Epidemiology, clinical manifestations, diagnosis, and treatment of fibrolamellar carcinoma

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INTRODUCTION

Primary malignant liver tumors resemble and arise from the major constituent cells of the liver, namely hepatocytes (giving rise to hepatocellular carcinoma [HCC]), biliary epithelial cells (cholangiocarcinoma and biliary cystadenocarcinoma), endothelial cells (angiosarcoma, epithelioid hemangioendothelioma), or combinations of these cells with various mesenchymal cells (eg, hepatoblastoma) [1]. Some (eg, combined hepatocellular-cholangiocellular carcinoma) represent collision of two different tumors or may result from malignant transformation of hepatic progenitor cells with differentiation along two different cell lineages.

HCC is the most common primary liver tumor, followed by cholangiocarcinoma. (See "Epidemiology and risk factors for hepatocellular carcinoma" and "Epidemiology, pathogenesis, and classification of cholangiocarcinoma".)

This topic review will cover the epidemiology, clinical manifestations, diagnosis, and treatment of the fibrolamellar carcinoma (FLC). Although previously felt to represent an HCC subtype, advances in the genomic analysis of FLC have helped to clarify that this tumor represents a unique disease process separate from HCC. The pathology of all primary malignant liver tumors and their precursors is discussed elsewhere. (See "Pathology of malignant liver tumors".)

EPIDEMIOLOGY

Fibrolamellar carcinoma (FLC) was historically considered a variant of primary hepatocellular carcinoma (HCC) [2]. It was originally called eosinophilic hepatoma with lamellar fibrosis in view of its distinguishing features: tumor cells with eosinophilic cytoplasm and parallel arrangement of the collagen in conspicuous fibrous septa [3]. (See "Pathology of malignant liver tumors", section on 'Fibrolamellar subtype'.)

FLC is a very rare tumor, although the incidence varies geographically. In the United States and Thailand, less than 1 percent of all primary liver tumors are FLC [4,5], while in Mexico, FLC is reported to represent 5.8 percent of all primary liver cancers [5,6].

Epidemiologically, FLC differs from HCC in several ways:

- FLC affects younger individuals 5 to 35 years of age. However, there appear to be two peak incidences: one from age 10 to 30 years and another age 70 to 79 years [7]. In a large database series, the average age at diagnosis was 39 years, and 60 percent of patients were diagnosed under the age of 40 [8].
- In contrast to conventional HCC, FLC does not have a male predominance; in fact, some series report a female predominance [8,9], although other data support sex equivalence [7,10].
- A recent review suggested that compared with other races, Asian patients may be older at the time of diagnosis [11].
- There are no identified risk factors for FLC [10,12,13]. (See "Epidemiology and risk factors for hepatocellular carcinoma".)

ETIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of fibrolamellar carcinoma (FLC) are unknown. While considered historically to be derived from hepatocytes, FLC tumor cells have markers of both hepatocyte and biliary differentiation. Furthermore, the results of transcriptional profiling have questioned its presumed hepatocytic origin [14].

Despite some early reports [15-17], there is no solid evidence to suggest hepatitis B virus (HBV) infection as an etiologic agent or that focal nodular hyperplasia is a precursor lesion [18].

A recurrent unique fusion gene between *DNAJB1* (DnaJ/HSP40 homolog, subfamily B, member 1) and *PRKACA* (protein kinase, cAMP-dependent, catalytic, alpha; *DNAJB1-PRKACA*) has been reported in the majority of FLC studied. The fusion is not specific to FLC and has been reported

in other malignancies [19]. A pathogenetic role for this fusion transcript is not yet established. No clear diagnostic utility of this fusion gene is known. This is discussed further below. (See 'Molecular diagnostics' below and "Pathology of malignant liver tumors", section on 'Fibrolamellar subtype'.)

CLINICAL PRESENTATION

The clinical symptoms of fibrolamellar carcinoma (FLC) are usually nonspecific and may include nausea, abdominal discomfort or fullness, weight loss, and/or night sweats [20]. In a series of 95 patients with FLC, the most common symptom at presentation was abdominal pain (42 percent), followed by abdominal mass and/or distention (24 percent), and anorexia and/or weight loss (23 percent) [21]. Jaundice caused by biliary obstruction may be present in up to 40 percent of cases [18].

Patients may also present with symptoms related to metastatic disease. In the review of 95 cases of FLC, 60 percent presented with extrahepatic metastases [21]. Common sites are regional lymph nodes, the lungs, and the peritoneum, but metastasis to other locations, including skeletal muscle, are described [21-23].

Rarely, patients present with symptoms related to tumoral hormone production, such as gynecomastia from aromatization of androgens, or paraneoplastic production of thyroid hormones or beta-human chorionic gonadotropin (beta-hCG) [24-26]. Hypoglycemia related to increased utilization of glucose by the tumor has also been described [27], as has hyperammonemia that is consistent with an acquired ornithine transcarbamylase deficiency [28,29]. (See "Urea cycle disorders: Clinical features and diagnosis", section on 'Pathogenesis'.)

