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Clinicopathologic Characteristics and Survival Outcomes of Patients With Fibrolamellar Carcinoma: Data From the Fibrolamellar Carcinoma Consortium

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ABSTRACT

BACKGROUND: Fibrolamellar carcinoma is a rare and poorly understood malignancy that affects the young in the absence of underlying liver disease. Despite reported small review series, the literature lacks large retrospective studies that may help in understanding this disease.

METHODS: Medical record review was undertaken for all patients histopathologically diagnosed with fibrolamellar carcinoma, seen at Memorial Sloan-Kettering Cancer Center, the University of California San Francisco, and Johns Hopkins Hospital from 1986 to 2011. Demographic, clinical, pathologic, and treatment data were recorded. Overall survival was estimated by using Kaplan-Meier methods. The impact of different clinicopathologic variables on survival was assessed with Cox regression models.

RESULTS: Ninety-five patients were identified. Median age was 22 years, 86% were Caucasian, and 50% presented with stage IV disease. There were more females than males (58% vs. 42%). Seventy-seven percent of the patients underwent surgical resection and/or liver transplantation; of these 31.5% received perioperative therapy. Patients with unresectable disease, including 8 patients treated in clinical trials, were treated with chemotherapy, occasionally given with interferon or biologic agents. Ten patients received sorafenib, and 7 received best supportive care. Median survival was 6.7 years. Factors significantly associated with poor survival were female sex, advanced stage, lymph node metastases, macrovascular invasion, and unresectable disease.

CONCLUSIONS: The clinicopathologic characteristics and survival outcomes from this dataset are consistent with those reported in the literature. Surgical resection and disease extent were confirmed as important predictors of survival. The possibility of a negative association between female sex and prognosis could represent a clue as to future therapeutic strategies.

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Fibrolamellar carcinoma (FLC) is a distinctly uncommon primary liver neoplasm, representing 0.6% to 8.6% of all hepatocellular carcinomas, according to 1986 to 1999 SEER data and various international series.[1–3] In contrast to typical hepatocellular carcinoma (HCC), FLC most often affects adolescents and young adults of both sexes, often Caucasian, and without a history of parenchymal liver disease.[4–8]

Pathologically, large polygonal cells with abundant eosinophilic cytoplasm and large nucleoli characterize FLC. The term fibrolamellar is derived from the presence of thick fibrous collagen bands surrounding these cells.[9,10] Cytoplasmic pale bodies and copper deposits may be present, and an ultrastructural resemblance to neuroendocrine tumors has been reported.[9,11] On immunohistochemistry, α-fetoprotein (AFP), synaptophysin, and chromogranin are typically absent. In contrast, immunoreactivity for HepPar-1, pCEA, cytokeratin 7, and epithelial membrane antigen is present in nearly all FLC tumors, suggesting that this disease entity may be a hepatobiliary hy-

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brid.[12] Clinically, compared to typical HCC tumors, those in FLC tend to be larger and demonstrate a higher propensity for lymph node metastases.[9,13]

Since FLC was first described by Edmondson[14] in 1956, little progress has been made toward uncovering the molecular and genetic mechanisms that underlie its genesis and clinical behavior. Along with the rarity of this disease, reports of long-term survival with resection and/or transplantation[10,15] have fueled the perception of FLC as being an indolent disease, possibly lessening its relevance as a research priority. However, more recent data suggest that this perception is probably inaccurate, given the high recurrence rates after surgery and the morbidity, mortality, and poor prognosis associated with unresectable disease.[3,8,13,15]

The Fibrolamellar Carcinoma Consortium is a tri-institutional collaboration involving Memorial Sloan-Kettering Cancer Center (MSKCC), the University of California at San Francisco (UCSF), and Johns Hopkins Hospital. The Consortium was developed in an effort to address the challenges associated with studying FLC, such as small study samples and the lack of awareness of this disease within the oncology community, and to identify new treatment options. We present the pooled demographic, clinical, pathologic, treatment, and survival data of 95 patients with FLC seen at the Consortium institutions from 1986 to 2011. Portions of this work have been published in abstract form.

