

Clinical characteristics and outcome of hepatocellular carcinoma in children and adolescents

Xu-Feng Zhang · Xue-Min Liu · Tao Wei ·
Chang Liu · Mu-Xing Li · Zhi-Da Long ·
Yi Lv

Accepted: 11 June 2013 / Published online: 22 June 2013
© Springer-Verlag Berlin Heidelberg 2013

Abstract

Purpose Hepatocellular carcinoma (HCC) rarely occurs in children and adolescents and has been reported to be highly hepatitis B related more than 10 years ago. However, after global vaccination for hepatitis B virus (HBV), the characteristics and outcome of pediatric HCC remain undefined.

Methods Patients with HCC admitted from 2004 to 2010 were retrospectively reviewed in a large tertiary hospital.

Results 45 (1.97 %) pediatric HCC were diagnosed (age ≤ 18 years), with predominantly male patients (93.3 %). 32 (71.1 %) children were HBV positive, 30 of whom had vertical transmission from their mothers. HBV positivity was associated with liver cirrhosis and portal vein invasion, and thus compromised survival. Advanced disease prevented surgical resection due to large tumor size (>10 cm, 66.7 %), early metastasis (24.4 %), bilateral involvement (57.8 %) and portal vein invasion (46.7 %). The median survival for resectable, transarterial chemotherapy and embolization and untreated patients was 28.6, 4 and 5 months, respectively ($p < 0.001$). Patients with distal metastasis had significantly poorer survival rate than those without metastasis ($p < 0.001$).

Conclusion Screening of children whose mothers are HBV carriers is important in early detection of pediatric HCC. HBV-associated HCC in pediatric patients, especially in endemic areas, should be detected earlier for more resectability and improvement of surgical prognosis.

Keywords Hepatocellular carcinoma · Children · Hepatitis B · Surgical resection

Introduction

Hepatocellular carcinoma (HCC) in childhood is extremely rare and accounts for less than 0.5 % of all pediatric malignancies [1]. HCC and hepatoblastoma are two major liver malignant tumors in children, which, however, are totally different in etiology and clinical progression. In endemic areas with hepatitis B virus (HBV) infection, such as China, the incidence of HCC is higher than that of HB, which is different from the reports in Western countries [2]. HBV infection (~ 100 %) and subsequent development of liver cirrhosis (~ 70 %) were recognized as the main causes of HCC in children in East Asia several decades ago [3, 4]; however, after universal HBV vaccination, the incidence of pediatric HCC declined from one out of three before hepatitis B vaccination to one out of four [5–7]. A comprehensive epidemiological study found that underlying liver or metabolic disease was absent in most cases of pediatric HCC, which was different from HCC in adults [8]. Therefore, HCC in children must be discussed individually as a different subgroup from that in adults.

Surgical resection remains the mainstay of curative therapy for long-term survival of children with HCC [3, 4, 9]. However, the survival rate was still poor for children with HCC as reported in the 1980s and 1990s [3, 4, 9]. The reports on HCC in children in large single series were limited to those more than 10 years ago, and the surgical outcome of pediatric HCC remained undefined. After universal HBV vaccination 10–20 years ago, the clinical characteristics and progression of pediatric HCC must be different from those reported earlier. In the present study,

X.-F. Zhang · X.-M. Liu · T. Wei · C. Liu · M.-X. Li ·
Z.-D. Long · Y. Lv (✉)
Department of Hepatobiliary Surgery, The First Affiliated
Hospital of Medical College, Xi'an Jiaotong University,
No. 277 West Yanta Road, Xi'an 710061,
Shaanxi province, PR China
e-mail: luyi169@126.com

we retrospectively analyzed clinicopathological characteristics and outcome of pediatric HCC in one single center.

