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Epidemiology of fibrolamellar hepatocellular carcinoma in the U.S., 2000–2010

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We read with great interest the article by Tremosini et al in *Gut* ¹, which prospectively validated the use of a panel of three antibodies (glypican 3, heat shock protein 70 and glutamine synthetase) for the histopathological diagnosis of hepatocellular carcinoma. According to the International Classification of Diseases for Oncology², hepatocellular carcinomas (HCC) are classified into HCC not otherwise specified (HCC-NOS) which accounts for the vast majority of HCC, fibrolamellar HCC (fHCC), scirrhous HCC, spindle cell variant HCC, clear cell HCC and pleomorphic HCC. While many studies including the one from Tremosini and colleagues restrict their focus on HCC-NOS, we decided to study fHCC in more depth. fHCC is a rare tumor with limited clinical information available. Current data suggest that demographic attributes of fHCC cases are very different from cases of HCC-NOS not only in terms of gender but also with regard to the presence for the existence of pre-existing liver disease^{3–5}. Unlike most HCCs, fHCCs typically arise in the absence of liver cirrhosis^{6, 7}.

Because of differences between HCC-NOS and fHCC, many clinical trials specifically exclude patients with fHCC⁸. However, the tumor is commonly treated similarly to HCC-NOS in the absence of better knowledge.

With the aim of increasing existing knowledge of fHCC, we examined data from the Surveillance, Epidemiology, and End Results (SEER) program for fHCC. Cases included in this report were reported by the SEER 18 registries. Cases were diagnosed with fHCC between January 1, 2000 and December 31, 2010.

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Gender, age and reported frontline treatment, including radiofrequency ablation, resection, and transplantation were examined. To protect confidentiality, counts with fewer than 10 cases are not displayed. Radiofrequency ablation, resection, and transplant cases were combined as “treatments with curative intent” in survival analyses. Analyses were performed using SEER*Stat software version 7.1.0 (IMS Incorporated, Silver Spring, MD). Analyses calculated chi-squared tests using SAS v 9.2 (Cary, NC) to estimate P-values for differences in both tumor size and receipt of surgery by histology.

Between 2000 and 2010, a total of 46,392 cases of HCC-NOS, 339 cases of clear cell HCC, 19 cases of HCC and 118 cases of the remaining 3 HCC subtypes were reported. For all histologies, including fHCC, a higher proportion of cases were male with HCC-NOS having the highest male to female case ratio (3.2), and fHCC having the lowest ratio (1.7). Unexpectedly, age-specific incidence analysis, revealed two age-specific peaks for patients with fHCC, one among young persons between the ages of 10–30 years and a second among persons aged 60–69 years (Figure 1). For the other HCC types combined, the age specific rates and peak incidence (70–79 years) were very similar to those of HCC-NOS. fHCC patients experienced significantly better 5-year relative survival (34%) than patients with HCC-NOS (16%) (Table 1). In summary this case series of 191 fHCC patients, which is the largest to date, revealed the new finding of the existence of two age-specific peaks for fHCC, one at younger ages and one at more typical ages for HCC-NOS. Furthermore, while five year survival was significantly better among fHCC cases than HCC-NOS cases, no difference in survival was found by HCC type among cases who received a curative treatment procedure (surgery, radiofrequency ablation and transplantation) as a first line treatment.

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Abbreviations

HCC	hepatocellular carcinoma
NOS	not otherwise specified
SEER	Surveillance, Epidemiology, and End Results

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Figure 1.
Age-specific hepatocellular carcinoma incidence rates per 100,000 by tumor histology,
SEER 18 registries, 2000–2010

Table 1

5-year relative survival by surgery, fHCC and HCC-NOS cases by age group, SEER 18 2000–2010*

Case Group	HCC, Not Otherwise Specified		Fibrolamellar HCC		P [‡]
	N	5-year relative survival, CI [‡]	N	5-year relative survival, CI [‡]	
All Cases	880	25.0% (21.7%, 28.5%)	115	40.3% (29.9%, 50.5%)	
RFA, Resection, Transplant	9,047	51.1% (49.6%, 52.5%)	88	56.8% (43.5%, 68.1%)	<0.0001
Non-curative treatment [§]	34,665	6.2% (5.8%, 6.6%)	94	7.4% (2.2%, 16.9%)	

* Radiofrequency ablation (RFA), resection and transplants combined due to small counts for specific fibrolamellar therapy as treatment with curative intent
Results for other types of surgery that are not potentially curative were not reported.

[‡] CI= 95% confidence interval

[‡] Radiofrequency ablation (RFA), resection, or transplantation versus no surgery by Fibrolamellar versus HCC, NOS

[§] Non-curative treatment include transarterial chemoembolization, radiation and systemic therapies