<sup>[7, 35, 80, 83]</sup>. While recurrence of the disease after over five years postoperative is a rare event<sup>[81, 84]</sup>. The significant recurrence rate after surgery may come as a surprise, particularly given that these patients were treated at highly skilled hepatobiliary facilities. These patients, on the other hand, were often in late stages, with large primary tumors and lymph node metastases, both of which have been recognized as poor prognostic indicators<sup>[81-83]</sup>. Surgical resection may also be beneficial for patients with recurrent illness. Yamashita et al found that 86 percent of patients had recurrent illness following resection in their investigations. Surgical excision of recurrent FLC was linked to a longer median overall survival of 122 months, compared to 37 months without surgery<sup>[79]</sup>.

FLC recurrence occurred in all patients after first surgery in Maniaci et al's analysis of ten patients, with a median time to recurrence of 2.2 years, and seven patients were surgically handled, with a median survival of 4.7 years and an OS of 48% at five years<sup>[63]</sup>. Patients who are not surgical candidates, on the other hand, have few therapy alternatives, with a median overall survival of less than 12 months<sup>[7, 85]</sup>.

### **Liver transplantation**

A curative alternative with transplantation has comparable survival rates to transplanted classical HCC in unresectable FLC<sup>[86]</sup>. Liver transplantation should be

regarded a 3-year survival rate if 75–80% of the liver is transplanted<sup>[80]</sup>. Because HCC is more prevalent than FLC, and regional lymph node metastases (a relative contraindication to transplant) is more likely in FLC (42.2%) compared to HCC (22.2%), liver transplantation is considerably more typically demonstrated for HCC than FLC<sup>[76]</sup>.

### **Systemic chemotherapy**

Because of the limited incidence of FLC, no available RCT has shown the most effective chemotherapeutic option. It's worth noting that no neo-adjuvant/adjuvant systemic therapy have yet been found to increase survival in patients with excised FLC<sup>[14]</sup>.

Furthermore, FLC is not normally sensitive to chemotherapy; nevertheless, platinum-based chemotherapy regimens and combination regimens, including interferon alpha-2b, have been utilized successfully<sup>[83, 87, 88]</sup>.

A full or partial response has been observed in five out of eight patients treated with fluorouracil plus recombinant interferon alpha-2b in a Phase II trial<sup>[87, 88]</sup>. Gemcitabine, cisplatin, 5-fluorouracil, interferon, and oxaliplatin are examples of agents that must be taken and have varied degrees of response<sup>[16]</sup>. Better results have been seen with combined treatment regimens that involve surgery, chemotherapy, and radiation<sup>[83]</sup>. Furthermore, percutaneous radioembolization has been used to reduce the size of the tumor prior to surgical excision<sup>[89]</sup>. One of the targeted therapies that have shown efficacy in treating HCC, sorafenib, was evaluated in cases with FLC but has shown limited efficiency<sup>[16]</sup>.

### **Radiation therapy**

Because FLC is not frequently responsive to systemic chemotherapy, only a few cases of FLC treated with radiation treatment have been reported<sup>[83, 90]</sup>. Radiation treatment was utilized to treat unresectable primary tumors<sup>[90]</sup>, to convert unresectable to resectable tumors<sup>[91]</sup>, and to treat metastases or relapses<sup>[83]</sup> in these reports. One report found that employing targeted internal radiation treatment with Yttrium-90 resulted in a substantial FLC response, enabled the patient to undergo curative surgical resection<sup>[89]</sup>. Using 40 Gy in ten parts over 13 days, one case report demonstrated an 85 percent reduction in tumor volume of FLC metastases<sup>[92]</sup>. Three patients achieved objective

partial responses, six patients had tumour volume stability, and one patient had early progression<sup>1</sup> in a separate retrospective analysis of 10 patients with nonresectable metastatic cancer treated with external beam radiation in addition to chemotherapy<sup>[90]</sup>.

### **Recent developments**

In the IMbrave150 study,<sup>3</sup> the combination of atezolizumab and bevacizumab improved survival and considerably delayed deterioration, lowering the chance of death by 42% compared to sorafenib monotherapy in the treatment of patients with unresectable classical cancer (HCC). Patients with FLC, on the other hand, were not included in this study<sup>[93]</sup>. Another research found that<sup>3</sup> three cases with metastatic FLC progressed after 2-3 months of initiating PD-L1 antibodies, one of them was treated with pembrolizumab and the other two with nivolumab<sup>[16]</sup>. Checkpoint inhibitors have been shown to be effective in the treatment of melanoma, lung cancer, renal cell carcinoma, and head and neck cancers<sup>[94]</sup>, and they seem to be a viable therapeutic strategy in HCC<sup>[95, 96]</sup>. Several tumor features seem to encourage a response to checkpoint inhibitors, including tumor-inherent genomic instability and a high mutational burden, both of which are linked to increased overall survival<sup>[94, 97]</sup>. In a Phase II trial of advanced HCC, checkpoint inhibitors showed acceptable efficacy<sup>[39]</sup>. However, there are no controlled studies testing checkpoint inhibitors in FLC, and case reports are few and contradictory<sup>[14, 16]</sup>. FLC's molecular characterization has recently identified potential targets such as the mTOR pathway and Aurora A kinase. Despite the positive findings of mTOR inhibition in sporadic cases<sup>[98]</sup>, no encouraging results from controlled studies have been revealed to date<sup>[99]</sup>.

