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Predictors of Outcome in Patients With Fibrolamellar Carcinoma: Analysis of the National Cancer Database

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Abstract. *Background: Fibrolamellar carcinoma (FLC) is a very rare liver tumor. We aimed to retrospectively analyze the clinicopathological factors and treatment modalities affecting overall survival (OS) in FLC. The objective of the study was to identify predictors of survival in FLC. Patients and Methods: Using the National Cancer Database, we identified 496 patients diagnosed with FLC between 2004 and 2015. Clinicopathological, treatment, and survival data were collected. Results: Hepatic resection was performed on 254 (51.2%) patients, liver-directed therapy on 13 (2.6%) patients, and liver transplantation on 15 (3.0%) patients. Median OS by stage were 142.1, 87.2, 32.3, and 14.1 months for stages 1, 2, 3, and 4, respectively. Metastatectomy was not associated with superior median OS (23.4 vs. 10.5 months, p=0.163). Age ≤40, low Charlson-Deyo comorbidity score, early stage and hepatic resection were independently associated with longer OS. Conclusion: Our study reports current trends in FLC management, and identifies independent predictors of OS.*

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related deaths worldwide (1). In the United States, the incidence of HCC is rising faster than that of any other cancer, both in men and women (2). Historically, fibrolamellar carcinoma (FLC) was classified as a rare variant of HCC, comprising only 0.4-5% of all primary liver tumors in the United Sates (3, 4). However, FLC has a unique pathogenesis, with distinct histological, clinical, and epidemiological characteristics compared to conventional HCC (4, 5). FLC occurs in a distinct population, usually in young patients without the presence of liver cirrhosis or viral hepatitis (6, 7). A characteristic somatic gene fusion, namely *DNAJB1-PRKACA*, has been discovered as the primary oncogenic driver in FLC, with subsequent studies confirming its presence in 79-100% of FLC cases (8-10). In addition, FLC appears to have a more stable genome in comparison to HCC, with fewer somatic mutations and lower levels of promoter methylation (7, 11-13). This difference in tumor biology and clinicopathological features necessitates a better understanding of factors influencing outcomes in patients with FLC.

Due to the rarity of this tumor, management of FLC has posed several challenges to physicians, and treatment approaches have been largely extrapolated from that of HCC (6, 14-17). Liver resection remain the only potentially curative treatment options (6, 18, 19). For unresectable disease, there is no standard of care, and several treatment modalities have been implemented, including chemotherapy, liver-directed therapy (LDT), and external beam radiotherapy (14, 20-22). However, these current practices are generally based on small institutional retrospective studies and case series, and therefore lack the statistical power to draw robust conclusions (17). As such, querying large national databases may better delineate patterns of care and outcome in low-incidence cancers such as FLC.

The present study sought to perform a comprehensive analysis of the clinicopathological characteristics, treatment modalities, and outcome of patients with FLC from the National Cancer Database (NCDB). We also aimed to compare our findings to historical data on conventional

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HCC, as well as identifying independent prognostic factors in FLC patients.

Patients and Methods

Data source. The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB captures information from approximately 1,500 CoC-accredited hospitals and >70% of all newly-diagnosed malignancies in the USA. All data within the NCDB are de-identified of specific patient and hospital factors and are thus in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

Study design. An NCDB participant Use Data File containing data on patients with liver cancer was obtained. Patients diagnosed with FLC were identified using the diagnostic histology code 8171 associated with FLC as per the International Classification of Diseases for Oncology 3rd edition (ICD-O-3 code) (23). Patients' clinicopathological characteristics and treatment modalities were analyzed using frequency statistics and the Chi-square method. Covariates included age, sex, race, Charlson-Deyo Score, grade, tumor size, pathological regional lymph nodes (pN+), stage, alpha-fetoprotein (AFP) level, local therapy, chemotherapy, and radiation therapy. Local therapy was further categorized into hepatic resection (which includes any type of liver resection), LDT, and liver transplantation. The disease stage was determined according to the American Joint Committee on Cancer (AJCC) staging system of primary liver cancer, 7th edition. The Charlson-Deyo score is a weighted score derived from the sum of the scores for each of the comorbid conditions listed in the Charlson Comorbidity Score Mapping Table (24). Overall survival (OS) was defined as the number of months between date of diagnosis and date of death (if known) or last follow-up (last known alive date). Follow-up time was calculated from the date of diagnosis to the last date of contact. AFP level >20 ng/ml was considered positive as per the American Association for the Study of Liver Diseases (25). This study was determined by the institutional review board to be exempt as a result of the de-identified nature of the data.