DIAGNOSIS

The diagnosis of fibrolamellar carcinoma (FLC) is typically made on the basis of clinical presentation and imaging studies; negative serum tumor markers such as alpha-fetoprotein (AFP) may also support the diagnosis. Pathology is the gold standard in confirming the diagnosis. If diagnostic uncertainty persists following cross-sectional imaging or in the setting of metastatic disease, percutaneous core biopsy guided by ultrasound or computed tomography (CT) may confirm the diagnosis. However, the diagnosis of FLC can be difficult to establish, even with an adequate core biopsy specimen, and open or wedge biopsy may be necessary to obtain adequate tissue for diagnosis. (See 'Tumor markers' below and 'Histology' below.)

Imaging — Cross-sectional imaging is an essential part of the diagnostic workup for FLC. On CT scans, FLC most often appears as a large, sharply defined, heterogeneously enhancing mass within a noncirrhotic liver; a central scar and/or calcifications may be present [23,30,31]. Occasionally, FLC may present with multiple intrahepatic lesions of a cystic appearance on CT [32]. Contrast enhancement relative to the adjacent liver parenchyma is more variable on magnetic resonance imaging (MRI), with hypointense signal on T1-weighted imaging in 62 percent of cases and hyperintensity on T2-weighted imaging in 54 percent of cases [23]. The central scar is hypointense on both T1 and T2 images as a result of its fibrous composition (image 1). This helps in distinguishing this lesion from the hyperintense scar associated with focal nodular hyperplasia. Additionally, more recent data support the use of contrast-enhanced ultrasound, which can show central scars, and the more specific finding of arterial hyperenhancement and early venous washout [33]. (See "Contrast-enhanced ultrasound for the evaluation of liver lesions".)

The utility of positron emission tomography (PET) with fluorodeoxyglucose (FDG) is uncertain. In contrast to primary hepatocellular carcinoma (HCC), for which FDG-PET has limited sensitivity, case reports describe unequivocal FDG uptake in FLC [34,35], but uptake is variable (image 2). Further study is needed to ascertain the role of FDG-PET for diagnosing primary or recurrent FLC [34].

Tumor markers — Commonly used tumor markers for HCC, such as AFP, are of little help for diagnosing and monitoring disease progression with FLC. Only 7 to 11 percent of patients have an elevated serum AFP level, and it is typically in the range of 100 to 200 ng/L [13,36-38]. (See "Clinical features and diagnosis of hepatocellular carcinoma", section on 'Alpha-fetoprotein'.)

Some small studies suggest utility for other tumor markers, such as serum des-gamma-carboxy prothrombin (DCP) [39], vitamin B12 binding capacity (B12BC), haptocorrin, and neurotensin [40-43]. At least some institutions use periodic assay of serum levels of B12BC as a component of post-treatment surveillance [44].

Histology — Pathology is the gold standard for establishing the diagnosis. Grossly, FLC forms a solitary, large, firm, well-circumscribed tumor, which may be encapsulated. The cut surface demonstrates gray-white fibrous bands, which subdivide the tumor into smaller nodules resembling focal nodular hyperplasia. Microscopic evaluation generally reveals well-differentiated, large, polygonal tumor cells with eosinophilic hyaline cytoplasmic bodies and abundant fibrous stroma arranged in thin parallel lamellae around tumor cells (picture 1) [3]. Cytoplasmic pale bodies are frequently found. This subject is discussed in detail elsewhere. (See "Pathology of malignant liver tumors", section on 'Fibrolamellar subtype'.)

Molecular diagnostics — The *DNAJB1-PRKACA* (DnaJ/HSP40 homolog, subfamily B, member 1 and protein kinase, cAMP-dependent, catalytic, alpha) fusion is detected in nearly all FLC but is not specific [45]. A unique deletion on chromosome 19 leads to the fusion gene and a functional DNAJB1-PRKACA fusion protein. There was previous enthusiasm that detection of the fusion transcript in biopsy specimens by RNA in situ hybridization, reverse transcriptase polymerase chain reaction (RT-PCR), or fluorescent in situ hybridization (FISH) methods would hold promise for accurate and sensitive diagnosis of FLC in needle biopsy specimens [46], but more recent data have emerged documenting this fusion protein in other malignancies of pancreaticobiliary origin [19,47].

Differential diagnosis — Despite differences in clinical, imaging, and pathologic features, FLCs are frequently misdiagnosed as HCCs. In addition, FLC can mimic benign liver masses, such as adenomas, focal nodular hyperplasia, mesenchymal hamartoma, and hemangioma, as well as malignant lesions, such as hepatoblastoma, and fibrotic metastatic tumors, such as breast cancer, neuroendocrine (carcinoid, islet cell) tumors, cholangiocarcinoma, thyroid cancer, and salivary gland tumors [18].

It is important to differentiate FLC from HCCs and other liver masses because treatment and prognosis may differ substantially.

STAGING

The current eighth edition Tumor, Node, Metastasis (TNM) staging classification for liver cancer from the joint American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) includes both hepatocellular carcinoma (HCC) and fibrolamellar carcinoma (FLC) (table 1) [48]. Stage distribution at presentation was addressed in a review of 94 cases of FLC; 20 percent presented with stage I or II disease, 38 percent were stage III, and 42 percent were in stage IV at diagnosis (nodal or distant metastases) [13]. Other series note approximately 50 percent of patients with stage IV disease at presentation as well [21].

With the lack of effective systemic therapies, despite being classified as stage IVa disease, regional nodal metastases are not perceived as a contraindication to attempted curative resection for patients with FLC, in contrast to HCC. (See 'Potentially resectable disease' below and "Surgical management of potentially resectable hepatocellular carcinoma", section on 'Determining the extent of tumor involvement'.)