PATIENTS AND METHODS

Patients

Institutional review board approval was obtained at MSKCC, UCSF, and Johns Hopkins University to review the medical records of all patients with a histopathologic diagnosis of FLC from 1986 to 2011. Patient demographics, histopathology, and clinical information, including diagnosis and treatment histories, radiographic and operative reports, dates of last follow-up, and death, were extracted. The study was conducted, and the patients' identities protected in accordance with the Declaration of Helsinki.

Pathology

Tumors were examined by pathologists at each institution to confirm the diagnosis of FLC. Cases in which the diagnosis was in question were reviewed and adjudicated by expert pathologists (D.K., M.S.T., and L.F.). Patients who had mixed FLC and typical HCC features were excluded.

Immunohistochemistry

Tumors were stained for various epithelial markers at the discretion of expert pathologists (D.K., M.S.T., and L.F.) at each institution. Selected tumors also were stained for the epidermal growth factor receptor (EGFR), human epidermal growth factor receptor (Her)-2, c-kit, estrogen, and progesterone receptors.

Statistics

Patient demographics, disease characteristics, and treatment histories were summarized with descriptive statistics. Overall survival (OS) was calculated from date of pathologic diagnosis of FLC to date of death or last known follow-up. Median OS and 1- and 3-year OS were estimated by Kaplan-Meier methods. Clinical and pathologic variables were evaluated for their impact on survival by Cox regression univariate analysis stratified by study center and were compared by using the stratified log-rank test to control the effect of multiple centers. A univariate Cox model was also used to test the association of surgery with OS by treating surgery as the time-dependent covariate. A multivariate Cox model stratified by study center was built to examine the set of factors independently predictive of OS. Association between nodal metastasis, extrahepatic metastasis, and macrovascular invasion was evaluated by Fisher's exact test. All analyses were performed in SAS (ver. 9.2).

RESULTS

Patient Demographics, Referral Patterns, and Disease Characteristics

Of the 98 patients initially identified, 3 had mixed FLC-HCC and were excluded. Of the 95 patients with pure FLC, 62 (65%) were from MSKCC, 19 (20%) from UCSF, and 14 (15%) from Johns Hopkins University. The median age at diagnosis was 22 years (range, 11–65). Eighteen (19%) patients were 11 to 16 years of age. There were more females than males (58% vs. 42%), and they were predominantly Caucasian (86%).

Eighty-one (85%) patients were referred from outside institutions to one of the Consortium institutions for initial or postrelapse treatment or consultation. Of these, 28 (34.5%) returned to their community for subsequent treatment. Only 14 (15%) were diagnosed and received all treatment at the Consortium institutions.

Details on presenting symptomatology were available only for the MSKCC patients. Most of the patients presented with nonspecific symptoms, including abdominal pain in 26 (42%), an abdominal mass and/or distension in 15 (24%), anorexia and/or weight loss in 14 (23%), nausea in 9 (14.5%), flu-like symptoms in 10 (16%), and fatigue and/or malaise in 10 (16%). Patients were diagnosed immediately postpartum. Four, ages 14 to 16, had menstrual irregularities.

Patients who underwent resection had a median tumor diameter of 10 cm (range, 1.1–30 cm). Forty patients (42%) had vascular invasion: macrovascular (major branch of portal or hepatic vein) in 23 patients and microvascular in 17. Vascular involvement was pathologically confirmed in 28 cases, including all 17 patients with microvascular invasion.

Fifty-seven (60%) patients had extrahepatic metastases at presentation; 40 (74%) had lymph node involvement (27 biopsy confirmed, 13 radiographically enlarged), representing the most common site of metastasis; 9 (9%) had pulmonary metastases, and 8 (8%) had peritoneal metastases.