Statistical analysis. Patient clinicopathological categorical characteristics were reported using frequency statistics (n and %). For continuous variables, the median and interquartile range (IQR) were reported. Wilcoxon rank sum test was performed to compare medians. Kaplan-Meier Survival analysis and plots were created for all covariates to determine unadjusted OS. The log-rank test was used to determine significant associations between covariates and OS. Variables that showed significance with OS on a univariate basis or were potential confounders were included in Cox proportional hazards model for multivariable analysis. Hazard ratios with p-values<0.05 were considered statistically significant. SAS 9.4 was used to perform all analysis.

Results

Patient and tumor characteristics. Using the NCDB, we identified a total of 496 patients diagnosed with FLC between 2004 and 2015. The demographic and clinical characteristics of these patients are presented in Table I. The median age at diagnosis was 32 years. Fifty-six percent of patients were males. Most patients (77.2%) had a Charlson-Deyo Score of 0, reflecting the fact that FLC tends to occur in otherwise healthy patients. With respect to tumor characteristics, the median tumor size was 9.5 cm. Out of 120 patients with stage IV disease at diagnosis, 15 (12.5%) and 52 (43.3%) patients had stage IVA and IVB disease, respectively, with the remaining 53 (44.2%) patients being unspecified. In patients with distant metastasis, lung, bone, and brain metastasis were reported in 26 (50%), 10 (19.2%) patients, and 1 (1.9%) of patient, respectively. Data on grade and pN+ status was missing in a significant proportion of

Table I. *Descriptive statistics for patients with FLC in the NCDB registry between 2004 and 2015.*

Characteristics	All patients (n=496)
Age (years), n (%)	
<40	301 (60.7)
≥40	195 (39.3)
Median (IQR)	32 (23-59)
Gender, n (%)	
Male	277 (55.9)
Female	219 (44.1)
Race, n (%)	
White	346 (69.7)
Black	54 (10.9)
Hispanic	58 (11.7)
Other	38 (7.7)
Charlson-Deyo Score, n (%)	
0	383 (77.2)
1	67 (13.5)
2	18 (3.6)
3	28 (5.7)
Tumor size (cm)	
Median (IQR)	9.5 (5.9-13.0)
Pathologic regional LNs (pN+), n (%)	
No	80 (16.5)
Yes	70 (14.5)
Unknown	334 (69)
Stage, n (%)	
1	114 (31.2)
2	43 (11.8)
3	89 (24.3)
4	120 (32.8)
Grade, n (%)	
Well-differentiated	46 (9.3)
Moderately differentiated	127 (25.6)
Poorly differentiated	37 (7.5)
Undifferentiated	3 (0.6)
Unknown	283 (57.1)
AFP, n (%)	
Negative	196 (39.5)
Positive	146 (29.4)
Unknown	154 (31.1)

IQR: Interquartile range; LN: lymph node; AFP: alpha-fetoprotein.

Table II. *Treatment modalities of FLC patients.*

Treatment	All patients n=496
Local therapy, n (%)	
Hepatic resection	254 (51.2)
Liver-directed therapy	13 (2.6)
Liver transplantation	15 (3.0)
No local therapy	214 (43.2)
Regional LN surgery, n (%)	146 (30.2)
Chemotherapy, n (%)	
No	300 (60.5)
Yes	180 (36.3)
Unknown	16 (3.2)
Radiation therapy, n (%)	
No	450 (90.7)
Yes	42 (8.5)
Unknown	4 (0.8)

LN: Lymph node.

patients. AFP was positive in 146 patients (29.4%); however, only 27 patients (5.4%) had an AFP level >400 ng/ml. As far as management is concerned, local therapy was performed on 56.8% of patients. The majority consisted of hepatic resection, representing over 90% of local interventions. Details on the use of different treatment modalities are presented in Table II. Among FLC patients with metastatic disease, 19 (15.8%) of patients underwent metastatectomy.