Patients and methods

Patients

From January 2004 to May 2010, about 2,280 cases of HCC were diagnosed in our hospital, which is the largest tertiary hospital in Northwest China. Among them, 45 (1.97 %) were children of 3–18 years old, comprising 42 boys and 3 girls. 21 (46.7 %) HCC were diagnosed by liver biopsy, 18 (40 %) by open surgical biopsy and the rest 6 (13.3 %) by computed tomography (CT) and combined alpha-fetoprotein (AFP) test. The clinical data of pediatric HCC were retrospectively collected based on paper medical document and computer database. The relevant information included sex, age, chief complaint, HBV serological test of patients and their mother, HBV-DNA copies, Child–Pugh classification, liver function test, routine blood test, AFP, and tumor size, number, location, portal vein involvement, intrahepatic or distal metastasis, treatments, etc. On admission, patients were evaluated for operability of HCC by imaging studies including chest film, sonography, CT or angiography. Liver cirrhosis was diagnosed based on pathological examination indicating the presence of regenerating nodules of hepatocytes and fibrosis, and/or evaluated by ultrasound or CT showing a small and nodular liver along with enlarged caudate lobe and widening of the liver fissures, etc. [10]. Hepatic resection was the choice of treatment based on the patient's general condition, tumor resectability, liver function and the residue parenchyma after resection. The contraindication of resection included extrahepatic metastasis, Child–Pugh C of the liver or poor general condition of the patient. Hepatic resection included wedge excision, segmentectomy, lobectomy, etc. Pringle's maneuver, if available, was routinely adopted to reduce blood inflow into liver during tumor resection. If surgical resection was not applicable, direct or percutaneous radiofrequency ablation (RB) or transarterial chemotherapy and embolization (TACE) was then the choice of treatment for some other patients.

Follow-up

Survival times were calculated from their admission (or surgery) to death or the end of 2011. All the patients were followed up based on telephone and outpatient department records. The survival curve of 45 patients was plotted, and 1-, 3- and 5-year survival rates were calculated. Differences in survival between different therapeutic groups,

patients with or without HBV infection and patients with or without distal metastasis were compared.

Statistical analysis

Numerical data were expressed as mean \pm SD, and categorical data as percentages. Survivals were calculated by the Kaplan–Meier method, and the differences in survival between groups were compared using the log-rank test. Statistical analysis was carried out using SPSS 15.0. $p < 0.05$ was considered to be statistically significant.

Results

Clinicopathological characteristics of pediatric HCC

The clinical characteristics of patients are summarized in Table 1. The mean age was 13.5 years (range 3–18) with predominantly male patients (42/45). Abdominal pain and abdominal palpable mass were the chief complaints in 33 and 12 patients, respectively. 32 (71.1 %) patients were HBV serologically positive. Among them, 30 patients and their mother were HBV positive concomitantly. Two patients were HBV infected, but their parents were HBV negative. One patient was HBV negative, but the mother was positive. Liver cirrhosis was present in almost half of them (21/45, 46.7 %) radiographically and/or pathologically. Liver function was evaluated in all the patients. None of the patients had hepatic encephalopathy; 10 of them had observable ascites sonographically or radiographically. Prothrombin time (PT) was mostly within normal range, while the maximal prolongation of PT was 2 s. Hyperbilirubinemia (total bilirubin $>20 \mu\text{mol/L}$) was found in 24 patients, while hypoalbuminemia (albumin $<35 \text{ g/L}$) was found in 6 patients. Finally, 32 were classified as grade A, 8 as grade B and 5 as grade C by Child–Pugh classification. 39 showed abnormally high AFP level.

Tumor size, number, distribution and vascular invasion were assessed radiographically (Table 2). Multiple nodules were identified in 25 patients, among which only 2 underwent surgical resection. Bilateral involvement was found in 26 patients, while none of them underwent resection. 33 of the patients displayed large tumors with maximal diameter $>5 \text{ cm}$ (30 with maximal diameter $>10 \text{ cm}$, 66.7 %), and 8 of them underwent hepatic resection. There were thrombi of the portal vein or its branches in 21, hepatic vein invasion in 3, inferior vena cava invasion in 2 and hilar invasion in 4. Intrahepatic and distal metastasis was found in 8 and 11 patients, respectively, and none of them underwent resection. Metastatic spread to lung occurred in ten, to bone in 2 and to the left adrenal gland in 1 at first admission.