Pathology and Molecular Markers

All of the patients had a histopathologically confirmed diagnosis of FLC. In 2, a 15-year-old girl and 20-year-old man, the initial diagnosis was hepatoid germ cell tumors. The results of immunohistochemical tumor stains were available for 17 patients. Markers of biliary and hepatic differentiation such as cytokeratin 7, CAM5.2, epithelial membrane antigen, and HepPar-1 were present in 75% to 100% of tumors tested. One of the tumors was initially classified as a transformed germ cell tumor, having demonstrated the presence of isochromo-

Table 1. IHC markers and oncogenes in FLC

	Positive/tested (*n*)
Immunostains	
Cytokeratin 7	8/9
CAM5.2	3/3
AE1:AE3	1/1
Epithelial membrane antigen	3/4
HepPar-1	9/9
α-Fetoprotein	1/4
α1-Antitrypsin	0/2
Neurotensin	1/1
Cytokeratin	0/2
CEA	0/1
Oncogenes by IHC	
EGFR expression	5/5
EGFR vIII mutation expression	1/1
Her-2 expression	1/3
c-kit expression	0/2
Estrogen and progesterone receptor expression	0/1

IHC = immunohistochemistry; EGFR = epidermal growth factor receptor.

some 12p on fluorescence in situ hybridization (FISH) analysis.

Tumors were also examined for various oncogenes. All 5 patients in whom tumors were tested for EGFR demonstrated immunoreactivity. Of note, mutational analysis was not performed on these specimens. In another patient, the tumor harbored the EGFR vIII mutation. One tumor was weakly positive for Her-2 expression. Tumors tested for c-kit and the estrogen and progesterone receptors did not demonstrate immunoreactivity.

Immunostains and oncogenes evaluated in FLC specimens are summarized in Table 1.

Laboratory Markers

There are presently no validated tumor markers in FLC, although elevations in serum neurotensin,[16] vitamin B_{12} binding capacity (transcobalamin),[17,18] and plasma des-γ-carboxyprothrombin[19] have been associated with disease burden. Elevations in serum AFP are uncommon in FLC.[7,13]

Serum AFP, neurotensin, and/or vitamin B_{12} levels were measured in 34 patients at some point during their clinical course. Serum AFP was measured in a total of 31 patients and was normal or elevated to less than 25 ng/mL in 28; 5 patients had elevated levels ranging from 100 to 280 times above the normal range. In most of the patients, AFP levels were stable throughout their disease course. Vitamin B_{12} binding capacity was measured in 2 patients and was increased in both. Three patients had elevated serum vitamin B_{12} levels. Serum neurotensin was elevated in 4 of the 8 patients in whom it was measured. Plasma des-γ-carboxyprothrombin was not measured in any patient. With the exception of AFP, blood markers were not serially measured. The young female patient who was initially treated for a hepatoid germ cell tumor presented with elevated CA 125 levels that appeared to follow the disease course.

Management

Seventy-three (77%) patients underwent surgery, including 4 who underwent liver transplantation. Another 2 were considered surgical candidates, but there were no records to indicate whether surgery was actually performed. The extent and completeness of surgery was determined from operative and pathology reports where available. Surgery was performed with curative intent in 58 patients, and 15 patients underwent palliative debulking resections. Thirty-seven, 8, and 4 patients had R0, R1, and R2 resections, respectively. Lymph node dissections were performed in 44 (60%) patients.

Twenty-three (31.5%) of the patients who underwent resection received perioperative therapy. Nine of these were treated with preoperative chemotherapy, external beam radiation, and/or transarterial chemoembolization (TACE) with doxorubicin, cisplatin, and mitomycin-C. Eight patients received postoperative adjuvant chemotherapy, TACE, and/or radiation; 1 of these patients underwent transarterial radioembolization with Iodine-131-labeled lipiodol in Hong Kong. Five additional patients received postoperative therapy after palliative surgery. One patient received both pre- and postoperative chemotherapy.

Fifty-six (77%) of the patients who underwent surgery developed recurrent disease and were treated with various combinations of surgery, chemotherapy, and liver-directed therapies. Two patients underwent transplantation for recurrent disease, of whom 1 received a second liver transplant after developing a recurrence nearly 11 years after the first operation.

Twenty (21%) patients were considered to have unresectable disease because of major vessel involvement, lymph node metastases, and/or widespread extrahepatic metastases. Thirteen of them were treated with various combinations of systemic therapy, with or without locoregional therapies including TACE, radiofrequency ablation, external beam radiation, percutaneous ethanol injection, and hepatic arterial infusion of cisplatin. Seven received only best supportive care because of poor performance status and/or heavy disease burden.

