Fibrolamellar hepatocellular carcinoma in the USA, 2000–2010: A detailed report on frequency, treatment and outcome based on the Surveillance, Epidemiology, and End Results database

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Abstract

Objective: Epidemiological and clinical information on fibrolamellar hepatocellular carcinoma (fHCC) is scarce. We performed a Surveillance, Epidemiology and End Results (SEER) database analysis with the aim of collecting information to better understand the biology and clinical aspects of this rare disease.

Design: Incidence trends, race- and age-specific rates, tumor size, first course surgery and five-year relative survival of 191 US cases (SEER) diagnosed with fHCC during 2000–2010 were compared to cases with hepatocellular carcinoma (HCC), HCC-not otherwise specified (HCC-NOS) and other HCC-types.

Results: While HCC-NOS incidence rates increased by 5.2% annually from 2000–2008 ($p < 0.05$) before leveling, the 1.3% change in fHCC incidence was not statistically significant. The rates of fHCC were similar across ethnic groups while HCC-NOS incidence rates were higher among non-whites. Although 16% of fHCC patients had primary tumors ≤ 5 cm compared to 37% of HCC-NOS cases five-year survival was better among fHCC (34%) than HCC-NOS cases (16%). Fibrolamellar HCC cases of 0–39 years of age were more likely to receive radiofrequency ablation, transplant or resection than HCC-NOS cases of that age. Survival was similar among fibrolamellar and HCC-NOS cases receiving surgery.

Conclusion: In this largest case series, fibrolamellar and HCC-NOS age- and race-specific incidence rates and time trends differed. Despite larger tumor size than HCC-NOS cases fibrolamellar cases received surgery more often and had better survival rates. Differences in co-morbidity may influence treatment. Studies of fHCC biology, including by age, are recommended.

Keywords

Liver cancer, epidemiology, fibrolamellar

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Introduction

Liver cancer is the sixth most common cancer diagnosis worldwide (749,000 new cases) and the third most common cause of cancer-related death (692,000 cases), and accounts for 7% of all cancers.¹ Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and is a major global health problem. The majority of HCC cases occur in Asia and in patients with underlying liver disease such as viral hepatitis and consecutive liver cirrhosis.² The World Health Organization categorizes HCC

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in the International Classification of Disease for Oncology,³ as HCC-not otherwise specified (HCC-NOS), scirrhous HCC, spindle cell variant HCC, clear cell HCC, pleomorphic HCC and fibrolamellar HCC (fHCC). While most studies focus on the most common form of HCC, HCC-NOS, there have been few studies of the remaining histologic types.⁴ Fibrolamellar HCC is a relatively rare tumor of unknown biology and there is limited clinical information available due to its low incidence. As a result of its known tendency to occur in younger patients, fHCC is a tumor of interest.^{5–7} Current epidemiology data on fHCC suggest that demographic attributes of fHCC cases are very different from cases with HCC-NOS not only in terms of age but also gender and the absence of liver disease. Therefore fHCC is often excluded from clinical trials.⁸ Nevertheless, the disease is often treated like HCC-NOS. Most studies,^{4–7,9–13} including a large population-based study,⁵ have reported better survival rates for fHCC compared to HCC-NOS. As a result, fHCC is considered by some to be a less aggressive tumor than other HCCs.^{7,10–13} Other studies attribute better survival rates to the absence of underlying liver disease in patients with fHCC, as most HCCs arise on a background of liver cirrhosis.^{14,15} Also, in contrast with HCC-NOS, relatively little is known regarding the biology and clinical characteristics of fHCC.

We have studied fHCC data from the population-based cancer registries of the Surveillance, Epidemiology, and End Results (SEER) Program and previously described two age-specific incidence peaks from 10–30 years and 70–79 years of age.¹⁶ Here we describe more detailed findings from the SEER database.

Materials and methods

Study population

Cases included in this report were reported by the SEER 18 registries. Cases were diagnosed with malignant HCC between 1 January 2000–31 December 2010. The SEER 18 registries, which cover approximately 26% of the US population, are located in Metropolitan Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, Rural Georgia, the Alaska Native Tumor Registry, Greater California, Kentucky, Louisiana, New Jersey and Greater Georgia.