PROGNOSIS AND PROGNOSTIC FACTORS

The most important prognostic factors are disease stage and resectability. Poorer outcomes are consistently described for patients whose disease cannot be resected completely and for those with extrahepatic disease, including positive regional lymph nodes [21,39,49-51]:

- The prognostic influence of stage distribution was shown in a series of 94 patients with fibrolamellar cancer; median survival of patients with stage I to II disease (according to the sixth edition of the American Joint Committee on Cancer [AJCC] staging classification from 2002) was 84.9 months; for stage III (T4 tumor or N1 disease), it was 54.2 months, and for stage IV (distant metastases), it was 28.9 months [13].

- A Chinese group proposed a nomogram based on age, N and M stage, tumor size, and surgery that was superior to the just the TNM staging system alone in terms of predicting survival [52].

- Patients who are candidates for resection may have a five-year survival of 40 to 70 percent (although relapse rates are high); in contrast, for the 20 to 30 percent of patients who cannot undergo surgery, median survival is less than 12 months. (See 'Potentially resectable disease' below.)

- In a review of the Surveillance, Epidemiology, and End Results database, age was best predictor of overall survival, while surgery and tumor stage were also important predictors [53].

- In a study from the Fibrolamellar Carcinoma Consortium, median overall survival for the entire cohort was 6.7 years, and was significantly reduced for women (63 versus 99 months for men) and in the presence of nodal metastases (46 versus 99 months), microvascular invasion (18 versus 99 months), and extrahepatic non-nodal metastases (38 versus 117 months) [21].

  The adverse effect of female sex is not a universal finding. Others have shown that female sex is a positive prognostic factor [13,54].

- Nodal metastases are classified as metastatic disease in the AJCC staging system (table 1); however, isolated nodal metastases may not affect overall or recurrence free survival. In a retrospective study of 65 patients with FLC who were compared with 158 noncirrhotic patients with HCC, 81 percent of patients with FLC had isolated metastases [55]. Overall survival in FLC was influenced by the number of tumors and the presence of vascular invasion, but not AJCC stage, in contrast to the patients with noncirrhotic HCC.

- Others suggest an adverse influence of elevated alpha-fetoprotein (AFP) levels on prognosis [13]. One study of patients undergoing resection with curative intent found reduced overall survival in patients with initial AFP >15 ng/mL [56]. In this study, 33 percent of patients undergoing curative resection had an elevated AFP, and the hazard ratio for death in this group was 2.81 (95% CI 1.083-7.33) in a multivariate cox proportional hazards model [56]. Although elevated AFP is rare in FLC overall, other studies have shown elevated AFP to be a predictor of poor outcomes in more advanced disease as well [13]. (See 'Tumor markers' above.)

There is some debate as to whether FLC has a better prognosis than conventional hepatocellular carcinoma (HCC) [10,21,38], or whether the better survival seen in some studies is simply due to the fact that FLC occurs generally in younger patients and in those without underlying chronic liver disease, such as cirrhosis, such that there is a greater opportunity for potentially curative resection [57,58]. More recent data suggest that five-year survival rates are comparable between patients with noncirrhotic HCC and those with FLC (67 versus 58 percent) [55].

TREATMENT

Although patients often have advanced disease at diagnosis, 70 to 75 percent are amenable to complete resection, albeit often by very extensive resection, and approximately 40 to 70 percent are still alive 5 and even 10 years later [21]. There is a misperceived notion about the prognosis of the disease because of data such as these, but at the opposite end of the spectrum are the 20 to 25 percent of patients who have categorically unresectable disease, which is associated with a five-year survival rate of 0 to 5 percent and a median survival of 12 months or less. The best form of therapy for these individuals is not established, and there is no standard of care for unresectable disease. There is no consistently effective form of systemic therapy, and the role of liver transplantation for either locally advanced or recurrent disease is debated [21].

Potentially resectable disease — Aggressive surgical resection is the mainstay of treatment for potentially resectable fibrolamellar carcinoma (FLC). Because many cases are diagnosed at an advanced stage with large size, a major anatomic resection, such as right hepatectomy, is often necessary. However, as most patients have no underlying liver disease, a substantial amount of the liver parenchyma can be removed because of the potential for regeneration. (See "Overview of hepatic resection", section on 'Liver function and regeneration after resection'.)

Patients undergoing resection may benefit from concomitant regional lymphadenectomy. In a report from the Surveillance, Epidemiology, and End Results (SEER) database, five-year survival

rates were superior in patients who underwent lymphadenectomy compared with those who did not (70 versus 57 percent) [59]. This is not a universal finding. Others have not shown that lymphadenectomy has a significant impact on survival [13].

Five-year overall survival rates following aggressive resection range from 58 to 82 percent [8,36,38,39,60-63], but 50 to 100 percent of patients relapse [13,38,44,51,61,62,64], including some late recurrences. However, outcomes can be highly variable, and there are some long-term survivors with resection alone [8,21].

As an example, in a multi-institutional review series of 95 patients presented by the Fibrolamellar Carcinoma Consortium, despite aggressive surgery in 73 (77 percent of cases), which included liver resection with or without lymphadenectomy, transplant in eight, and perioperative systemic or local therapy in 23 (32 percent), approximately 30 percent of patients were still alive beyond 10 years; 77 percent developed recurrent disease [21]. However, outcomes can be highly variable. Common sites of recurrence include the liver, regional lymph nodes, peritoneum, bone, and lung. Median time to relapse is between 10 and 33 months [13,38,39,51,60,65].