The chemotherapy agents used included fluoropyrimidines, doxorubicin, cisplatin, oxaliplatin, gemcitabine, and irinotecan. Pediatric patients tended to be treated according to a hepatoblastoma paradigm using various combinations of cisplatin, doxorubicin, ifosfamide, vincristine, cyclophosphamide, etoposide, and fluoropyrimidines. Three patients received thalidomide. One patient underwent intraperitoneal chemotherapy with mitomycin-C. Another developed brain metastases and was treated with concurrent whole-brain radiation and

temozolomide. Four patients were treated with fluoropyrimidine and interferon combinations. One patient was treated with the PIAF (cisplatin, interferon, doxorubicin, and 5-fluorouracil) regimen.[20] Eight patients were enrolled in various clinical trials evaluating flavopiridol with cisplatin/irinotecan, the Chk inhibitor XL 844 plus gemcitabine, rapamycin, huang lian, the anti-endosialin antibody MORAb 004, and bland vs. doxorubicin-eluting bead chemoembolization. Of note, 2 patients enrolled in the flavopiridol protocol had stable disease for 17 months. Two patients received megestrol acetate, and one received octreotide although an octreotide scan was negative. Five patients received bevacizumab, 3 received EGFR tyrosine kinase inhibitors, and 1 received imatinib. In no patients was a durable, RECIST (response evaluation criteria in solid tumors)-defined radiologic response seen with systemic therapy.

Ten patients received sorafenib at some point during the treatment course. Best responses to sorafenib included 8 with disease progression after 2.5 to 7 months of treatment, 1 with a mixed response followed by progression, and 1 lost to follow-up shortly after starting therapy. Three patients who initially progressed while on sorafenib were subsequently treated with sorafenib and doxorubicin; 2 progressed after 3 and 4 months of therapy; 1 had stable disease for 3 months but subsequently discontinued treatment because of an asymptomatic drop in left ventricular ejection fraction from 65% to 55%. Treatment data are summarized in Table 2.

Table 2. Therapeutic modalities

Therapy	Patients *n* (%)
Surgery	**73/95 (77%)**
Liver resection	69/73 (94.5%)
R0/R1/R2	37/8/4
Lymphadenectomy	44/73 (60%)
Transplant (curative + salvage)	6/73 (8%)
Perioperative systemic/locoregional therapy	**23/73 (31.5%)**
Preoperative only	9/73 (12%)
Postoperative (adjuvant+palliative) only	13/73 (18%)
Pre- and postoperative	1/73 (1%)
Nonsurgical therapies used	
Systemic (chemotherapy, immunotherapy, biologic)	41/95 (43%)
Regional chemotherapy (HAI, intraperitoneal)	2/95 (2%)
Liver-directed ablative therapy (TAE, PEI, RFA)	16/95 (17%)
External beam radiation	14/95 (15%)
Best supportive care only	7/95 (7%)

N = 95 patients. HAI = hepatic arterial infusion; TAE = transarterial embolization (bland, with chemotherapy or radiation); PEI = percutaneous ethanol injection; RFA = radiofrequency ablation.

