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A review of 218 pediatric cases of hepatocellular carcinoma

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ABSTRACT

Purpose: This study evaluates the incidence trends and clinical outcomes of children with hepatocellular carcinoma (HCC) and assesses factors predictive of patient survival.
Methods: The Surveillance, Epidemiology, and End Results registry was queried from 1973 to 2009 for all patients between ages 0 and 19 with primary HCC. Demographics, tumor histology, surgical intervention, and patient survival were collected.
Results: Overall, 218 patients were identified. The annual age-adjusted incidence was 0.05 cases per 100,000 in 2009. Fibrolamellar subtype tumors were exclusive to children >5 years old and exhibited greater survival compared to non-fibrolamellar subtype (57% vs. 28%, respectively, $p = 0.002$). Tumor extirpation for patients with resectable disease significantly improved overall survival at 5 years compared to no surgery (60% vs. 0%, respectively, $p < 0.0001$). Overall 5-, 10- and 20-year survival for the entire cohort was 24%, 23%, and 8%, respectively. Independent prognostic factors of lower mortality according to multivariate analysis were surgical resection (hazard ratio (HR) = 0.18), non-Hispanic ethnicity (HR = 0.52), and local disease at presentation (HR = 0.46).
Conclusion: Over the past four decades, the incidence of HCC has remained relatively stable. Children of Hispanic ethnicity have high mortality rates. However, HCC resection for curative intent significantly improves outcomes.

Primary pediatric liver malignancies are a challenging entity for the clinician and patient alike, comprising 1–2% of all pediatric tumors [1]. Arguably, the most common cause of primary liver cancer in children is hepatoblastoma, which composes the plurality of liver malignancies at a 43% incidence rate [1]. Hepatocellular carcinoma (HCC) is the second most common pediatric malignancy at a 23% incidence rate, albeit they are more common than hepatoblastomas in areas harboring endemic hepatitis B virus (HBV) [2,3]. While hepatoblastomas are generally chemosensitive and provide auspicious odds for a cure, HCCs are often chemoresistant with contrastingly poorer cure rates estimated at 25–30% [1,4].

HCCs are traditionally divided into two distinct histopathologic variants, as first suggested by Edmonson in 1956: fibrolamellar (FLC) and non-fibrolamellar (NFL-HCC) [5,6]. The FLC variant is a well-circumscribed solitary tumor, as opposed to the multi-centric presentation in NFL-HCC. FLC tumors also often present with bilobar involvement and multicentric tumor nodules or diffuse intrahepatic spread [7]. Furthermore, a few retrospective case series suggest that FLCs have higher rate of resectability and greater overall survival in comparison to patients with NFL-HCC [8–13]. However, other reports argue that patients with FLC do not respond any differently to surgical resection than patients with NFL-HCC [14,15].

To date, HCC treatment and prognosis is based mainly on a number of small retrospective studies. Likewise, there are no large, population-based analyses of primary pediatric HCC, corresponding patient outcomes and prognostic factors. The purpose of this study is to analyze the current trends in tumor incidence and clinical outcomes and the factors predictive of survival in a large sample of pediatric patients with HCC based on a national cancer registry.

1. Methods

The Surveillance, Epidemiology and End Results (SEER) database released on July 2012 was used to identify all cases of primary pediatric malignant epithelial tumors reported to SEER between 1973 and 2009. SEER collects data on a number of cancers throughout the United States. SEER began data collection in 1973 with a limited number of registries and has continued to expand to include more areas and demographics. Tumor location and histology were based on topography and morphology codes according to the International Classification of Disease for Oncology (ICD-O), 3rd edition codes. The SEER database was first queried for all patients less than 20 years of age with primary malignant hepatic tumors (topography codes: C22.0). A total of 946 primary malignant liver tumors were identified. Of those, 218 patients were identified as having hepatocellular carcinoma (ICD-O codes: 8010, 8170, 8171 and 8174) and were included in this analysis. There were no duplicate cases. Unknown values were excluded from all calculations. The study period has

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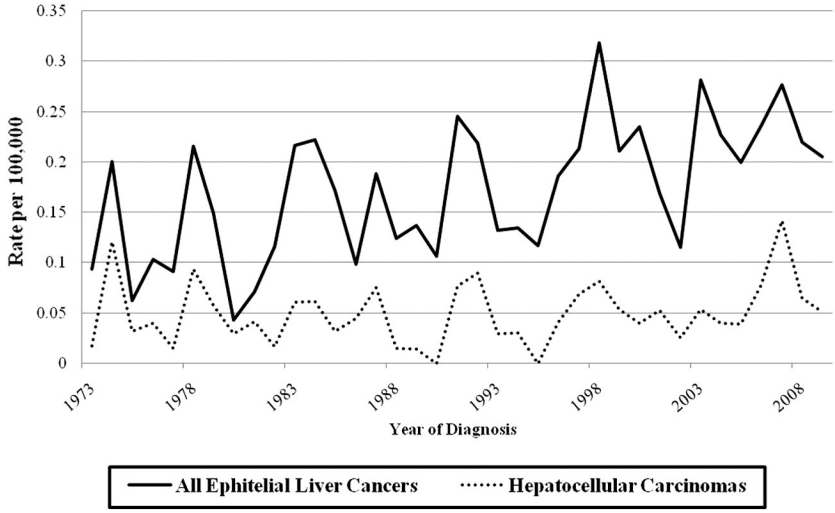