Univariate analysis of outcome. Survival data were available on 461 FLC patients. Using Kaplan-Meier survival analyses, unadjusted median OS stratified by various covariates were calculated (Table III). Age ≥40, male gender, non-white race, high Charlson-Deyo Score, tumor size ≥10 cm, pN+ status, higher stage, higher grade, and AFP positivity were all associated with poor OS. Concerning the association between different treatment modalities and outcome, hepatic resection, chemotherapy, and radiation therapy were evaluated individually. LDT and liver transplantation were excluded from the survival analysis due to the small sample size, precluding from drawing meaningful conclusions. Patients undergoing hepatic resection had a significantly higher median OS compared to those who did not (68.5 *vs*. 10.3 months, p=0.001). Patients who received chemotherapy in any setting (*i.e*. neoadjuvant, adjuvant, or metastatic) had a worse median OS compared those who did not receive chemotherapy (42.8 *vs*. 22 months, p=0.001). Interestingly, when the analysis was limited to FLC patients who underwent local therapy, adjuvant/neoadjuvant chemotherapy was still associated with worse median OS [44.0 (95%CI=38.5-51.8) *vs*. 97.1 (95%CI=76.7-142.1) months, respectively; p=0.001] (Figure 1). Only 12 patients received neoadjuvant chemotherapy; thus, a sub-analysis of this group was not performed. Radiation therapy was not associated with outcome on a univariate basis, and therefore was excluded from the multivariable Cox proportional hazards

Table III. *Kaplan–Meier product limit survival analysis (OS)-Median OS with 95% CI.*

Variable	Total number of patients (n)	Median OS in months (95% CI)	p-Value
Age (years)			
<40	461	39.9 (33.5-47.9)	<0.001
≥40		15.7 (9.9-26.6)	
Gender			
Male	461	24.3 (20.1-34.5)	0.004
Female		40.6 (32.5-54.6)	
Race			
White	461	39.5 (32.5-47.9)	0.048
Black		19.7 (11.0-33.7)	
Hispanic		19.7 (8.3-33.5)	
Other		13.3 (7.3-87.2)	
Charlson-Deyo score			
0	461	39.4 (28.6-47.9)	<0.001
1		39.0 (20.5-56.2)	
2		9.2 (3.5-40.1)	
3		4.0 (0.8-6.4)	
Tumor size			
<10 cm	411	47.9 (37.8-70.9)	0.025
≥10 cm		32.3 (23.5-40.6)	
Pathologic regional LNs (pN+)			
No	450	97.1 (49.2-142.1)	<0.001
Yes		32.5 (27.6-44.0)	
Unknown		20.4 (15.7-26.1)	
Stage			
1	461	142.1 (77.4-142.1)	<0.001
2		87.2 (38.9-NR)	
3		32.3 (20.6-40.9)	
4		14.1 (10.5-20.1)	
Grade			
Well-differentiated	461	54.6 (33.5-NR)	<0.001
Moderately differentiated		63.3 (39.9-78.5)	
Poorly differentiated		14.1 (8.3-40.9)	
Undifferentiated		4.7 (2.7-75.1)	
Unknown		23.4 (18.6-29.8)	
AFP			
Negative	319	42.9 (33.5-64.6)	<0.001
Positive		18.3 (11.6-23.1)	
Hepatic resection			
No	433	10.3 (7.7-13.4)	<0.001
Yes		68.5 (49.2-81.8)	
Chemotherapy			
No	447	42.8 (33.7-77.4)	<0.001
Yes		22.0 (18.2-28.3)	
Radiation therapy			
No	457	34.1 (28.3-41.2)	0.130
Yes		22.9 (13.4-26.3)	

LN: Lymph node; NR: not reached; AFP: alpha-fetoprotein, CI: confidence interval.