Table 1 Clinical characteristics of 45 children with HCC

Variables	Coefficient
Age	13.5 (3–18)
Sex (M/F)	42/3
Chief complaint	
Abdominal pain	33
Abdominal mass	12
Fatigue and weak appetite	7
Routine physical examination	4
Hepatitis B virus infection	32 (71.1 %)
Hepatitis B surface antigen positive	32 (71.1 %)
Hepatitis B e antigen positive	2 (4.4 %)
Hepatitis B e antibody positive	24 (53.3 %)
Hepatitis B core antibody positive	29 (64.4 %)
Maternal Hepatitis B virus infection	31 (68.9 %)
Hepatitis B virus DNA (IU/mL)	
<10 ³ /≥10 ³	19/10
Liver cirrhosis	21 (46.7 %)
Child–Pugh classification (A/B/C)	32/8/5
White blood cell count (×10 ⁹ /L)	6.9 ± 0.4
Hemoglobin (g/L)	123.7 ± 2.9
Platelet count (×10 ⁹ /L)	239 ± 18.7
ALT (U/L)	97 ± 14.7
AST (U/L)	156.8 ± 17.2
Total bilirubin (μmol/L)	52.3 ± 10.5
Albumin (g/L)	39.9 ± 0.8
Prothrombin time (s)	13.3 ± 0.2
AFP (ng/mL)	93,999.9 ± 31,228.4

HCC hepatocellular carcinoma, ALT alanine aminotransferase, AST aspartate aminotransferase, AFP alpha-fetoprotein

Table 2 Pathological data of 45 children with HCC

Variables	Coefficient
Tumor number (single/multiple)	20/25
Tumor size (≤5 cm/>5 cm)	12/33
Tumor distribution (left lobe/right lobe/bilobe)	6/13/26
Portal vein invasion	21 (46.7 %)
Intrahepatic metastasis	8 (17.8 %)
Distal metastasis	11 (24.4 %)
Treatments (hepatectomy/TACE/untreated/others)	12/10/19/4
In-hospital death	1 (2.2 %)

HCC hepatocellular carcinoma, TACE transarterial chemotherapy and embolization

Modalities of treatments

Totally, 18 patients underwent surgical exploration; among them 12 had curative resection, 1 had direct RB, 1 had intratumoral ethanol injection and the other 4 patients had only biopsy. 12 patients with mean age of 11 years had

curative resection at first admission. The resection rate was 26.7 %. Their clinical and pathological data are summarized in Table 3. The average maximal diameter of the resected tumors was 10 cm, and the resected tumors were located on one lobe in each case. TACE was undertaken in five patients from 1 month postoperatively for prevention of tumor recurrence: three are still surviving 11–14 months without HCC recurrence; however, two died of tumor metastasis. Notably, one patient is living 90 months after surgery, tumor free without any adjuvant therapies.

TACE was the treatment at first admission in ten patients because of unresectable tumor and poor liver function. Among them, three had repeated TACE 2–6 months after the first time. However, none of them could undergo resection. 19 patients were given no special medication, but only nutritional support.

Comparison of pediatric HCC with or without HBV

Since HBV infection was recognized as the main reason of pediatric HCC, we examined the difference in clinical and pathological characteristics of pediatric HCC with or without HBV (Table 4). Children without HBV infection were younger than those with HBV infection (*p* = 0.023), but were no differences in gender distribution. Liver cirrhosis was more frequently observed in HBV-positive children (*p* = 0.055). Platelet count and albumin were higher in HBV-positive than HBV-negative children (*p* < 0.05, respectively); however both were in normal range. Portal vein invasion was predominantly observed in HBV-positive children (*p* = 0.055), but tumor size, number and distal metastasis were not different in HBV-positive and -negative children.

Survival of pediatric HCC

The median survival time of the 45 patients was 6 months (Fig. 1). 1-, 3- and 5-year survival rate was 34, 4 and 4 %, respectively. Survival curves of the patients with different therapeutics are plotted and compared in Fig. 2. The median survival time of the patients with surgical resection, TACE and no treatment was 28.6, 4 and 5 months, respectively. Patients with curative resection had significantly better survival than other treatments (log-rank, *p* < 0.001), although pre-treatment tumor status and patient’s condition were different between the groups. The 3-year survival rate of patients with surgical resection was 13 %. However, there were no significant benefits of survival from TACE compared with the untreated group (log-rank, *p* > 0.05).