Fig. 1. Incidence of hepatocellular carcinomas in children according to SEER.

allowed for a minimum of a 5-year follow-up for all cases. Data on liver transplantation rates is not available in SEER and therefore not analyzed. Only the percentages based on available data for each individual variable are given. SEER Stat software (version 7.1.0, NCI, Bethesda, MD) was used to analyze incidence rates and trends from 1973 to 2009. All incidence data were age-adjusted and normalized to the 2000 U.S. Standard Population. Annual percentage change (APC) was calculated using the weighted least squares method.

The staging criteria used in this analysis was adopted from the SEER summary staging guidelines and is different from the TNM (tumor, node, and metastasis) staging system. In this study, local staging represents disease that does not extend beyond the primary organ while regional disease includes tumor extension to adjacent organs, regional lymph nodes or both. Documentation of distant metastases during the perioperative period led to the classification of affected patients as having distant disease.

Statistical analysis was performed with SPSS Statistical Package 20 (SPSS Inc., Chicago, IL). Correlations between categorical variables were made using the chi-square test. Data with a normal distribution were compared using Student's *t* test and nonparametric data were compared using the Mann-Whitney *U* test. Five-, 10- and 20-year overall survival rates were calculated by the life-tables method. The Kaplan-Meier method was used to calculate survival curves. Survival was calculated from the time of the initial diagnosis to the date of last contact (or the date of death if the patient was deceased). The effect of demographic, clinical and treatment variables on survival was tested utilizing the log rank test for categorical values. A Cox logistic regression was used to identify predictors of survival using all variables found to be significant ($p < 0.05$) or near significant ($p < 0.10$) in univariate analysis.

2. Results

2.1. Patient demographics and tumor characteristics

Over the study period, a total of 218 HCC patients were identified. On average, patients were 12.9 ± 5.2 years old, male (58%), overwhelmingly white (72%) and non-Hispanic (82%). The overall age-adjusted incidence was 0.17 cases per 100,000 for malignant epithelial liver tumors and 0.05 cases per 100,000 for HCCs in particular. The majority of HCCs were seen in children greater than 10 years old (75%). Specifically, adolescents exhibited the highest tumor incidence (0.08 cases per 100,000).

The annual percent change (APC) of all-cause malignant epithelial liver tumors was 1.79% (95% CI: 0.74–2.84%, $p < 0.05$). The incidence of HCC has remained relatively stable over the study period (Fig. 1). The most common histological subtype encountered was NFL-HCC (73%), followed by FLC (25%) and clear cell carcinomas (2%). Fibrolamellar subtype tumors were exclusive to children older than 5 years of age. Patient demographics and tumors characteristics are further summarized in Table 1.

Table 1
Demographics of pediatric hepatocellular carcinomas according to most common tumor variants.

	Overall[¥] (n = 218)	NFL-HCC (n = 160)	FLC (n = 55)	*P*[*]
Age, mean ± SD	12.9 ± 5.2	11.9 ± 5.5	15.2 ± 3.0	<0.0001
Gender				0.349
Male	126 (58)	94 (59)	30 (55)	
Female	92 (42)	66 (41)	25 (45)	
Age, years				0.003
0	9 (4)	9 (5)	0 (0)	
1–4	10 (5)	10 (6)	0 (0)	
5–9	34 (16)	30 (19)	4 (7)	
10–14	60 (27)	45 (28)	14 (26)	
15–19	105 (48)	66 (41)	37 (67)	
Race				0.102
White	158 (72)	113 (71)	43 (78)	
Black	27 (12)	17 (11)	9 (16)	
Asian	32 (15)	29 (18)	3 (6)	
Other	1 (0.5)	1 (0.5)	0 (0)	
Ethnicity				0.106
Non-Hispanic	179 (82)	136 (85)	42 (76)	
Hispanic	39 (18)	24 (15)	13 (24)	
Tumor Stage				0.670
Local	58 (27)	44 (28)	14 (26)	
Regional	77 (35)	57 (36)	19 (35)	
Distal	74 (34)	51 (32)	21 (38)	
Unstaged	9 (4)	8 (5)	1 (2)	
Surgery				0.003
No	105 (48)	86 (54)	17 (31)	
Yes	113 (52)	74 (46)	38 (69)	
Radiation				0.140
No	206 (95)	149 (93)	54 (98)	
Yes	12 (5)	11 (7)	1 (2)	

All values expressed as number (percentage) unless otherwise specified.
NFL-HCC = Non-fibrolamellar hepatocellular carcinoma; FLC = Fibrolamellar hepatocellular carcinoma.
[*] Values for comparisons between non-fibrolamellar and fibrolamellar variants calculated by chi-square test.
[¥] Includes clear cell carcinoma variant (N = 3).