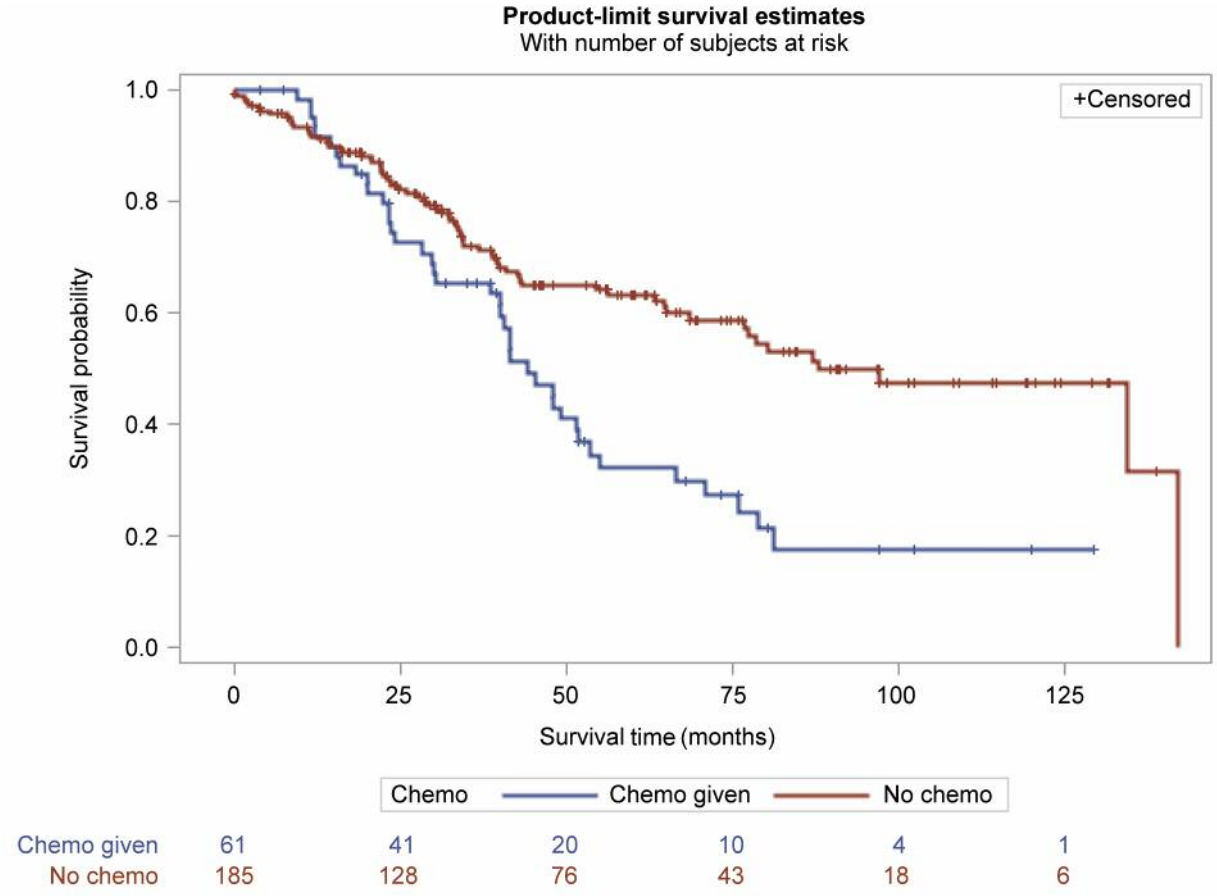

Figure 1. *Kaplan-Meier curves for overall survival stratified by chemotherapy in FLC patients who received local therapy (n=246).*

model analysis. Among patients with stage IV disease, there was no significant difference in median OS between those who underwent metastatectomy and those who did not [23.4 (95%CI=16.0-38.5) *vs.* 10.5 (95%CI=6.6-14.1) months, respectively; p=0.163] (Figure 2).

Multivariable analysis of outcome. We carried out a multivariable Cox Proportional Hazards analysis to control for competing clinicopathological risk factors as well as treatment modalities (Table IV). Variables that remained independently associated with OS were age at diagnosis, Charlson-Deyo comorbidity score, stage and hepatic resection. Patients who underwent surgical resection had a better prognosis than patients who did not. Patients receiving surgery had a 68% reduction in the risk of death relative to those who didn't (p=0.001). Poorly differentiated FLC was associated with an increased risk of death compared to well-differentiated tumors (HR=2.35, 95% CI=1.13-4.87; p=0.022). However, there was no difference in OS when moderately differentiated (p=0.111) and undifferentiated (p=0.527) tumors were respectively compared to well-differentiated tumors. Gender, race, tumor size, pN+ status, AFP level and chemotherapy were not independently associated with OS.

