


A Multidisciplinary Approach to the Management of Fibrolamellar Carcinoma: Current Perspectives and Future Prospects

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Abstract: Fibrolamellar carcinoma (FLC) is a rare primary liver tumor affecting predominantly younger and otherwise healthy patients. Typically, FLC presents with advanced disease due to the paucity of typical symptoms and no history of underlying liver disease. Depending on tumor characteristics and the patient’s general condition, surgical treatment is the most promising treatment modality. Aggressive resection and liver transplantation have been utilized and are presently indispensable curative treatment options. Under certain circumstances surgical resection is also possible for metachronous metastases or local recurrence. Recent tumor biology discoveries have contributed to improved diagnostic specificity and systemic treatment options.

Keywords: hepatocellular carcinoma, fibrolamellar carcinoma, tumor recurrence, liver resection, surgery, transarterial radioembolization

Background

Fibrolamellar carcinoma (FLC) is a rare liver cell carcinoma which is not associated with cirrhosis or chronic hepatitis and is more common in younger ages (adolescents and young adults), with an estimated age-adjusted incidence rate of 0.02 per 100,000 in the United States.¹ Originally described in 1956, it derives its name from its presentation ie, abundant fibrosis which is organized in characteristic lamellar bands.^{2,3} In the majority of the literature there is a slightly higher incidence among women and no specific race or geographical region related imbalance in incidence.⁴⁻⁶ No environmental exposures or toxins such as aflatoxin have been directly associated with FLC and neither have alcohol use, iron overload or other factors that contribute to conventional hepatocellular carcinomas. This is substantiated by the fact that the liver tissue surrounding the tumors seldom demonstrates any pathological findings.^{7,8}

Clinical Findings

FLC lacks early or specific signs. A wide range of symptoms has been described, ranging from abdominal pain and distention, to more general symptoms such as malaise and weight loss.⁹ The most common symptom is a palpable mass or abdominal pain; however, FLC lesions are most often detected by chance during examinations for other clinical conditions.⁹ An array of other symptoms has been described spanning from gynecomastia to refractory hyperammonemic encephalopathy, to fulminant liver failure.⁹⁻¹³ Paraneoplastic symptoms are rarely described and not fully understood. A previous study has suggested that molecular pathogenesis resulting in overexpression of Aurora Kinase A may cause a urea cycle dysregulation, through upregulation of ornithine decarboxylase, which ultimately leads to excessive ornithine consumption and hyperammonemia.¹⁴ Gynecomastia may result from overexpression of aromatase P450 within

the tumor cells, which catalyzes conversion of steroids to estrogens, thus leading to severely elevated levels of estrone and estradiol.^{12,15} As for markers, AFP is often normal or only slightly increased.⁹

Radiology

FLC habitually presents as a large single mass. Due to radiomorphological similarities to focal nodular hyperplasia (FNH), as both frequently present with a central scar, a misdiagnosis is possible. In fact, an association has often been reported between FNH and FLC, with some patients presenting with FLC and a history of surveillance for FNH and some presenting with both lesions simultaneously.^{16,17} FNH has previously been suspected to be a precursor of FLC but current evidence does not imply causality.¹⁸ FLC may first be viewed on an ultrasound as an incidental finding. Sonographic features are nonspecific, and a sonographer may merely see a heterogeneous echogenic lesion with echogenic center correlating to the central scar.¹⁹

Gadolinium-enhanced MRI is the preferred imaging modality for FLC. A central hypointensity on T2-weighted images correlates to the fibrous central scar and is a feature that can help distinguish between FLC and FNH, as the latter is frequently T2 hyperintense.¹⁹ Additionally, FLC may display T1 hypointensity, T2-hyperintensity, inhomogeneous arterial phase enhancement, hepatobiliary phase hypointensity, which may also help distinguish FLC from FNH, as well as high signal intensity on diffusion weighted imaging.^{19,20} On a contrast-enhanced CT, a FLC can exhibit lobulated margins. Without enhancement, FLC is hypoattenuating, while enhanced images show a heterogeneous hyperattenuation. A large central scar is a frequent feature in CT scans as well, albeit with low specificity. Oftentimes, calcifications within FLC can be seen, a feature infrequently encountered in FNH. Generally, as FLC frequently exhibits more aggressive features, such as vascular invasion, biliary obstruction, lymph node enlargement and distant metastases, those features may not only help differentiate the lesion from benign diagnoses, but also have a prognostic significance.²⁰ In all, FLC should be considered in patients with suspected benign lesions other than FNH. Hemangioma exhibits a centripetal enhancement during the delayed phase, which has not been reported in FLC.¹⁹ Hepatic adenomas have a homogeneous hypervascularized enhancement.¹⁹