**DNAJB1-PRKACA:** In conventional HCC and cholangiocellular cancers, DNAJB1-PRKACA rearrangements are absent<sup>[100]</sup>. In primary hepatocellular neoplastic processes,<sup>5</sup> DNAJB1-PRKACA and PRKACA rearrangement detection using a break-apart fluorescence in situ hybridization probe or a polymerase chain reaction provides both sensitive and specific elucidation<sup>[100]</sup>. Introducing the DNAJB1-PRKACA fusion gene into wild-type mice resulted in hepatic tumors in mice with characteristics similar to human FLC, according to Engelholm et al<sup>[101]</sup>. The kinase activity of PRKACA, the

catalytic subunit of protein kinase A (PKA), has been shown in this newly characterized predominant fusion protein<sup>[43, 102, 103]</sup>. This fusion is not unique to FLC, since it has been shown in other cancers<sup>[104]</sup>. However, significant levels of DNAJB1-PRKACA protein expression (amplified in over 70% of FLC) compared to a normal liver or HCC<sup>[103]</sup> make DNAJB1-PRKACA a promising therapeutic target. Because PKA regulates so many oncogenic signaling pathways<sup>[105, 106]</sup>, kinase inhibitors that bind at the active region of the PKA catalytic subunit may simultaneously target many oncogenic proteins. There are no known clinical studies utilizing such inhibitors against FLC<sup>[107]</sup>.

**mTOR:** <sup>3</sup> The first randomized Phase II clinical trial for FLC had three arms: the mTOR inhibitor everolimus, estrogen-deprivation therapy with leuprolide plus letrozole, and everolimus plus estrogen-deprivation therapy. This study was discontinued due to a lack of improvement in progression-free survival among the three study arms<sup>[108]</sup>. <sup>4</sup> The mammalian target of rapamycin (mTOR) is an intracellular protein kinase expressed in mammalian cells and is important for the development of many cancers<sup>[109]</sup>. When this route is disrupted, mTOR is activated, resulting in enhanced cell proliferation, angiogenesis, and apoptosis evasion<sup>[110]</sup>.

For low and intermediate-grade neuroendocrine tumors, the mTOR inhibitor everolimus coupled with octreotide is helpful. The majority of patients had a partial response or stable disease, with a small percentage having tumor progression<sup>[111]</sup>.

### OUTCOME & PROGNOSTIC FACTORS IN FLC

Despite the fact that FLC patients frequently have advanced illness, around 50 percent to 84 percent of them are surgically treatable and have a five-year survival rate of up to 76 percent. FLC patients tend <sup>4</sup> to have a better prognosis than HCC patients, who have a far poorer prognosis, with a 5-year survival rate of just 6.8% <sup>4</sup> <sup>[112]</sup>. Those with FLC, on the other hand, do not have a better prognosis and do not react to therapy any differently than patients with HCC in non-cirrhotic livers at the same stage of disease<sup>[113-116]</sup>. The apparent superior result reported in FLC might be due to the lack of

liver cirrhosis, as well as the disease's indolent character and younger age, which allows for intensive surgical treatment<sup>[6, 7, 113, 117]</sup>.

Tumor stage, number and size of tumors, vascular invasion, regional lymph node metastases, extrahepatic disease, non-white race, and female gender have all been linked to poor surgical outcomes<sup>[7, 78, 81, 82]</sup>. However, it seems that the tumor's early stage at the time of treatment is the most important driver of prognosis. Patients with stage I–III illness had a better prognosis than those with stage IV disease<sup>[7, 84, 118, 119]</sup>, and sometimes, this difference attains statistical significance<sup>[81, 84, 119]</sup>.

### **CONCLUSION**

Fibrolamellar carcinoma is a rare liver cancer & this relative rarity makes data collection and clinical research protocol designing difficult.

Collaboration between international institutes and societies in conducting large scale global research addressing epidemiologic aspects of FLC is needed.

No predictive standards have been elucidated for FLC.

Unfortunately, non-surgical options for FLC patients remain limited.

Experimental animal studies may be needed to better understand FLC's pathogenesis and molecular genetics.

Evidence supporting systemic therapies in FLC is scarce, further research is required on the chemotherapeutic compounds used, including cisplatin, epirubicin, 5-fluorouracil (5-FU).

There is a need to expand our understanding of the molecular underpinnings of FLC and outline the current knowledge gaps to reach a consensus regarding effective treatment modalities.

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Daryl Ramai, Andrew Ofosu, Jonathan K. Lai, Zu-Hua Gao, Douglas G. Adler. "Fibrolamellar Hepatocellular Carcinoma: A Population-Based Observational Study", Digestive Diseases and Sciences, 2020

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