Discussion

To our knowledge, this retrospective analysis is the largest cancer registry-based study on fibrolamellar carcinoma. Our findings are consistent with and support previously published data on the demographic distribution and clinicopathological characteristics of FLC. In our study, 60.7% of FLC patients were diagnosed before the age of 40, in concordance with the reported proportion of 63.2% from SEER data (26). This is in contrast to conventional HCC, where only 2-4% of cases occurred in this age group (3, 26). Furthermore, 69.7% of patients were Caucasian, which is slightly lower than the 83-86% range reported in other studies (8, 17). Data on liver cirrhosis were not available; however, 77.2% of patients had a Charlson-Deyo comorbidity score of 0 (*i.e.* no liver disease), supporting the notion that FLC usually occurs in healthy livers

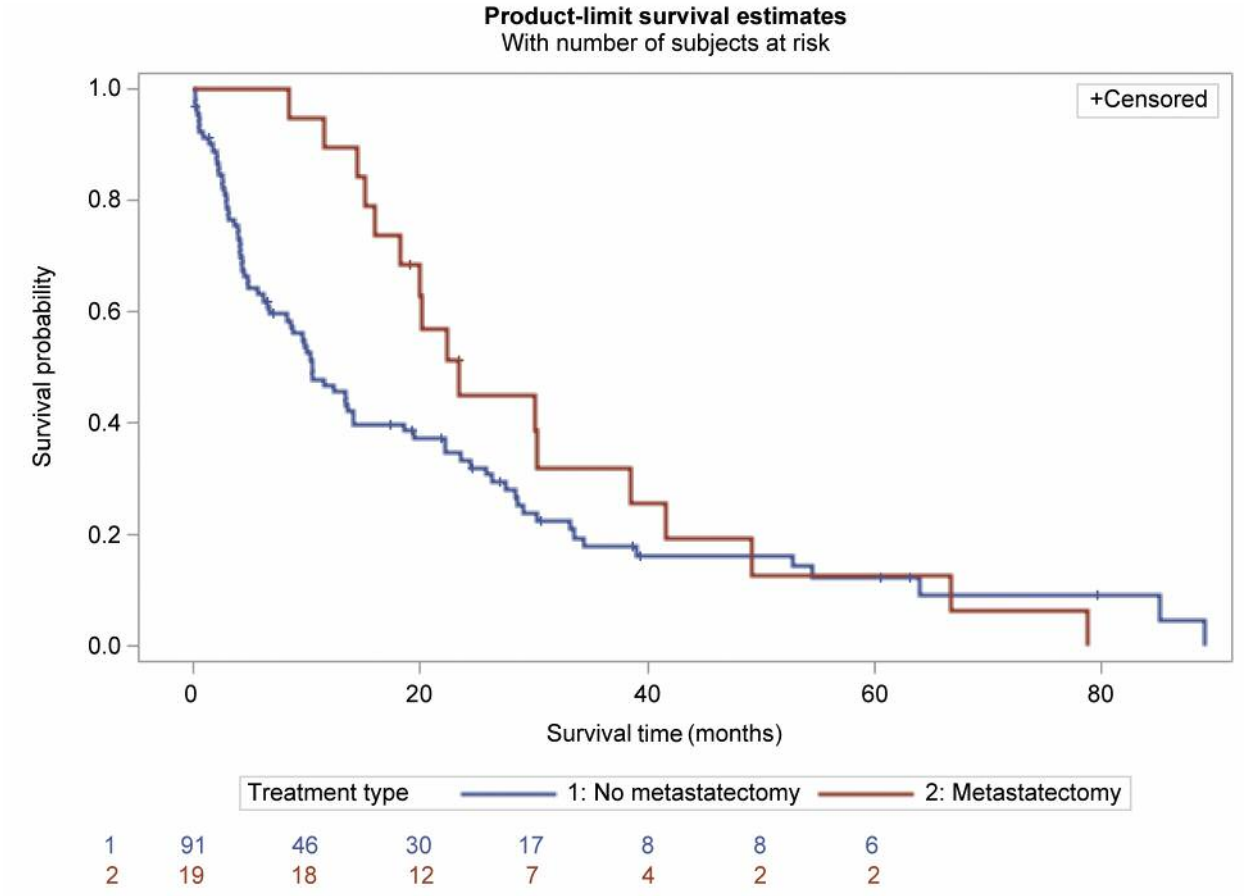

Figure 2. *Kaplan-Meier curves for overall survival stratified by metastatectomy status in stage IV FLC patients (n=110).*