Since HBV-positive HCC in children was associated with predominant liver cirrhosis and portal vein invasion, we then compared the overall survival between HBV-

Table 3 Summary of 12 children with resectable hepatocellular carcinoma

Gender/age (years)	HBV/M-HBV	TN	Lobe	Size (cm)	Pathology stage and findings	Procedure	Adjuvant	Survival (months)	Outcome
M/9	+/+	1	Lt	9.5	II, LC (–), CF (–), PVI (–)	Lb		32	Dead, meta
M/11	+/+	1	Lt	15	III, LC (+), CF (+), PVI (+)	Lb		9	Dead, meta
M/16	+/+	1	Rt	4	II, LC (+), CF (+), PVI (–)	Seg		90	Surviving
M/9	+/+	1	Rt	10	II, LC (–), CF (+), PVI (–)	WE		18	Dead, rupture
M/10	+/+	1	Lt	15	III, LC (+), CF (+), PVI (+)	Lb		16	Dead, meta
M/15	+/+	1	Rt	4	II, LC (+), CF (–), PVI (–)	WE		9	Surviving
M/18	–/–	1	Lt	5	II, LC (–), CF (–), PVI (–)	Lb	TACE	20	Dead, meta
M/13	–/+	2	Rt	7	II, LC (+), CF (+), PVI (–)	WE ^a	TACE	14	Surviving
M/15	–/–	1	Rt	20	I, LC (–), CF (+), PVI (–)	Lb	TACE	12	Surviving
F/4	–/–	1	Rt	5	II, LC (–), CF (–), PVI (–)	WE		7	Dead, meta
M/3	–/–	2	Rt	9	II, LC (–), CF (+), PVI (–)	Lb	TACE	9	Dead, meta
M/7	–/–	1	Rt	15	I, LC (–), CF (+), PVI (–)	Lb	TACE	11	Surviving

HBV hepatitis B virus, M-HBV maternal hepatitis B virus infection, TN tumor number, Lt left lobe, Rt right lobe, LC liver cirrhosis, CF capsular formation, PVI portal vein invasion, Lb lobectomy, Seg segmentectomy, WE wedge excision, TACE transarterial chemotherapy and embolization, Meta metastasis

^a The patient underwent cholecystectomy, thrombectomy and T tube drainage because of bile duct thrombi

Table 4 Comparison of characteristics of children with HCC with or without HBV infection

Variables	HBV (+) (n = 32)	HBV (–) (n = 13)	p value
Gender (male/female)	30/2	12/1	1.000
Age	14.5 (±0.5)	10.9 (± 1.4)	0.023
Child–Pugh classification			
A/B/C	23/4/5	9/4/0	0.151
Liver cirrhosis	18 (56.3 %)	3 (23.1 %)	0.055
Hemoglobin (g/L)	120.8 (±3.9)	130.3 (±2.7)	0.088
Platelet count (×10 ⁹ /L)	204.2 (±20.8)	319.2 (±29.4)	0.004
ALT (U/L)	85.6 (±7.8)	125.7 (±47.4)	0.234
AST (U/L)	169.0 (±19.4)	126.8 (±35.8)	0.273
Total bilirubin (μmol/L)	56.3 (±12.9)	42.6 (±17.9)	0.561
Albumin(g/L)	38.5 (±1.0)	43.4 (±0.7)	0.001
Prothrombin time (s)	13.5 (±0.3)	12.9 (±0.2)	0.347
AFP (ng/mL)	71,504.8 (±31,645.2)	151,260.3 (±76155.3)	0.694
Tumor size (cm)	10.0 (±0.9)	12.5 (±2.2)	0.544
tumor number (≥2)	17 (53.1 %)	8 (61.5 %)	0.607
Portal vein invasion	18 (56.3 %)	3 (23.1 %)	0.055
Distal metastasis	7 (21.9 %)	4 (30.8 %)	0.704

HCC hepatocellular carcinoma, HBV hepatitis B virus, ALT alanine aminotransferase, AST aspartate aminotransferase, AFP alpha-fetoprotein

positive and -negative patients. The 1-year survival rate was significantly higher in HBV-negative patients than in HBV-positive patients (62 vs. 25 %, $p < 0.001$), although the overall survival between the two groups was not statistically different (Fig. 3, $p > 0.05$). Distal metastasis at admission was important in survival of the patients. As shown in Fig. 4, there was a significant difference in survival between metastatic and non-metastatic patients (log-rank, $p < 0.001$). The median survival in metastatic patients was only 4 months (Fig. 4).