There is no proven effective adjuvant systemic therapy.

Post-treatment surveillance — There are no data on the appropriate tests or frequency of tests for post-treatment surveillance after a complete surgical resection. However, at least some data suggest that early detection of relapse combined with multimodality treatment may result in prolonged survival. Many clinicians perform CT scans of the chest, abdomen, and pelvis at intervals of three to six months for at least the first two to three years [44]. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) should be reserved for cases being considered for reoperation because of locally recurrent disease, or if recurrent disease is suspected based upon elevated tumor markers but cross-sectional imaging is unrevealing. Some authors suggest serial assay of B12 binding capacity (B12BC) [44].

Unresectable cases — Approximately one-fifth of patients have unresectable disease due to multifocal metastases, extensive nodal spread, and/or major vessel involvement [21]. These patients have a dismal outcome, with five-year survival rates of 0 to 5 percent and a median survival of 12 months or less [38,57,61,62,66].

Options for unresectable nonmetastatic disease

Liver transplantation — The role of liver transplantation in FLC is controversial. Liver transplantation may be considered for selected patients without extrahepatic metastases if partial hepatectomy is not technically feasible because of the size of the tumor or because of

local extension and/or adhesion to other organs [18,60,67]. However, unlike hepatocellular carcinoma (HCC), patients with FLC are not prioritized for orthotopic liver transplantation (OLT) in the United States [68,69]. (See "Liver transplantation for hepatocellular carcinoma", section on 'Allocation of donor organs'.)

Nonetheless, over the last 25 years, there have been some reports of OLT for FLC suggesting the potential for long-term recurrence-free survival, but as with aggressive resection, recurrence rates are high [39,60,68-70].

In a review of data from the United Network for Organ Sharing (UNOS) database over a 25-year period, overall survival at one, three, and five years was 96, 80, and 48 percent, respectively [69]. Because of the shortage of cadaveric donors, living donor liver transplantation may represent a potential treatment option for FLC, but the data are extremely limited [71,72].

There is at least one case report suggesting systemic therapy that includes immune checkpoint inhibitor immunotherapy could be potentially utilized to downstage patients to within liver transplant criteria [73]. Further discussion on systemic therapy in FLC can be found below. (See 'Systemic therapy' below.)

Embolization — Although data are scant, hepatic artery chemoembolization has been used as an alternative treatment approach for patients without extrahepatic metastases who are not candidates for resection or liver transplantation, or who do not respond to chemotherapy [74-76]. The place of embolization in the treatment paradigm is not established. Embolization can be considered for patients with large tumor to improve resectability, and portal vein embolization can be utilized to ensure adequate liver reserve post resection.

Combined modality therapy — Multimodality therapy may be an option for nonmetastatic relapsed or initially unresectable disease [44]. At least two case reports and a series from the Childhood Liver Tumour Strategy Group suggest FLC can be downstaged to resectability using a variety of neoadjuvant chemotherapy approaches (gemcitabine plus oxaliplatin [GEMOX], cisplatin plus epirubicin and fluorouracil [FU], and carboplatin plus doxorubicin alternating with cisplatin) [77-79]. In the pediatric series, partial response to preoperative chemotherapy occurred in 4 of 13 patients with FLC, all of whom were subsequently able to be resected [77]. Long-term outcomes were not reported for this group separately from those who had initial surgery or did not undergo resection after neoadjuvant chemotherapy.

Systemic therapy — Systemic therapy alone is an appropriate option for patients with locally advanced unresectable tumors, as well as for those with metastatic disease. There is no

consistently effective form of systemic therapy, and there are no trials supporting benefit of any regimen over another; as such, the choice of regimen is empiric.

Cytotoxic chemotherapy — Case reports suggest some efficacy for platinum-based regimens, such as cisplatin, epirubicin, and fluorouracil (FU) combinations [13,44,78]. In one series of 25 patients treated with FU and recombinant interferon alpha 2B (IFNa), there was a 32 percent objective response rate, and two patients had complete response [13]. In another study, two of nine patients had a partial response to cisplatin plus FU [44]. Additional case reports have shown response to gemcitabine plus oxaliplatin (GEMOX) [80] and erlotinib and bevacizumab [81].

Children are more commonly treated with regimens that are used for hepatoblastoma, such as cisplatin plus epirubicin and FU, and carboplatin plus doxorubicin alternating with cisplatin [77,78]. (See "Overview of hepatoblastoma".)

Overall, outcomes with systemic chemotherapy are generally poor for individuals with advanced unresectable disease (five-year survival of less than 10 percent and median survival of less than two years) [8,13,21].

Targeted agents — Sorafenib modestly prolongs survival in patients with advanced HCC and is an option for first-line therapy, although immunotherapy approaches are generally preferred for patients who are eligible for them. (See "Systemic treatment for advanced hepatocellular carcinoma", section on 'Sorafenib'.)