(5, 26, 27). Concerning tumor characteristics, our results were similar to published data, with a median tumor size ranging from 9-13 cm and pN+ rate of 43-46% (8, 28, 29). On the other hand, conventional HCC patients have a median tumor size of 6.6 cm and pN+ rate of 22.1% (8, 17). Proposed hypotheses for the lower rate of lymph node metastasis in conventional HCC include smaller tumor size and possible inhibition of lymphatic outflow in cirrhotic livers compared to healthy liver in FLC (30). The AFP positivity in our study was higher than previously reported values in other studies (29.4% *vs*. 7-10%, respectively) (30, 31). This is likely due to the use of different cutoffs, as many studies use 200-400 ng/ml to represent elevation in AFP levels (32, 33). This could also be partially due to conventional HCC cases being misdiagnosed or miscoded as FLC.

As far as treatment is concerned, surgical resection is the treatment of choice for FLC patients (6, 18). The rate of LDT and liver transplantation are much lower in FLC compared to conventional HCC from the SEER database (2.6% *vs*. 27.4% and 3.0% *vs*. 31.2%, respectively) (17). FLC is not typically responsive to chemotherapy, and there are no established regimens that have shown survival benefits (5). In the metastatic setting, sorafenib, although approved for first-line treatment in conventional HCC, has shown conflicting results in FLC patients (34, 35). A recent retrospective study by Chakrabarti *et al*., which included 42 FLC patients, showed stable disease in 4 out of 9 unresectable FLC patients who received sorafenib (35). Other regimens used in this study include gemcitabine, doxorubicin, cisplatin-based doublet, and 5-FU/folinic acid/oxaliplatin, although meaningful conclusions on their respective benefit cannot be drawn due to the very small sample sizes (35). In the peri-operative setting, chemotherapy was used in an attempt to downstage FLC in one case report, which eventually lead to curative resection (21). However, other studies did not reflect this benefit (8, 35). As for the role of radiation therapy, it remains poorly defined in FLC (5). In a retrospective study of 10 unresectable metastatic FLC patients treated with external beam radiotherapy in addition to chemotherapy, objective partial response and tumor stabilization were achieved in

Table IV. *Cox proportional hazards model-multivariable analysis.*

Characteristic	Hazard ratio	95% CI	*p*-Value
Age (years)			
<40	Ref	Ref	
≥40	1.56	1.08-2.25	0.019
Gender			
Male	Ref	Ref	
Female	0.92	0.70-1.21	0.542
Race			
White	Ref	Ref	
Black	1.40	0.96-2.05	0.081
Hispanic	1.45	1.00-2.11	0.051
Other	1.30	0.82-2.06	0.268
Charlson-Deyo score			
0	Ref	Ref	
1	1.25	0.83-1.90	0.289
2	2.39	1.22-4.67	0.011
3	6.66	3.91-11.4	<0.001
Tumor size			
<10 cm	Ref	Ref	
≥10 cm	1.16	0.87-1.54	0.318
Pathologic regional LNs (pN+)			
No	Ref	Ref	
Yes	1.25	0.72-2.17	0.423
Unknown	0.76	0.45-1.28	0.304
Stage			
1	Ref	Ref	
2	1.26	0.69-2.30	0.447
3	2.69	1.70-4.27	<0.001
4	4.56	2.74-7.59	<0.001
Grade			
Well-differentiated	Ref	Ref	
Moderately differentiated	1.62	0.90-2.92	0.111
Poorly differentiated	2.35	1.13-4.87	0.022
Undifferentiated	1.53	0.41-5.71	0.527
Unknown	1.81	1.05-3.11	0.032
AFP			
Negative	Ref	Ref	
Positive	0.96	0.65-1.40	0.820
Hepatic resection			
No	Ref		
Yes	0.32	0.21-0.50	<0.001
Chemotherapy			
No	Ref		
Yes	1.04	0.76-1.43	0.821

CI: Confidence interval; Ref: reference; AFP: alpha-fetoprotein.

30% and 60%, respectively (36). In our study, however, radiation therapy was not associated with improved OS.