Discussion

HCC mainly occurs in adults. However, in hyperendemic area of HBV infection, such as China, HCC develops in children as well [11]. In China, chronic HBV infection ranks first among 27 infectious diseases, and more than 60 % of the Chinese population has a history of HBV infection [12]. Many HBV infections were through vertical transmission from the mother to the child in the perinatal period [12, 13]. Reports from Taiwan showed that pediatric HCC was exclusively HBV correlated [4, 9, 14]. The present study identified that HBV infection was present in around 71 % pediatric HCC, compared with ~74 % in adults in our hospital [15], and 29 % patients developed HCC with unknown reasons. These findings are different from the previous reports from Taiwan more than 10 years ago [3, 4, 9]. The incidence of HCC in children has declined dramatically since the universal vaccination of

Fig. 1 Overall survival of the 45 cases of pediatric hepatocellular carcinoma

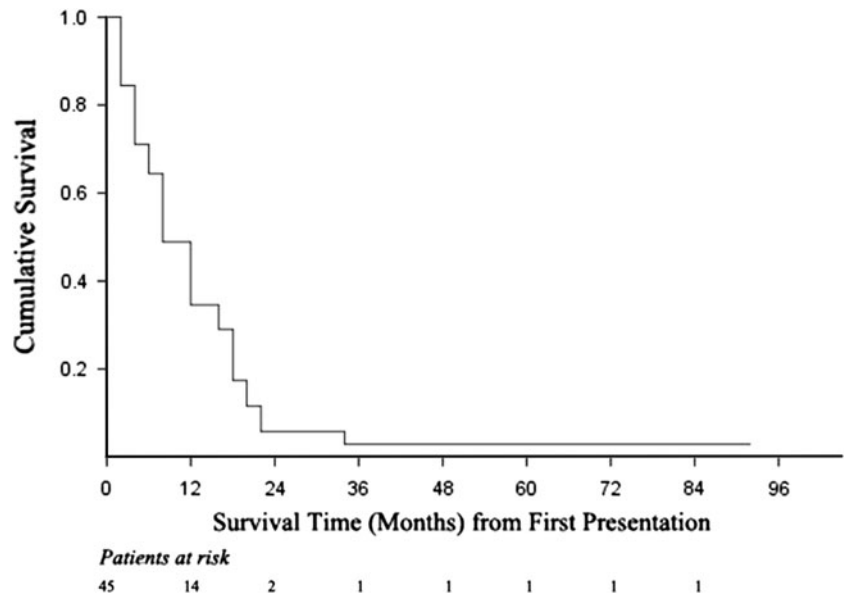
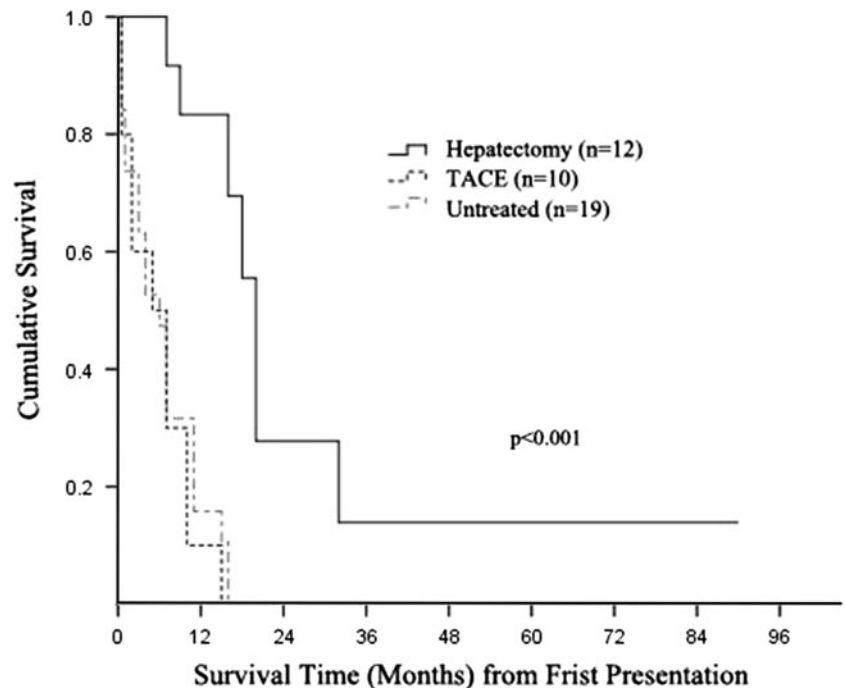