Pathophysiology

After sequencing FLC tumors, Honeyman et al demonstrated a deletion in chromosome 19 which leads to a combination of the subunits of the heat shock protein and the protein kinase A (PKA) into the DNABJ1-PRKACA.^{21,22} The transcription of this DNAJ-PKAc chimeric protein is expressed exclusively in FLC, in what has been shown to be a somatic mutation.^{21,23} The chimera can subsequently be separated into specific subcellular locations by fusion into the A-Kinase Anchoring Protein (AKAP) signaling complexes.^{24,25} Attributed to the DNAJ part, the protein interacts with the chaperonin heat shock protein 70 (Hsp70).²⁶ The latter causes protein folding which could account for the high levels of DNAJ-PKAc compared to wildtype PKA in FLC tumors. Of note, although PKA is not classified as an oncogene, the subunit PKAc has been detected in the serum of various carcinomas.²⁷ Recent advances in the understanding of the formation of this chimeric protein have led to the hypothesis that its chaperonin binding properties could facilitate oncogenesis while transforming the Protein Kinase A into a protein with tumorigenic potential.²⁶

Pathology

Until now, no specific serum biomarkers have been detected. Contrary to conventional hepatocellular carcinomas, AFP is elevated in less than 5% of FLC patients, while there have been reports of elevated vitamin B12 binding capacity.^{28–30} The most common immune-histochemistry markers of the tumor cells are CD 68 and Cytokeratin 7.^{29,31,32} Although FLC has distinctive histologic and clinical features, hepatocellular carcinomas are often misidentified as FLC creating misconceptions on survival and recurrence rates. Some authors have reported RASSF1 methylation as grounds for this and showed distinctly different prognosis for mixed FLC tumors in retrospective studies.³³ This misclassification could account for the discrepancies in patient ages reported in original studies and the SEER database analyses where a higher proportion of patients older than 50 years of age are commonly described.^{1,4,34–38} After the discovery of the DNAJB1-PRKACA chimera, FISH DNAJB1-PRKACA has been introduced as a diagnostic technique increasing specificity to almost 100% but has not yet been introduced to routine practice.^{31,39}

Staging

Due to the differences in categorization and its rarity, there is no specific FLC classification and tumors are classified according to the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) classification for hepatocellular carcinoma (Table 1).⁴⁰ In the available reports the tumor stage was most often T1, comprising 42%, but vascular invasion is frequent in the tumor, thus T2 (13%) and T3 (28%) are also prevalent at diagnosis.³⁴ T4 has been reported in approximately 8% of cases. Unknown stage at presentation was reported in 9% of cases, as reported by a recent SEER database analysis.³⁴ Most FLC are diagnosed at an advanced stage, with AJCC stage III and IV amounting to 70–80% due to frequent lymph node and major blood vessels' involvements.⁴¹

Surgical Treatment

Primary Resection and Liver Transplantation

The majority of FLC patients present with large tumors, often larger than 10cm.^{42,43} Notwithstanding, complete surgical resection is feasible mainly due to young age and the lack of cirrhosis, reaching rates up to 73% in adult and 84% in pediatric patients.^{28,44} Achieving negative resection margins is a cardinal priority, hence the majority of patients require a hemi-hepatectomy or trisectionectomy.⁴⁵ Major resections are reported more often in smaller case series, such as in the study by Wahab et al with 90% of patients treated as such.⁴⁶ Curative intent resections achieve R0 resection rates from 81% (reported by Darcy et al in pediatric patients) up to 96% (McDonald et al, National Cancer Database), although there is a notable selection bias and omission of missing data in such estimates.^{6,44,47} In very selected cases, palliative surgical tumor reduction can be performed in order to alleviate symptoms such as hyperammonemic encephalopathy but this is absolutely not standard.⁴⁸