We reported univariate analyses of OS using demographic, clinicopathological and treatment variables. As per previous studies, the median OS varied significantly based on disease stage, ranging from 14.1 to 142.1 months. A systematic review by Mavros *et al.* showed a similar median OS range of 14 to 112 months. Compared to FLC, conventional HCC appears to have worse outcome, with median OS range from 8 to 39 months at best in patients with non-cirrhotic livers (18, 30, 37). Whether the superior survival outcomes of FLC is due to the differential tumor biology compared to conventional HCC is a matter of debate (38). A meta-analysis of 11 studies by Njei *et al.* showed that the survival advantage is no longer present when a subset analysis of non-cirrhotic HCC patients was compared to FLC patients (HR=1.69; 95%CI=0.69-4.17; p=0.25) (18). On the other hand, Eggert *et al.* found that FLC patients less than 40 years of age are more likely to receive curative treatments than conventional HCC (59% *vs.* 32%, p=0.001), which may be partly due to limitation of therapeutic options in HCC due to underlying liver disease (3). Therefore, among patients who received curative treatments, there was no difference in the 5-year relative survival between FLC and conventional HCC (56.8% *vs.* 51.1%) (3). Looking at the addition of chemotherapy to local therapy, our study showed that peri-operative chemotherapy was associated with worse OS (Figure 1). Pinna *et al.* also found that adjuvant chemotherapy decreased tumor-free survival (39). This may in part reflect the selection to give chemotherapy in higher risk patients. Indeed, chemotherapy lost its prognostic significance when multivariable analysis was performed. Metastatectomy was evaluated in one study where 18 patients undergoing the procedure had superior OS compared to their non-resected metastatic counterparts (40). We were not able to replicate this finding in our study.

Elucidating prognostic clinicopathological factors in FLC is of paramount importance to allow clinicians to gain insight into the natural history of the disease. Moreover, they can serve to better inform patients and their families about the risk of death from this rare entity. Since the rarity of FLC precludes from performing prospective or single-center studies, retrospective analysis is necessary in delineating the clinical behavior of FLC. Yamashita *et al.* reported vascular invasion and number of tumors as prognostic factors, and Darcy *et al.* proposed disease stage and pN+ status; however, both these studies were performed on a univariate analysis basis (8, 41). Only 1 out of 8 studies reported in the systematic review by Mavros *et al.* assessed prognostic factors using multivariable analysis, which suggested age and resectability as independent predictors of survival (29, 42). Our study showed that independent predictors of OS in patients with FLC, after controlling for covariates, include age at diagnosis, Charlson-Deyo comorbidity score, stage and hepatic resection.

The current study has several limitations. Most importantly, the retrospective nature of data precludes the ability to make definite recommendations on management of FLC. Also, no direct comparison was done between FLC and conventional HCC cases from the NCDB. Moreover, the NCDB does not record data on progression-free survival and disease-specific mortality, which would have been interesting outcomes to analyze. Another limitation is the grading of tumors, which

not only was missing in a significant proportion of patients, but also lacked centralized pathology review. That being said, the NCDB undergoes extensive data quality checks, ensuring accurate diagnosis. Moreover, treatment details such as the type of chemotherapy, the number of cycles, and radiation dose are not reported in the NCDB. Although important, these details would not have a major effect on our findings. Nevertheless, our data shed light on the general trends in management and prognosis of patients with rare tumors such as FLC. By using a national database such as the NCDB, a sufficient patient population is created to identify important associations with FLC outcomes.

In summary, this study provides new insight into overall survival in different subpopulations of FLC patients. Our data showed that peri-operative chemotherapy did not seem to improve OS in FLC patients. Furthermore, there was no associated survival benefit with metastatectomy in patients with stage IV disease. Further investigation, ideally with prospective evaluation, is warranted to validate these findings.

Conflicts of Interest

The Authors of this manuscript have no conflicts of interest to declare.

Authors' Contributions

Hussein Assi: Conceptualization, data curation, formal analysis, software, writing – original draft, and writing – review and editing. Sarbajit Mukherjee: Conceptualization, data curation, methodology, project administration, writing – original draft, and writing – review and editing. Michael Machiorlatti: Methodology, data curation, formal analysis, software, and writing – review and editing. Sara Vesely: Methodology, formal analysis, software, and writing – review and editing. Vipul Pareek: Supervision, project administration, and writing – review and editing. Hassan Hatoum: Conceptualization, supervision, formal analysis, writing – original draft, and writing – review and editing.

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