Only limited data are available on the efficacy of sorafenib in FLC, and its use cannot be recommended given the paucity of available data:

- In a report from the Fibrolamellar Carcinoma Consortium, sorafenib was given to 10 patients; eight had disease progression after 2.5 to 7 months of treatment, one had a mixed response followed by progression, and one was lost to follow-up [21].
- Another limited case series demonstrated four out of nine patients treated with sorafenib to have stable disease; there were no objective responders [82].

More recently, the finding of differential outcomes according to sex, prior reports noting high levels of aromatase activity and elevated estradiol levels in patients with FLC [24,83,84], and the finding of activation of the mechanistic (previously called mammalian) target of rapamycin (mTOR) pathway in FLC cells [85,86] have suggested a potential therapeutic role for antiestrogenic therapy and mTOR inhibitors.

In particular, there are isolated case reports suggesting mTOR inhibition may be beneficial in FLC [87]. These findings led to the first randomized clinical trial for FLC with three arms: the mTOR inhibitor everolimus, estrogen deprivation therapy with leuprolide plus letrozole, and everolimus plus estrogen deprivation therapy. Unfortunately, the study revealed no improvement in progression-free survival and a lack of clinical activity in all three study arms, which led to the study being closed early [88].

Many FLC tumors contain the *DNAJB1-PRKACA* gene fusion, which represents a true oncogene and has prompted interest in its potential as a target for therapy. (See 'Molecular diagnostics' above.)

In mouse models, clustered regularly interspaced short palindromic repeats (CRISPR) technology has demonstrated that fusion of *DNAJB1* increased tumorigenesis and further validated the potential for future therapeutic studies [89]. This has led to interest in its encoded protein Aurora kinase A (AURKA) as a druggable target. ENMD-2076 is a selective inhibitor of AURKA, but unfortunately a phase II study showed disappointing results with 3 percent partial response and only 57 percent stable disease, leading the authors to conclude no future studies be conducted as a single agent for FLC [90].

More recent preclinical data suggests *DNAJB1-PRKACA* phosphorylates beta catenin resulting in oncogene activation; these data suggest that beta catenin might be a potential therapeutic target [91]. Clinical studies are needed.

Immunotherapy — Case reports have showed mixed outcomes [82,92,93].

The combination of atezolizumab and bevacizumab was the first study in over a decade to show improved survival over the standard of care, sorafenib, in metastatic HCC. Since that time additional immunotherapy options have become available for HCC [94]. (See "Systemic treatment for advanced hepatocellular carcinoma", section on 'First-line therapy'.)

Patients with FLC have not been included in these studies. Case reports have had mixed outcomes with immune checkpoint inhibitor immunotherapy and further studies will be necessary [82,92,93].

Ongoing trials — For most patients, we prefer enrollment in a clinical trial testing new strategies, if one is available. Since FLC is such a rare disease without established treatment regimens, patients with FLC should be considered for referral to tertiary care centers with clinical trial availability. At present, there are studies involving *DNAJB1-PRKACA* fusion peptide vaccine combined with checkpoint inhibitors (NCT04248569), another study using combination of checkpoint inhibitor with fluorouracil and interferon (NCT04380545) and dual

checkpoint inhibition is also under study [95]. This novel approach is evaluating the Fc-engineered anti-CTLA-4 agent botensilimab in combination with anti-PD-1 agent balstilimab, and there is a specific cohort of patients with FLC.

DNAJB1-PRKACA chimeric transcripts, which are detected in almost all FLC, produce a fusion protein with retained kinase activity and increased expression of several oncogenic signaling pathways including, but not limited to, human epidermal growth factor receptor type 2 (*HER2*, *ERBB2*). Ongoing studies suggest potential efficacy for neratinib, a pan-HER signaling inhibitor and the combinations of immunotherapy plus targeted therapy that includes neratinib and everolimus [96]. (See 'Molecular diagnostics' above.)

Another critical effort still needed is to better understand the disease and define its etiology. Different registries to collect health information in individuals with FLC are underway (NCT04874519).

Radiation therapy — External beam radiation therapy has shown little benefit for FLC and is generally used in combination with chemotherapy [97]. Radiation therapy, while not typically used for primary management of FLC, can be helpful for symptomatic recurrent or metastatic disease [98]. There are also case reports of selective internal radiation with yttrium-90 beads in order to downsize tumors [99]. In this case report, the patient was downsized to allow curative resection.

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Fibrolamellar carcinoma (FLC) is a rare and malignant tumor that affects patients without a history of cirrhosis. (See 'Epidemiology' above.)
- **Clinical presentation** – The clinical symptoms of FLC are usually nonspecific and may include nausea, abdominal discomfort or fullness, weight loss, and/or night sweats. Uncommonly, patients present with a paraneoplastic hormone syndrome or with symptoms related to metastatic disease. (See 'Clinical presentation' above.)
- **Diagnosis and differential diagnosis**
  - The diagnosis of FLC is typically made on the basis of clinical presentation and imaging studies; negative serum tumor markers such as alpha-fetoprotein may also support the diagnosis. If diagnostic uncertainty persists following cross-sectional imaging or in the setting of metastatic disease, percutaneous biopsy may be necessary to confirm the diagnosis and remains the gold standard. (See 'Diagnosis' above.)

- Molecular diagnostics may also aid in the diagnosis. Most cases have a unique deletion on chromosome 19 that leads to a *DNAJB1-PRKACA* fusion gene and a functional DNA-KB1-PRKACA chimeric transcript. Although commonly found in FLC, the deletion and fusion gene are neither highly sensitive nor specific for FLC. (See 'Molecular diagnostics' above.)