Case definition

The time period of this report corresponds with implementation of the *International Classification of Diseases*

for Oncology, 3rd ed.³ During this period, morphology codes for HCC cases were expanded beyond 8170 (HCC, NOS) to also include fHCC (8171), scirrhous HCC (8172), spindle cell HCC (8173), clear cell HCC (8174) and pleomorphic HCC (8175).

Statistical analyses

Demographic and clinical attributes of cases were examined by tumor histology. Attributes of interest included non-Hispanic race and Hispanic ethnicity with American Indian and Alaskan Native rates restricted to Contract Health Service Delivery Areas to improve racial classification. Gender, age and reported liver surgery procedures, including radiofrequency ablation, resection, and transplantation were examined. To avoid disclosure of patient information, cells with fHCC case counts less than 10 cases were suppressed. This required the aggregation of radiofrequency ablation and transplant cases in overall analyses and radiofrequency ablation, resection, and transplant cases in survival analyses. In analyses stratified by age, extent of disease, size was categorized as ≤ 5 cm, > 5 cm, and unknown. Race- and age-adjusted rates and five-year relative survival were reported by histologic type. Analyses were performed using SEER*Stat software version 7.1.0 (IMS Incorporated, Silver Spring, Maryland, USA). Chi-squared tests were performed with SAS v 9.2 (Cary, North Carolina, USA) to estimate p -values for differences in age and both tumor size and receipt of surgery by histology. Incidence trends were considered statistically significant when Joinpoint regression slopes differed from zero ($p \leq 0.05$) using Joinpoint v 3.5.0 software (IMS Incorporated, Silver Spring, Maryland, USA).

Results

After HCC-NOS ($n = 46,392$), clear cell HCC ($n = 339$) and fHCC ($n = 191$) were the next most frequently reported histologic types of HCC, with 118 cases of the remaining three subtypes combined (Table 1). For all histologies, including fHCC, a higher proportion of cases were male than female, with HCC-NOS having the highest male to female case ratio (3.2), and fHCC having the lowest ratio (1.7). A higher proportion of HCC-NOS cases than fHCC cases were diagnosed with primary tumors < 5 cm in diameter (37% compared to 16%).

With the exception of HCC-NOS, which had an annual percent change (APC) of 5.2% from 2000–2008 ($p < 0.05$) followed by a non-significant annual increase of 1.0% thereafter, there were no statistically significant changes in incidence rates (Figure 1). Among HCC-NOS and clear cell HCC cases, Asians and Pacific

Table 1. Demographic and clinical attributes of 40,070 hepatocellular carcinoma cases by histology, 2000–2010, Surveillance, Epidemiology, and End Results (SEER) 18.^a

Attribute	HCC-NOS		Clear Cell HCC		Fibrolamellar HCC		Other HCC		p-value
	n	%	n	%	n	%	n	%	
Microscopic confirmation	31,278	67%	323	95%	183	96%	109	92%	
Race/ethnicity ^a									0.0076
Non-Hispanic white	23,135	50%	162	48%	114	60%	69	58%	
Non-Hispanic black	5816	13%	37	11%	26	14%	19	16%	
Non-Hispanic API ^b	8414	18%	66	19%	17	9%	13	11%	
Hispanic	8368	18%	71	21%	33	17%	17	14%	
Non-Hispanic AI/AN ^b	506	1%	^c		0	0%	0	0%	
Age (years)									<0.0001
<40	880	2%	10	3%	115	60%	^c		
40–49	4380	9%	17	5%	13	7%	13	11%	
50–59	14,089	30%	87	26%	21	11%	37	31%	
60–69	11,852	26%	93	27%	21	11%	26	22%	
70+	15,191	33%	132	39%	21	11%	41	35%	
Male: female ratio	3.2		1.8		1.7		2.3		<0.0001
Male	35,308	76%	219	65%	119	62%	82	69%	
Female	11,084	24%	120	35%	72	38%	36	31%	
Tumor size									<0.0001
≤5 cm	16,951	37%	95	28%	31	16%	35	30%	
>5 cm	15,608	34%	168	50%	120	63%	57	48%	
Unknown	13,773	30%	76	22%	40	21%	26	22%	
Reported therapy with curative intent									<0.0001
None	34,665	75%	207	61%	94	49%	79	67%	
RFA, transplant	5149	11%	30	9%	10	5%	18	15%	
Resection	3898	8%	90	27%	78	41%	19	16%	
Other, unknown	2680	6%	12	4%	^c	5%	^c	2%	
Stage at diagnosis									
Localized	20,808	45%	185	55%	64	34%	50	42%	
Regional	12,413	27%	77	23%	58	30%	37	31%	
Distant	7360	16%	59	17%	63	33%	26	22%	
Unknown/unstaged	5811	13%	18	5%	6	3%	5	4%	
Total	46,392		339		191		118		