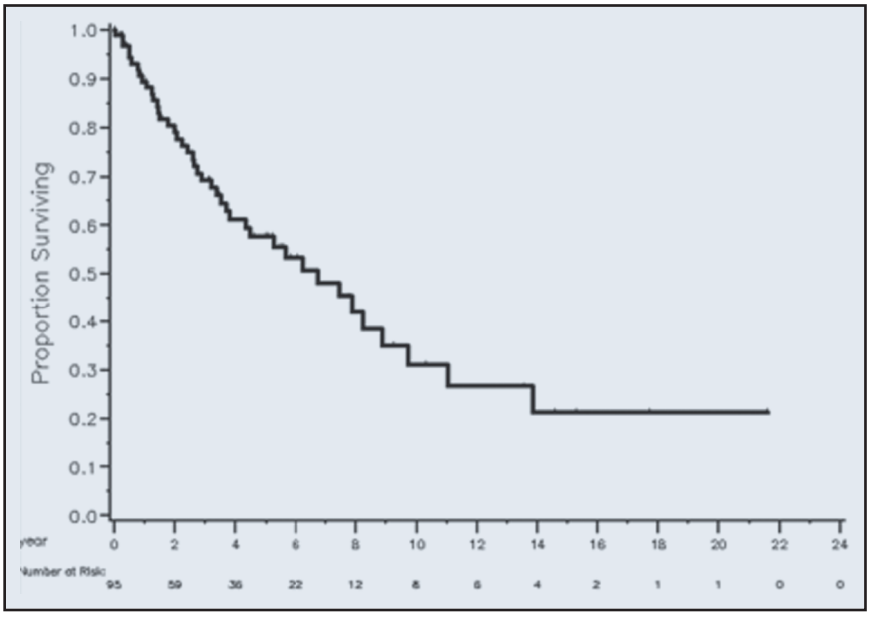

Figure 1. Overall survival after diagnosis.

Survival

At the time of data censoring in May 2011, 42 (44%) patients had died. Median overall survival for the entire cohort was 6.7 years (Figure 1). Median follow-up time for living patients was 3.4 years.

Univariate Analysis of Predictors of Survival

The impact of various demographic and disease characteristics on survival was evaluated by univariate analysis (Table 3). Female sex, macrovascular invasion, unresectable disease, and lymph node and extrahepatic metastases were significantly associated with worse overall survival. The presence of lymph node metastases, extrahepatic disease, and macrovascular invasion correlated highly with each other.

Multivariate Analysis

On multivariate analysis, female sex, lack of surgery, and extrahepatic metastases were found to independently predict poor overall survival (Table 4). Macrovascular invasion was not included in the multivariate model, given the large proportion (26%) of patients for whom this information was missing.

DISCUSSION

The pooled data of the Fibrolamellar Carcinoma Consortium are consistent with results of other retrospective studies describing the epidemiology, clinicopathologic characteristics, and survival outcomes of patients with this disease.[1,3,7,13] While most studies

Table 3. Univariate analysis of clinical/pathological variables and survival

Characteristics at presentation	Patients ($N = 95$)	Hazard ratio (95% CI)	1-year survival	3-year survival	Median survival (mo)	*P*-value*
Sex						
Female	55 (58%)	1.00	86%	59%	63.1	0.03
Male	40 (42%)	0.47 (0.23–0.92)	94%	84%	98.8	
Age (y)						
<20	44 (46%)	1.00	89%	72%	52.1	0.31
>20	51 (54%)	0.72 (0.37–1.36)	90%	65%	89.7	
Surgery						
Yes	73 (77%)	0.18 (0.09–0.35)				<0.0001†
No	20 (21%)	1.0				
Nodal metastases						
Yes	40 (42%)	2.64 (1.35–5.17)	81%	58%	45.6	0.005
No	49 (52%)	1.00	95%	77%	98.8	
Unknown	6 (6%)					
Macrovascular invasion						
Yes	23 (24%)	4.94 (2.22–10.97)‡	73%	24%	17.6	<0.0001
No	47 (49%)	1.00	90%	82%	98.8	
Unknown	25 (26%)					
Extrahepatic metastases						
Yes	48 (51%)	3.7 (173–7.97)	79%	52%	38.4	0.0004
No	41 (43%)	1.00	100%	87%	117	

*Obtained from a Cox regression model with surgery coded as the time-dependent variable.
†Calculated only for patients with known vascular status.
‡Calculated with a stratified log-rank test.

Table 4. Multivariate analysis and overall survival

	Hazard ratio	95% CI	*P*-value
Sex			
Female	1.00	0.10–0.54	0.0006
Male	0.24		
Extrahepatic metastases			
Yes	4.21	1.93–9.15	0.0003
No	1.00		
Surgery*			
Yes	0.09	0.04–0.20	<0.0001
No	1.00		

have reported an equal distribution between the sexes, the current study adds to the data suggesting a slight female preponderance.[1,3] The high prevalence of this disease among Caucasians, which has also been reported in other studies,[1,10] is noteworthy and may represent referral bias, with a possible socioeconomic undercurrent.