- Despite differences in clinical presentation, imaging, and pathologic features FLCs are frequently misdiagnosed as hepatocellular cancer (HCC). FLC can also mimic benign liver masses (eg, adenoma, focal nodular hyperplasia, mesenchymal hamartoma, hemangioma), as well as other malignant lesions. In difficult cases, open or wedge biopsy may be necessary to obtain adequate tissue for diagnosis. (See 'Differential diagnosis' above.)

- **Staging and prognosis**

  - The tumor, node, metastasis (TNM) staging classification from the American Joint Committee on Cancer /Union for International Cancer Control is used for both HCC and FLC (table 1)

  - The most important prognostic factors are disease stage and resectability. Although patients often have advanced disease at diagnosis, 70 to 75 percent are amenable to complete resection, and approximately 40 to 70 percent are still alive 5 and even 10 years later. However, between 50 and 100 percent relapse despite radical surgery, and most ultimately die of their disease. (See 'Prognosis and prognostic factors' above.)

- **Treatment**

  - **Resectable disease**

    - For patients with no evidence of disseminated disease, complete surgical resection with lymphadenectomy represents the best chance for long-term survival. (See 'Potentially resectable disease' above.)

    - There are no data on the appropriate tests or frequency of tests for post-treatment surveillance. However, early detection of relapse combined with aggressive treatment may prolong survival. Many physicians perform CT scans of the chest, abdomen, and pelvis at intervals of three to six months for at least the first two to three years. Some authors suggest serial assay of B12 binding capacity (B12BC). (See 'Tumor markers' above and 'Post-treatment surveillance' above.)

  - **Unresectable disease**

- Approximately 20 to 25 percent of patients have categorically unresectable disease, which is associated with a five-year survival rate of 0 to 5 percent and a median survival of 12 months or less. The best form of therapy for these individuals is not established, and there is no standard of care. (See 'Unresectable cases' above.)

- Liver transplantation may be considered for selected patients without extrahepatic metastases if partial hepatectomy is not technically feasible because of the size of the tumor or because of local extension and/or adhesion to other organs. However, unlike HCC, patients with FLC are not prioritized for orthotopic liver transplantation in the United States. Living donor liver transplantation may represent an option for FLC, but the data are extremely limited. (See 'Liver transplantation' above.)

- Hepatic artery chemoembolization has been used as an alternative approach for patients without extrahepatic metastases who are not candidates for resection or liver transplantation, or who do not respond to chemotherapy. (See 'Embolization' above.)

- Multimodality therapy may be an option for nonmetastatic relapsed or initially unresectable disease, and may allow some patients to be downstaged to the point of potential resectability. (See 'Combined modality therapy' above.)

- Systemic therapy is appropriate for patients with unresectable tumors, but there is no consistently effective form of systemic therapy, and the choice of regimen is empiric. We prefer enrollment in a clinical trial testing new strategies, if one is available. Since FLC is such a rare disease without established treatment regimens, all patients with FLC should be referred to tertiary care centers with clinical trial availability. (See 'Ongoing trials' above.)

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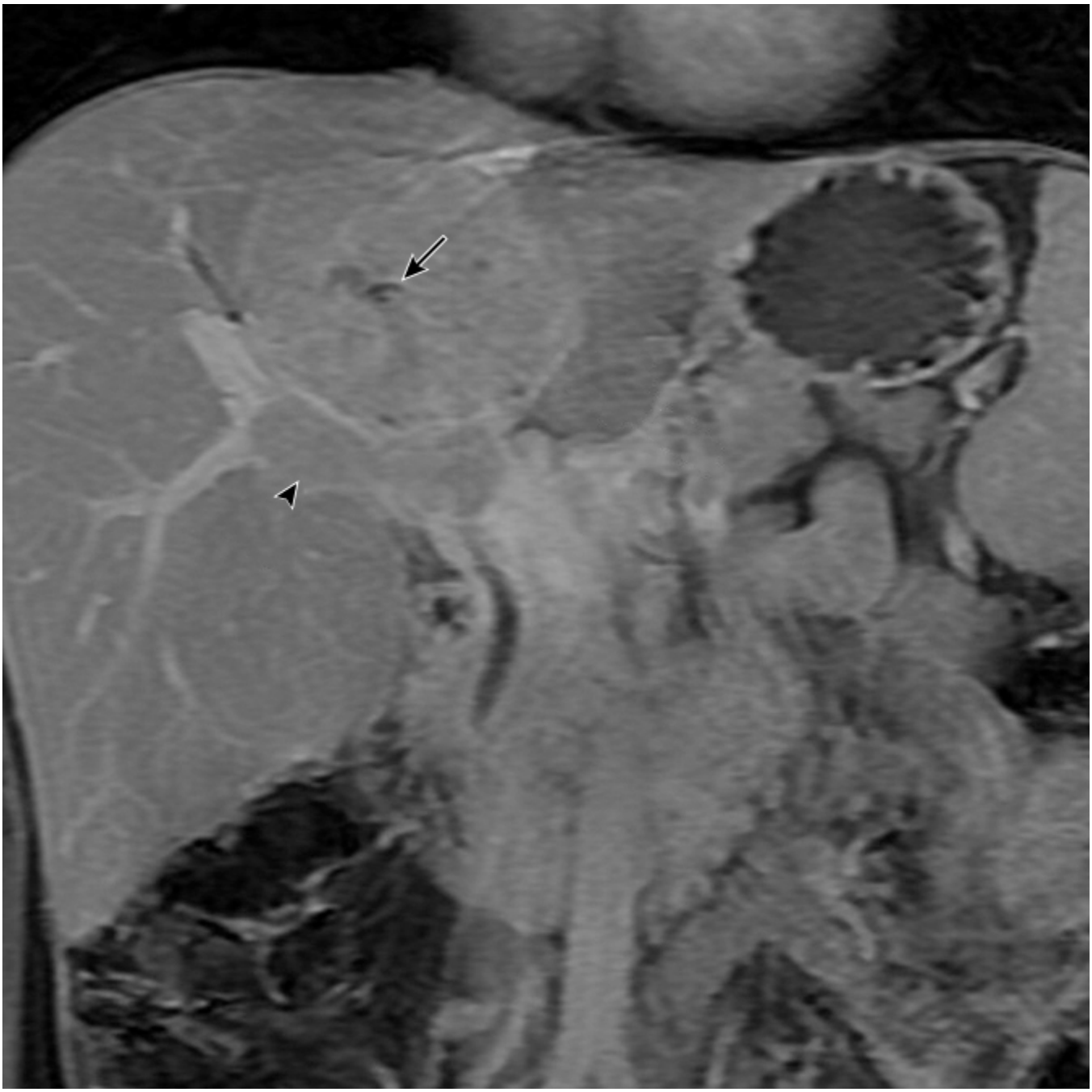
Topic 16571 Version 13.0