Fig. 2 Overall survival of pediatric hepatocellular carcinoma in different treatment groups



hepatitis B vaccine [5, 16]. National immunization of hepatitis B vaccination in China since 2002 might account for the decreased ratio of HBV-related HCC in children [17]. As observed in the present study, HBV positivity was associated with more frequent presence of liver cirrhosis and portal vein invasion, and thus poorer 1-year survival rate. However, the overall survival was not different between HBV-positive and -negative patients. Notably, among 32 children with HBV infection, the mother of 30 (94 %) had HBV serologically positive as well. This finding demonstrated high prevalence of vertical

transmission of HBV in the perinatal period, which was also the major cause of pediatric HCC. Therefore, screening of those children whose mothers are HBV carriers is worthwhile even after immunization. Children whose mothers are HBV carriers are recommended to receive a combination therapy of hepatitis B vaccine and hepatitis B immune globulin within 12 h of birth, which proved to be 85–95 % effective in reducing vertical transmission of HBV [13, 18]. Once the child is infected with HBV, serial AFP screening and combined imaging studies should be mandatory.

Fig. 3 Survival of pediatric hepatocellular carcinoma with or without hepatitis B virus infection

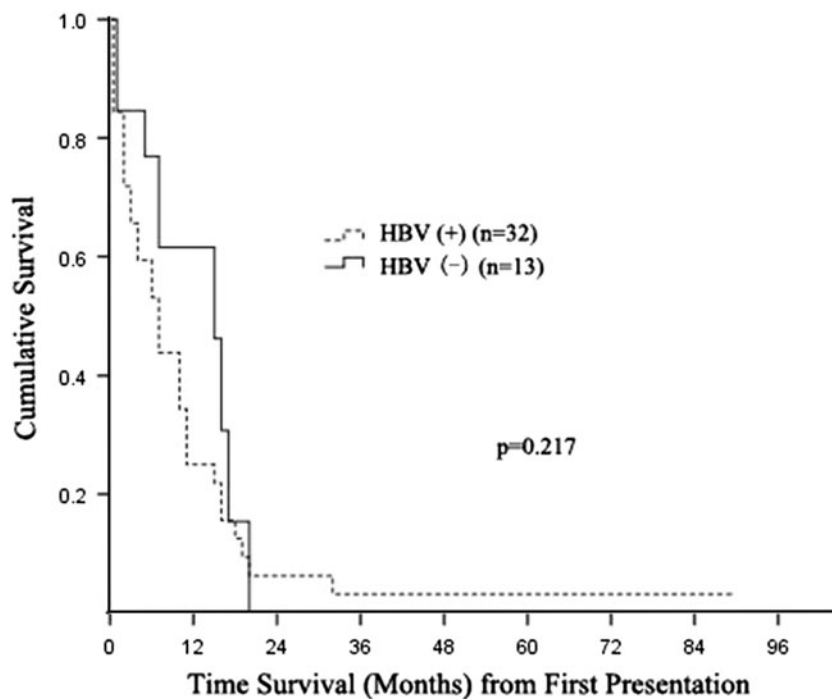
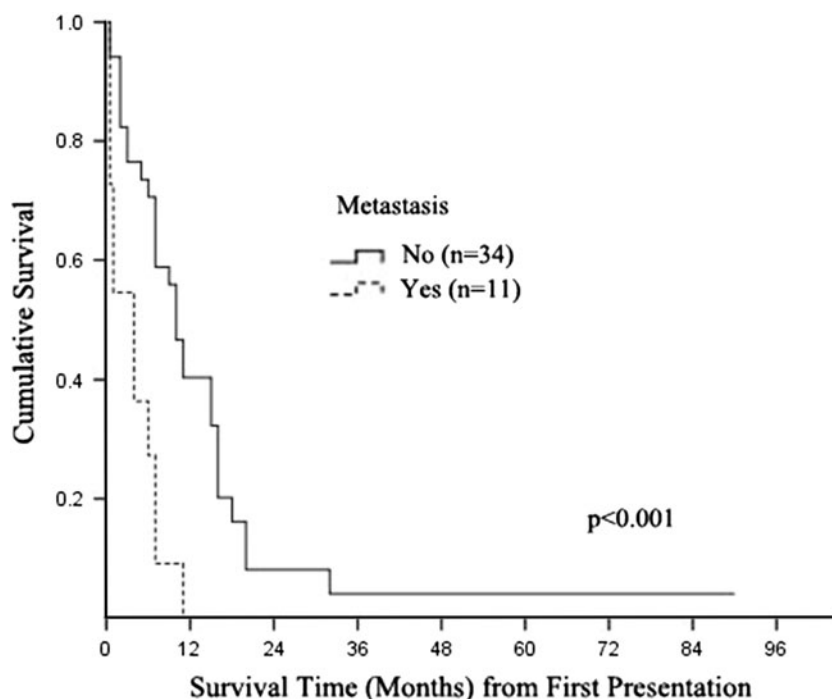