AI/AN: American Indian/Alaska Native; API: Asian/Pacific Islander; HCC: hepatocellular carcinoma; HCC-NOS: HCC-not otherwise specified; RFA: radio-frequency ablation.

^aHCC-NOS; Other HCC: Scirrhou, spindle cell variant, and pleomorphic types.

^bAPI, AI/AN in Contract Health Service Delivery Areas.

^cSuppressed when >10 cases. Cases with other or missing race are not shown.

Islanders had the highest rates, followed by Hispanics, blacks and American Indians and Alaska Natives. Among cases with fHCC and other specified HCC types, incidence rates were relatively homogeneous across racial and ethnic groups (Table 2).

Table 3 indicates that among patients 0–39 years of age at diagnosis, HCC-NOS cases were more likely than fHCC cases to be diagnosed with primary tumors <5 cm in size, (23% compared to 10%, $p < 0.001$). This association between histology and

Figure 1. Age-adjusted hepatocellular carcinoma (HCC) incidence trends by histologic type, Surveillance, Epidemiology, and End Results (SEER) 18 registries, 2000–2010. *indicates slope of regression line is statistically different from zero, $p < 0.05$. APC: annual percent change; HCC-NOS: HCC-not otherwise specified.

Table 2. Race/ethnic specific rates by hepatocellular carcinoma (HCC) histology, 2000–2010, Surveillance, Epidemiology, and End Results (SEER) 18 Registries.^a

Histology type	Non-Hispanic white	Non-Hispanic black	Non-Hispanic API ^b	Hispanic	AI/AN ^b
HCC-NOS	3.63	6.55	11.64	8.67	6.47
Clear cell HCC	0.025	0.043	0.091	0.076	0.034
Fibrolamellar HCC	0.022	0.025	0.022	0.020	0
Other HCC ^c	0.011	0.021	0.018	0.020	0

AI/AN: American Indian/Alaska Native; API: Asian/Pacific Islander; HCC-NOS: HCC-not otherwise specified.

^aAge-adjusted rates per 100,000 population (racial groups exclude Hispanics).

^bAPI, AI/AN in Contract Health Service Delivery Areas.

^cOther HCC: Scirrhus, spindle cell variant, and pleomorphic types.

Table 3. Size of primary tumor, fibrolamellar hepatocellular carcinoma (fHCC) and hepatocellular carcinoma (HCC)-not otherwise specified (NOS), by age at diagnosis, 2000–2010, Surveillance, Epidemiology, and End Results (SEER) 18 Registries

Age	HCC type	All cases	≤5 cm	%	5+ cm	%	Size by histology, p
0–39 years	HCC-NOS	880	205	23%	410	47%	<0.0001
	Fibrolamellar	115	11	10%	87	76%	
40+ years	HCC-NOS	45,512	16,783	37%	15,221	33%	0.0322
	Fibrolamellar	76	20	26%	33	43%	
All ages	HCC-NOS	46,392	16,988	37%	15,631	34%	<0.0001
	Fibrolamellar	191	31	16%	120	63%	

Patients with unknown tumor sizes were excluded from this analysis.