GRAPHICS

Fibrolamellar carcinoma coronal MRI image



T1-weighted coronal image of MRI with gadolinium enhancement demonstrated enhancing mass with characteristic central scar (arrow). Tumor thrombus is also noted in the adjacent portal vein (arrowhead).

MRI: magnetic resonance imaging.

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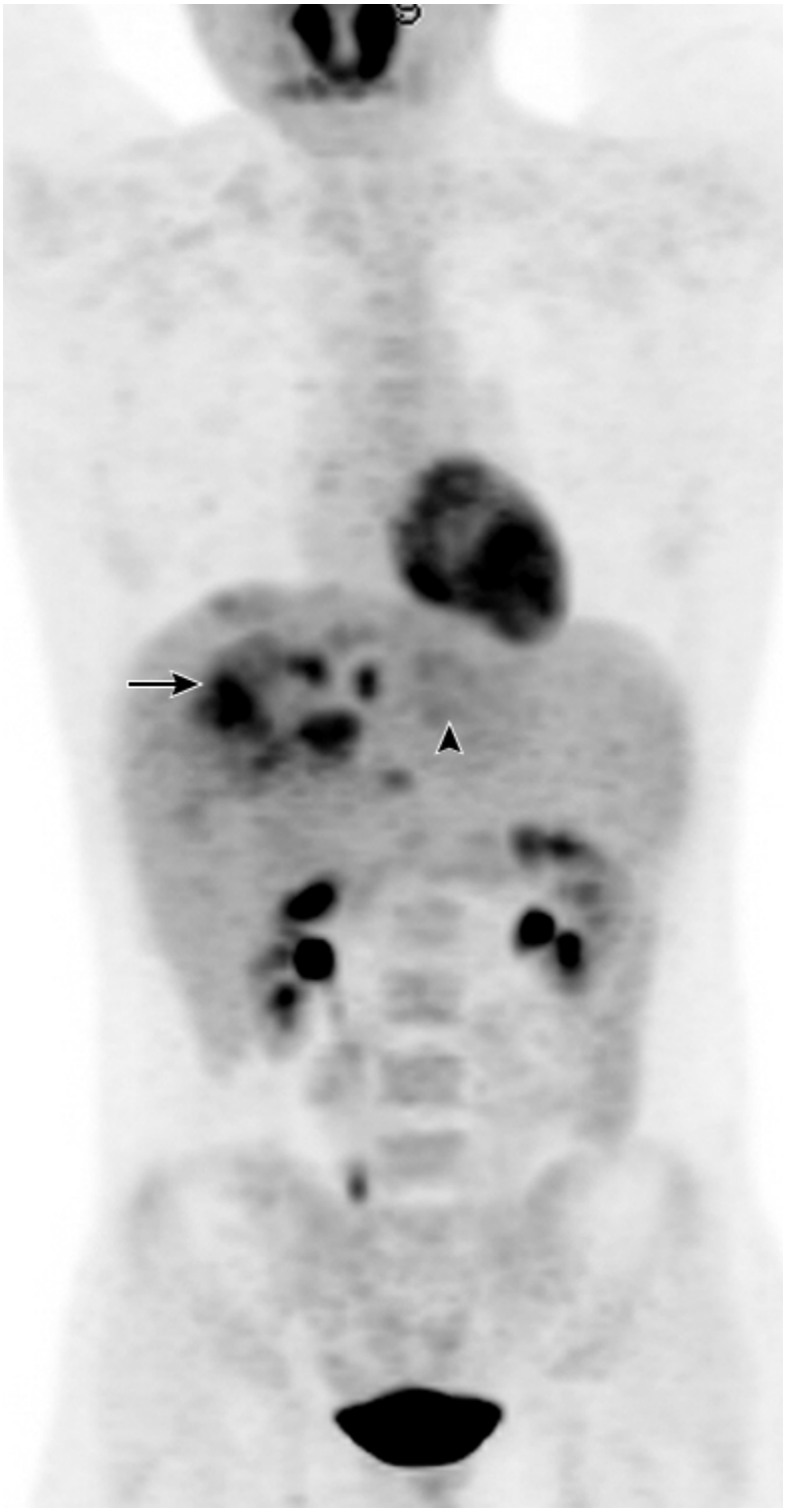
Graphic 114811 Version 1.0