Resection is a factor greatly influencing the prognosis, with 5-year survival rates reaching up to 86% for stage I patients.⁴³ Mavros et al reported of a 0% 5-year survival rate among patients who received chemotherapy (including palliative), intra-arterial therapy or other treatment instead.⁴⁹ Generally, the reported 5-year overall survival (OS) for resection varies widely in the literature between 26–76% and with 5-year recurrence-free survival (RFS) and as low as 18%, spanning from 14 to 87 months^{44,50–53} (Table 2). Negative resection margins have been associated with better OS in young adults and adolescents where the 5-year OS of those who underwent complete resection was 51.6% versus 42.6% for R1/R2 and improved long-term overall survival was associated with R0 resection. This association was not present in other monocentric studies or database analyses.⁴²

A number of other prognostic factors with variable significance have been described for FLC. Unfavorable factors include vascular and lymph-node invasion, tumor multiplicity and metastases at baseline.^{34,35,49,52} Furthermore, young

Table 1 Staging According to the AJCC/UICC 8th Edition

T	N	M	Stage
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IVA
Any T	Any N	M1	IVB

Notes: Reproduced from: Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer Cham; 2017.⁷³ Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2020).

Table 2 Studies Reporting Surgical Treatment Outcomes (for Data Used Repeatedly, Such as the SEER Database, the Largest Sample Size Has Been Used)

Study (First Author)	Year	N	Median Patients' Age at Diagnosis (Years \pm SD or Range)	Median Follow-Up (Months)	Database/ Cohort	Surgical Treatment	Median Survival (Months)	RFS for Resection (Months)	5-Year OS Rate for Resection
McDonald et al [47]	2020	496	32 \pm 21	70	NCDB	Resection	78.5 after resection	N/A	N/A
Ramai et al [71]	2021	300	27 \pm 22	30	SEER Database	Resection	32.9	N/A	37.3%
Kaseb et al [52]	2013	94	23 (14–75)	122	Monocentric USA	Resection & transplantation	57.2	13.9	N/A
Ang et al [28]	2013	69	22 (11–65)	41	Multicenter USA	Resection & transplantation	80	N/A	N/A
Chakrabarti et al [43]	2019	42	22 (15–39)	N/A	Monocentric USA	Resection	38	30.5	35% (stage IV)–86% (stage I)
Malouf et al [33]	2012	40	22 (9–65)	93.6	Multicenter France	Resection & transplantation	76.8	32.4	66% (pure FLC, R0)
Groeschl et al [51]	2013	35	39.3 (17.3–72.0)	40	Multicenter international	Resection	174 for Rx 37 for palliation	48	62%
Stipa et al [53]	2006	28	27 (14–72)	34	Monocentric USA	Resection	112 after resection	33	N/A
Darcy et al* [44]	2015	25	17.1 (11.6–20.5)	32.9	Monocentric USA	Resection	52.9 median FU for surviving patients	15.6	51.6%
Wahab et al [46]	2017	22	29 (21–58)	42	Monocentric Egypt	Resection	88	87	23%
Chagas et al [56]	2014	21	20 (13–49)	24	Monocentric Brazil	Resection	36	N/A	N/A
Ichikawa et al [72]	2000	21	Mean=29 (15–65)	N/A	Monocentric USA	Resection & transplantation	N/A	N/A	N/A
Lemekhova et al [16]	2020	8	27 (19–36)	47	Monocentric Germany	Resection	36.5 after resection	N/A	N/A
Bhaijee et al [55]	2009	7	21 (19–42)	61	Monocentric South Africa	Resection	60	N/A	67%

Note: *Darcy et al reported on pediatric patients.

Abbreviations: FLC, fibrolamellar carcinoma; DNABJ1, DnaJ homolog subfamily B member 1; PRKACA, catalytic subunit α of protein kinase A; AFP, α -fetoprotein; FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; RASSF1, ras association domain family member 1; SEER, surveillance, epidemiology, and end results; FISH, fluorescence in situ hybridization; OS, overall survival; RFS, recurrence-free survival; UNOS, United Network for Organ Sharing; 5-FU, fluorouracil; IFN, interferon; TARE, transarterial radioembolization; FCF, Fibrolamellar Cancer Foundation.

age has been shown to positively influence survival, especially in the SEER database analyses, while risk estimates on sex are either insignificant or in favor of advantageous prognosis for female patients.