Table 4. Age, hepatocellular carcinoma (HCC) type and receipt of curative therapy, Surveillance, Epidemiology, and End Results (SEER) 18, 2000–2010

Age	Case group	HCC-NOS		Fibrolamellar HCC		<i>p</i> ^a
		<i>n</i>	%	<i>n</i>	%	
0–39	All cases	880	100%	115	100%	<0.0001
	Resection	201	23%	64	56%	
	RFA, resection, transplant ^b	282	32%	68	59%	
	No surgery	574	65%	42	37%	
40+	All cases	45,512	100%	76	100%	0.1
	Resection	3697	8%	14	18%	
	RFA, resection, transplant ^b	8765	19%	20	26%	
	No surgery	34,091	75%	52	68%	
All	All cases	46,392	100%	191	100%	<0.0001
	Resection	3898	8%	78	41%	
	RFA, resection, transplant ^b	9047	20%	88	46%	
	No surgery	34,665	75%	94	49%	

HCC-NOS: HCC-not otherwise specified; RFA: radiofrequency ablation.

^aRFA, resection, or transplantation versus no surgery by fibrolamellar HCC versus HCC-NOS.

^bRFA, resection and transplants combined due to small counts for specific fibrolamellar therapy. Uncommon ablation procedures and surgery not otherwise specified not reported.

primary tumor size was also significant among older cases, although the strength of the association was attenuated ($p=0.0322$). Despite the larger tumor size of fHCC cases compared to HCC-NOS cases, Table 4 indicates that among individuals 0–39 years of age, fHCC cases were more likely than HCC-NOS cases to have received one of the potentially curative therapies of radiofrequency ablation, resection or transplantation versus no surgery of the liver (59% versus 32%, $p<0.001$). In most instances the procedure was a surgical resection. Based on small numbers of cases, no significant association between fHCC and surgery was seen among cases 40 years of age and older (Table 4).

Fibrolamellar HCC patients experienced significantly better five-year relative survival (34%) than patients with HCC-NOS (16%), despite larger tumor size distribution. This association was seen among cases up to 39 years of age but not among older patients (Table 5). Among patients receiving the potentially curative therapies of radiofrequency ablation, resection or transplantation surgery there was no statistical significant difference in five-year survival between cases with HCC-NOS (51%) and those with fHCC (57%).

Discussion

To our knowledge this case series of 191 fHCC patients is the largest studied to date. Despite a less favorable stage distribution, fHCC cases were more likely to receive initial treatment with radiofrequency ablation,

resection or transplantation. While five year survival was significantly higher among fHCC cases than HCC-NOS cases, no difference in survival was found by HCC type among cases who received therapy with curative intent. Our findings do not support the general assumption that fHCC is less aggressive than HCC-NOS^{5,7,12,17} but rather suggest that a lower prevalence of underlying liver disease¹⁴ or younger age at diagnosis may predispose a higher percent of fHCC cases to be considered as candidates for potentially curative therapies.^{15,18}

To date fHCC is a tumor of unknown biology. Our findings are consistent with the previous finding based on SEER data⁵ that the majority of cases with fHCC (64%) were diagnosed before the age of 40 years, while only 4% of HCC-NOS cases occurred in this age group. The mean age for fHCC in the prior study was 39 years compared to 65 years for HCC-NOS. However, more recent SEER data indicate that fHCC has two distinct age-specific peaks in incidence, unlike any of the other HCC subtypes.¹⁶ The findings of these two age-specific incidence peaks led us to separate the fHCC and the HCC-NOS cases into cases younger than 40 years of age versus older than 40 years of age in subsequent analyses. When this was done, age-specific differences in tumor size distribution, treatment and survival emerged. For this reason, studies of fHCC biology by age at diagnosis may have merit. Unlike a previous case series,⁵ in the present study fHCC patients were more likely to be male than female. In further contrast to

Table 5. Five-year relative survival by surgery, fibrolamellar hepatocellular carcinoma (fHCC) and hepatocellular carcinoma-not otherwise specified (HCC-NOS) cases by age group, Surveillance, Epidemiology, and End Results (SEER) 18, 2000–2010