Fibrolamellar carcinoma: Imaging with fluorodeoxyglucose positron emission tomography (FDG-PET)



PET scan demonstrates multifocal fibrolamellar carcinoma in the liver with variable uptake of FDG. Some tumors are FDG avid (arrow), and others demonstrate less uptake (arrowhead).

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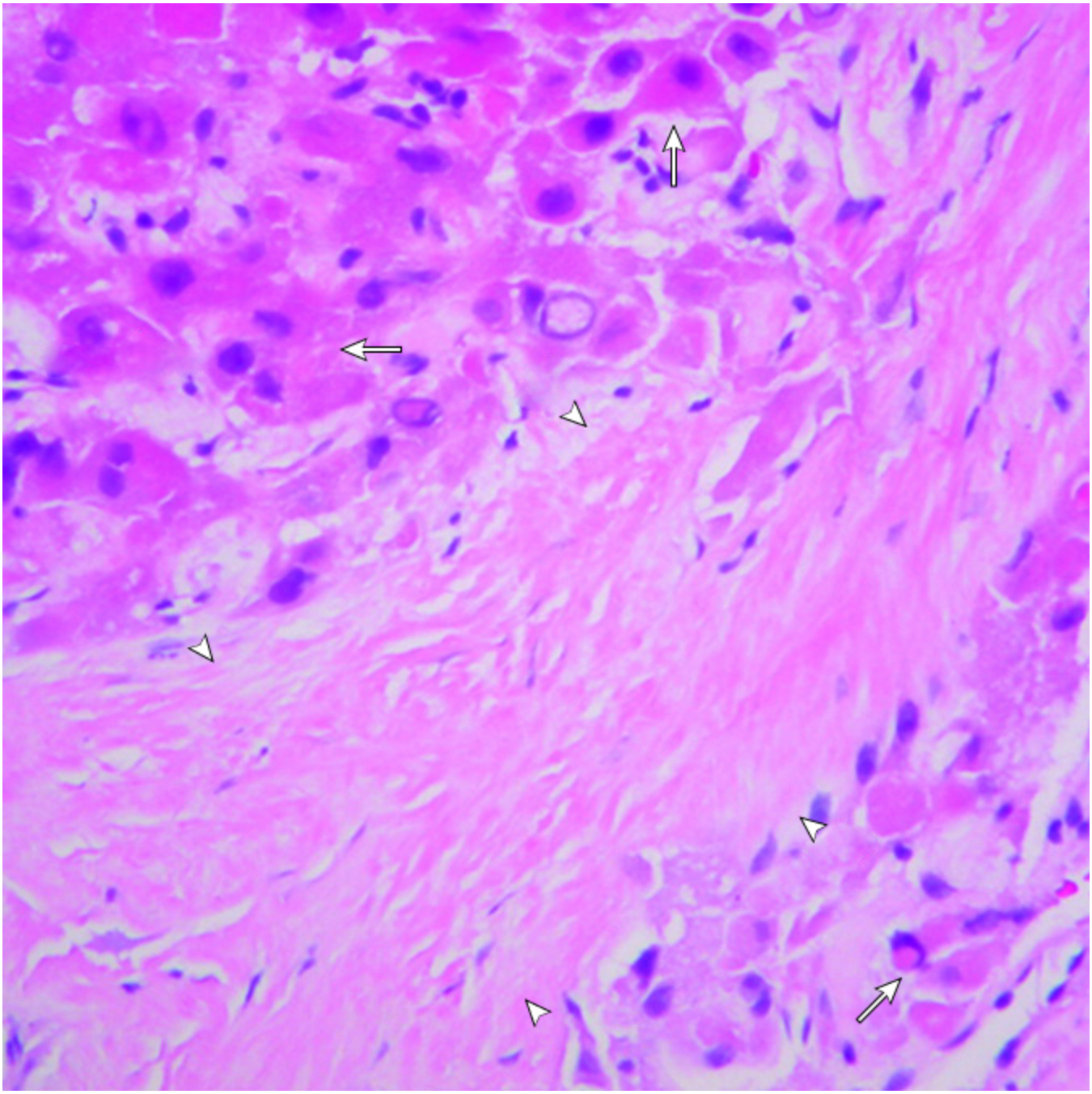
Fibrolamellar carcinoma histopathology



Hematoxylin and eosin (H&E) stain photomicrograph of fibrolamellar carcinoma with characteristic large, polygonal cells filed with eosinophilic cystoplasmic bodies (arrow) and adjacent parallel arrangement of abundant fibrous stroma (arrowheads).

Graphic 114808 Version 1.0

Hepatocellular cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2 cm, or >2 cm without vascular invasion
T1a	Solitary tumor ≤2 cm
T1b	Solitary tumor >2 cm without vascular invasion
T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
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

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Contributor Disclosures

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