Fig. 4 Survival of pediatric hepatocellular carcinoma with or without distal metastasis



In the present study, 42 (93.3 %) children with HCC were of school age (≥ 6 years old) and only 3 were below 6 years old. Abdominal pain was the most common complaint of children, followed by abdominal mass. However, HCC has been rarely suspected in children based on these unspecific symptoms, but some other gastric or intestinal disease. This might delay the diagnosis and treatment of

HCC at the proper time, which accounted for advanced or metastatic disease at first admission in the liver unit.

Liver cirrhosis was present in almost 50 % of children, which was lower than 70 % of adults in our hospital [15, 19]. This was probably a result of shorter duration of chronic hepatitis in childhood. The present study showed that surgical resection remained the only hope of long-term

survival of children with HCC compared with other therapeutics. The resection rate of pediatric HCC in our study was 26.7 %, which was, however, higher than 18.2 % in previous reports [9]. Tumor size, early metastasis and vascular invasion might be the main reasons hindering the availability of curative resection. In our study, 30 (66.7 %) patients presented with tumor maximal size >10 cm, 19 (42.2 %) were found to have intra or extrahepatic metastasis and 26 (46.7 %) had vascular involvement at first admission. Distal metastasis was also a risk factor implying poor survival in pediatric HCC, which was identified in 24 % patients at admission in the present study. Therefore, advanced disease prevented effective treatment of pediatric HCC. The median survival of children with HCC after surgical resection was 28.6 months, which was slightly better than that previously reported [9]. The 3-year survival rate after surgical treatment was significantly lower in children with HCC than adult cases in our hospital (13 vs. 53 %) [15, 19]. TACE should be an adjuvant treatment for unresectable pediatric HCC or reducing probability of recurrence postoperatively as in adults. However, the overall survival of ten patients receiving TACE was not significantly different from those untreated in our study. Therefore, the status of TACE in pediatric HCC needs to be further evaluated.

Liver transplantation might be another choice of treatment theoretically. Several reports with limited number of patients advocate that liver transplant is a life-saving procedure for children with chronic liver disease and accompanying HCC [20, 21]. However, advanced stage of the disease including large size of tumor and high frequency of local or distal spread contraindicates liver transplantation as an alternative treatment for pediatric HCC. Therefore, liver transplantation, although available in our hospital, was not performed for children with HCC. Although chemotherapy is also recommended by oncologists, it has very little positive effect in improving patient's survival or shrinking tumors [9, 22–24]. Therefore, it was not a routine modality for pediatric HCC in our unit. However, several comprehensive studies recently demonstrated that cisplatin-based chemotherapy regimen might benefit children with resectable HCC [25–27]. Thus, with these convincing studies, new regimens should be further looked for and tested as alternative treatment approaches of pediatric HCC.

HCC in children might be different from that in adults in aspects of clinical characteristics, disease progression and outcomes. After national Hepatitis B vaccination for several decades, the ratio of HBV-related HCC in children has declined to almost equivalent to that in adults. However, HBV in children is mostly transmitted vertically from their mothers. The results of the present study suggest that screening of those children whose mothers are HBV

carriers is important in early detection of pediatric HCC, which might increase resectability rate and improve surgical prognosis of the children with HCC. HBV positivity was associated with more frequent liver cirrhosis and portal vein invasion, and thus compromised survival, compared with HBV-negative children with HCC. Advanced stage of disease with huge hepatomas and early metastasis due to more rapid progression of tumors and delay in treatment resulted in poorer survival in children than in adults. Although TACE and chemotherapy are candidate treatments for unresectable HCC in children, their efficacy needs to be further evaluated.