Age	Case group	HCC-NOC	fHCC
		Five-year relative survival, (CI)	Five-year relative survival, (CI)
0–39	All cases	25.0% (21.7–28.5)	40.3% (29.9–50.5)
	Resection	51.2% (42.4–59.4)	57.8% (42.4–70.5)
	RFA, resection, transplant	56.4% (49.1–63.2)	55.2% (40.4–67.7)
	No surgery	8.7% (6.2–11.8)	10.4% (2.2–26.2)
40+	All cases	15.9% (15.4–16.4)	21.3% (11.0–33.9)
	Resection	43.5% (41–45.9)	60.7% (20.9–85.3)
	RFA, resection, transplant	50.9% (49.3–52.4)	62.1% (29.5–83)
	No surgery	6.1% (5.8–6.5)	4.4% (0.4–16.7)
All	All cases	16.1% (15.6–16.6)	33.6% (25.7–41.6)
	Resection	44.0% (41.7–46.3)	58.2% (44.0–70.0)
	RFA, resection, transplant	51.1% (49.6–52.5)	56.8% (43.5–68.1)
	No surgery	6.2% (5.8–6.6)	7.4% (2.2–16.9)

CI: confidence interval; RFA: radiofrequency ablation.

previous findings,⁵ fHCC cases in the current study had a more homogeneous racial and ethnic distribution.

The better survival among fHCC cases compared to cases diagnosed with other HCC histologies has been previously reported.^{5,13} We found that fibrolamellar cases were more likely than other cases of HCC to receive potentially curative therapies including radiofrequency ablation, resection, or transplant. This is noteworthy because, although current data suggest that fibrolamellar cases differ from HCC-NOS cases with respect to age, gender and liver disease, there is very limited clinical information on fHCC treatment and survival. In addition, although most clinical trials exclude fHCC cases, the disease is often treated according to guidelines developed for HCC-NOS. Among patients receiving such therapy, survival was similar for fHCC and other HCC types. Stratified survival analyses of patients treated with initial liver surgery, and further stratification by age may have restricted the analysis to patients with more stable liver function and less co-morbidity. A possible reason for the finding that patients younger than 40 years of age were more likely to be diagnosed at advanced stages than older cases is that older cases may have had more extensive underlying liver disease. The standard practice of periodic surveillance for suspicious liver nodules in patients with known liver disease may allow more cases in the older age group to be diagnosed at a localized stage.¹⁹

The evidence is equivocal as to whether fHCC carries a favorable prognosis compared to HCC-NOS due to its less aggressive tumor biology.^{5,7,12,17} The stable incidence trends and homogeneous race-specific

incidence rates present a clear contrast to trends and rates for HCC-NOS. The present report provides some reason to suspect that both tumor histologies are aggressive, based on stage distribution and similarities in survival among surgical and non-surgical groups. Prognosis may be affected by underlying cirrhosis, which can influence therapeutic options, including whether or not hepatic resection is considered.^{14,15,18} Of HCC-NOS patients, 37% had tumor sizes <5 cm, but only 19% of HCC-NOS patients received potentially curative therapies. This discrepancy might reflect the presence of underlying liver disease, which prevented these cases from undergoing potentially curative treatments. Our study lends supports to this hypothesis since patients with fHCC often had less favorable stage distribution and yet received potentially curative therapy more often than cases with HCC-NOS.

This study has several strengths. To our knowledge, it is the largest reported study of fHCC in the literature. Previously summarized in a brief report,¹⁶ the study presents extensive information on demographic attributes, stage, treatment, and survival. Limitations of the study included the absence of information on underlying liver disease, risk factors and other co-morbidities as well as the number of primary HCC tumors per case. In addition, registry-based cancer surveillance does not provide information on etiologic risk factors. Furthermore, information on specific therapy was restricted to those who underwent surgical resection due to small counts in other treatment categories. By analyzing data for patients receiving any therapy with curative intent, we selected a cohort of patients,

perhaps with comparatively greater likelihood of stable liver function and less co-morbidity. In summary, this study provides new insights into the age distribution, stage at diagnosis, and survival of fHCC cases. The findings support the hypothesis made by others¹⁴ that fHCC is a distinct and aggressive HCC type.

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Conflict of interest

The authors declare that there is no conflict of interest.

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