Liver transplantation is not a common therapeutic strategy for FLC on organizational grounds such as the need for specialized centers and lack of grafts in some regions but also due to the existence of nodal infiltration. When possible, transplantation has shown comparable OS to surgical resection treatment or at least far better OS than systemic therapy alone.⁵⁰ Recent data from the UNOS registry showed a 48% 5-year OS for FLC but comparable 1-year and 3-year OS to HCC (77% and 68% for HCC vs 80% and 48% for FLC).⁵⁴

Surgery for Recurrence

Recurrent disease is observed in the majority of patients after curative resection irrespective of resection margins, with a reported rate spanning from 50–80% for most reported studies and up to 100% in smaller monocentric analyses.^{6,16,42,55} Longer recurrence-free survival has been associated with younger age and lack of vascular invasion as well as lack of extrahepatic disease.^{42,51,56} While the most common sites of recurrence are the intraabdominal lymph nodes and the liver, FLC recurrence in terms of systemic disease is also diagnosed in the lungs and bones, with cases of peritoneal carcinomatosis or even duodenal recurrence.^{49,57–59} Malouf et al reported a 100% extrahepatic recurrence for pure FLC patients, with some also presenting with intrahepatic metachronous metastases.³³ Repeated resection of recurrent FLC or metachronous metastases has been shown to effect survival, albeit the effect is less evident compared to surgery for primary tumors. Yamashita et al reported a median overall survival of 122 months for aggressive recurrent disease resection compared to 37 months with non-surgical therapies for recurrence; while, with a multimodal approach, Maniaci et al achieved a 112-month median OS and 48% 5-year OS in a 10-patient series.^{42,59} In another series, only intrahepatic recurrence was present, with a 61% rate and mean time to recurrence of 37 months.⁵³ Metachronous metastasectomy was possible for all patients who had recurrence with an OS of 26 months as a result.⁵³ Similarly, Kaseb et al reported a median OS of 145 months after re-resection for recurrence in contrast with 35 months OS for non-surgical treatment.⁵² These results demonstrate that very favorable outcomes can be achieved with close follow-up, timely resection, and careful patient selection. Therefore, all cases with recurrent FLC should be presented to a multi-disciplinary tumor-board and to specialized HBP surgeons.

Non-Surgical Treatment

To date there are no standard systemic therapies for FLC, and surgery remains the mainstream therapy.¹⁶ Non-surgical treatment shows worst overall survival, with 5-year overall survival estimated at 0%.⁴⁹ Generally, chemotherapy in combination with surgery showed overall worse survival than surgery alone, potentially due to confounders and comparatively progressed disease.³⁴ Utilization of interventional radiological methods has only been reported sporadically and their safety and efficacy remain to be evaluated.

Chemotherapy

Administration of chemotherapy is controversial in FLC and utilized on a case-to-case basis. For patients who present with unresectable disease (approximately 20–25%), a median survival can be estimated at 12 months.⁴⁵ With chemotherapy, overall survival can be extended to 20.6 months.⁵²

Notably, chemotherapy regimens are extremely variable. Sorafenib, a first-line therapeutic agent for HCC, has been used with inconsistent results: while some patients achieved stable disease, median survival did not surpass 10 months.⁴³ Recently, it has been shown that the DNAJB1–PRKACA chimeric transcript can be detected in 100% of FLCs. This transcript leads to overexpression of Aurora kinase A, thus a selective Aurora kinase A inhibitor, ENMD-2076, has been evaluated in a Phase II multicenter open-label trial.⁶⁰ Of 35 patients, only 1 (3%) had a partial response and 20 (57%) had stable disease, while overall survival was 19 months. As immunotherapy has been gaining popularity in HCC treatment as well, triple immunochemotherapy with 5-fluorouracil, interferon, and nivolumab was applied in patients with unresectable, metastatic, or relapsed FLC.⁶¹ Fifty percent partially responded to therapy, while 93% had either a partial response or stable disease. After 26 months over 90% of patients were still alive.⁶¹ In a pediatric cohort, platinum-based chemotherapy has shown to lead to a partial response in 31% of patients; however, 3-year overall