FLC is an enigmatic disease entity. Our collective knowledge, principally derived from anecdotal reports and retrospective reviews such as the current one, demonstrates that it is a disease with many paradoxes. Although patients often have advanced disease at diagnosis, nearly 70% are amenable to complete resection, and approximately 40% to 70% are still alive 5 and even 10 years later, according to contemporary series.[3,8,13,15,21,22] However, 50% to 100% of patients relapse despite radical surgery, and most ultimately die of the disease.[8,13,15,23,24] At the opposite end of the spectrum, 20% to 30% of patients have unresectable disease[3,13] which is associated with a 5-year and median survival of 0% to 5% and ≤12 months,[3,9,13,15] respectively, and there are no active systemic therapies. These were all similar to the results we report herein. However, clinical experience with FLC has shown that patients within the resectable and unresectable groups and across disease stages can experience outcomes that are highly variable. Several retrospective studies and one clinical trial have reported a similar prognosis between FLC and typical HCC without cirrhosis,[9,22,25–27] raising questions about the relative effects of intrinsic biology vs. the absence of cirrhosis on the natural history of FLC.

The vast assortment of systemic and regional therapies employed reflects the

absence of a standard of care for unresectable disease. Novel contributions of this retrospective analysis include the first descriptions, to our knowledge, of a negative association of female sex with survival, as well as the extent of the use of sorafenib and other molecularly targeted agents in FLC.

This study has several weaknesses. Retrospective studies have known attendant biases that can limit the applicability of the conclusions. Guidelines for pathologic reporting and imaging techniques have evolved over time, thus affecting the completeness and consistency of the information in our database. Given the absence of pertinent data and the small sample size, we were unable to more closely examine the clinical course and outcomes of patients who underwent liver transplantation as primary therapy compared with those with a similar extent of disease treated with hepatectomy. At the present time, surgery remains the standard of care for resectable FLC, although it would be important to explore the role of transplantation in a larger population of eligible patients. Molecular markers were evaluated in a small number of patients and so we are unable to offer any new insights into the biological characteristics of FLC beyond its clinical and pathologic descriptions. However, many of the patients included in this series were seen at a time when the importance of molecular and genetic profiling was not prioritized or as widely accessible as it is today.

Patients with advanced FLC represent an orphan population in need of novel, effective treatments. Therapeutic development has lagged, given the paucity of patients with FLC, making it difficult to harness sufficient power to conduct clinical trials. The only two clinical trials for HCC to have included the FLC variant patients were conducted in mixed populations, composed primarily of patients with typical HCC without cirrhosis.[27,28] Progress is also limited, given that our understanding of the genetic and molecular determinants of FLC pathogenesis is only rudimentary at best. We found the differential outcomes by sex to be particularly intriguing, especially in view of prior reports describing aromatase overexpression and a hyperestrogenic phenotype in patients with FLC.[29–33] These observations form the basis of a phase II clinical trial that we have developed to test the antineoplastic activity of estrogen suppression in FLC by aromatase inhibition and use of a GnRH agonist (www.clinicaltrials.gov, NCT01642186). Although previous studies of anti-estrogen therapy with tamoxifen, a selective estrogen receptor modulator, failed to improve survival in typical HCC,[34] we speculate that this failure may have been due to its agonistic effects in the liver, which may have inadvertently promoted tumor growth. The trial will also assess the activity of mTOR inhibition administered alone or in combination with estrogen deprivation therapy, given data showing overexpression and upregulation of the PI3K/Akt/mTOR signal transduction cascade.[35,36] Recognizing the importance of tissue banking for DNA sequencing and molecular characterization in this disease, like any future efforts, this study will incorporate both serum and tissue correlative studies, including molecular markers for the chosen targets. A parallel effort to help establish a comprehensive FLC registry with tissue and blood banking is under way.

The clinicopathologic features and survival outcomes of FLC in this study are consistent with those in the published literature. However, the poorer prognosis of females is a novel observation that warrants further investigation, particularly in relation to the endocrine properties of the disease. Future efforts should focus on cooperative work to study this unusual and poorly understood disease with a focus on the development of a comprehensive registry, with tissue and blood banking and continued therapeutic development. Several therapeutic targets have been identified based on current knowledge of molecular and genetic alterations that may underlie the pathogenesis and clinical behavior of FLC.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.