survival was only 22%.⁶² Programmed cell death ligand-1 (PD-L1) is expressed on FLC tumor cells in approximately 63% and ca. 70% of patients exhibit PD-L1 positive tumor infiltrating lymphocytes and tumor-associated macrophages.⁶³ So far, PD-L1 therapy has singularly been described in a patient who responded well to the treatment but without long-term results.⁴³ At the moment there is one clinical trial recruiting patients for a DNAJB1-PRKACA Fusion Kinase Peptide Vaccine Combined with Nivolumab and Ipilimumab and one trial for Pembrolizumab in pediatric patients.^{23,64} Generally, chemotherapy in combination with surgery showed overall worse survival than surgery alone. From our point of view, this might be due to an already advanced tumor stage at time point of surgery necessitating (neo-) adjuvant treatment.

Neoadjuvant Treatment

Neoadjuvant chemotherapy for FLC is not habitually utilized and only reported sporadically. The regimens vary between sorafenib, sirolimus, 5-FU, Cisplatin, doxorubicin, carboplatin, bevacizumab, capecitabine, IFN, oxaliplatin, and often in various combinations. A report of ten patients with various regimes of neoadjuvant therapy showed a median survival of 60 months, which is marginally better than the survival after resection without neoadjuvant therapy according to a SEER database analysis.^{34,52} Oxaliplatin and gemcitabine have also been tried in one patient with a 16-cm FLC with extensive vascular invasion; the radiological response was favorable, with tumor reduction size to 8.5 cm. A follow-up of 14 months after resection was uneventful.⁶⁵ Overall, the evidence for neoadjuvant treatment is very low and patient numbers too small for a clear recommendation. Each case should be discussed individually by a tumor-board.

Adjuvant Treatment

Surgery with adjuvant therapy showed a median survival of 110.5 months.^{34,52} However, evaluated chemotherapy regimens are heterogeneous, with most patients receiving interferon in addition to 5-fluorouracil and/or platin-based agents.^{52,59} Also, here individual treatment strategies can be discussed since clear standards and data are missing.

Interventional Radiology

Interventional radiology has recently gained popularity, yet it remains highly unexplored in rare liver lesions. Hepatic chemoembolization in a patient has shown good clinical and laboratory response, although diameter remained unchanged after repeated chemoembolization and the patient developed new lesions two years after initial treatment.⁶⁶ Tumor embolization with lipiodol in otherwise unresectable disease led to overall survival of 38 months in one patient.⁵⁵ Transcatheter oily chemoembolization was utilized in three patients. After several courses every 4 months, two patients displayed a decrease in tumor size and good tolerability, so that hepatic resection was feasible.⁶⁷ Transarterial radioembolization (TARE) with Yttrium-90 has been introduced as a potential bridging therapy to hepatectomy or transplantation for HCC. Thus far it has been tried in two pediatric patients with unresectable FLC, both of which could be resected afterwards and had survived the follow-up of 12 months.⁶⁸ These studies demonstrate that multimodal therapy needs further development and consistency as more and more patients may be treated with curative intent.

Conclusion

Fibrolamellar carcinoma is a rare, highly malignant liver lesion; however, if managed surgically, a favorable long-term result can be obtained. A multimodal approach has achieved resectability in a few otherwise unresectable patients and should be evaluated further in multicenter trials with adequate follow-up.

As DNAJ-PKAc is in essence a hallmark of FLC, its use as a primary diagnostic marker in specific populations should be established after further evidence has been generated in order to speed up therapy. Presentation at a multidisciplinary tumor-board and to specialized HBP surgeons is absolutely mandatory to offer patients the best individual treatment. Advancements in systemic therapy can further support current surgical management to achieve better outcomes for patients with recurrent disease. Overall, clinical trials are important to gain more information and patient data should be summarized in an international registry such as Fibroregistry.org to create a collaborative research community amongst multiple academic specialties.⁶⁹ Patients' organizations such as the Fibrolamellar Cancer Foundation (FCF) can

be counseled since they support the search for the right specialist and improve awareness and education amongst patients with fibrolamellar carcinoma.⁷⁰

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