Acknowledgments The study was supported by Major Program of National Natural Science Foundation of China (30830099), National Natural Science Foundation (NO. 81101873), Shaanxi Province Natural Science Foundation (No. 2011JQ4007) and Fundamental Scientific Research Grant of Xi'an Jiaotong University (No. XJJ20100196).

Conflict of interest There is no conflict of interest to declare.

References

1. Moore SW, Hesseling PB, Wessels G et al (1997) Hepatocellular carcinoma in children. *Pediatr Surg Int* 12:266–270
2. Weinberg AG, Finegold MJ (1983) Primary hepatic tumors of childhood. *Hum Pathol* 14:512–537
3. Chen WJ, Lee JC, Hung WT (1988) Primary malignant tumor of liver in infants and children in Taiwan. *J Pediatr Surg* 23:457–461
4. Hsu HC, Wu MZ, Chang MH et al (1987) Childhood hepatocellular carcinoma develops exclusively in hepatitis B surface antigen carriers in three decades in Taiwan. Report of 51 cases strongly associated with rapid development of liver cirrhosis. *J Hepatol* 5:260–267
5. Chang MH, Chen CJ, Lai MS et al (1997) Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med* 336:1855–1859
6. Chang MH (2003) Decreasing incidence of hepatocellular carcinoma among children following universal hepatitis B immunization. *Liver Int* 23:309–314
7. Lee CL, Hsieh KS, Ko YC (2003) Trends in the incidence of hepatocellular carcinoma in boys and girls in Taiwan after large-scale hepatitis B vaccination. *Cancer Epidemiol Biomarkers Prev* 12:57–59
8. Darbari A, Sabin KM, Shapiro CN et al (2003) Epidemiology of primary hepatic malignancies in U.S. children. *Hepatology* 38:560–566
9. Chen JC, Chen CC, Chen WJ et al (1998) Hepatocellular carcinoma in children: clinical review and comparison with adult cases. *J Pediatr Surg* 33:1350–1354
10. Osterreicher CH, Stickel F, Brenner DA (2007) Genomics of liver fibrosis and cirrhosis. *Semin Liver Dis* 27:28–43
11. Chang MH, Chen DS, Hsu HC et al (1989) Maternal transmission of hepatitis B virus in childhood hepatocellular carcinoma. *Cancer* 64:2377–2380
12. Liang X, Bi S, Yang W et al (2009) Epidemiological serosurvey of hepatitis B in China—declining HBV prevalence due to hepatitis B vaccination. *Vaccine* 27:6550–6557

13. Lok AS, McMahon BJ (2007) Chronic hepatitis B. *Hepatology* 45:507–539
14. Chang MH, Chen PJ, Chen JY et al (1991) Hepatitis B virus integration in hepatitis B virus-related hepatocellular carcinoma in childhood. *Hepatology* 13:316–320
15. Zhang XF, Wei T, Liu XM et al (2012) Spontaneous tumor rupture and surgical prognosis of patients with hepatocellular carcinoma. *Scand J Gastroenterol* 8–9:968–974
16. Chang MH, Shau WY, Chen CJ et al (2000) Hepatitis B vaccination and hepatocellular carcinoma rates in boys and girls. *JAMA* 284:3040–3042
17. Cui FQ, Wang XJ, Cao L et al (2007) Progress in hepatitis B prevention through universal infant vaccination—China, 1997–2006. *MMWR* 56:441–445
18. Lam NC, Gotsch PB, Langan RC (2010) Caring for pregnant women and newborns with hepatitis B or C. *Am Fam Physician* 82:1225–1229
19. Zhang XF, Meng B, Qi X et al (2009) Prognostic factors after liver resection for hepatocellular carcinoma with hepatitis B virus-related cirrhosis: surgeon's role in survival. *Eur J Surg Oncol* 35:622–628
20. Romano F, Stroppa P, Bravi M et al (2011) Favorable outcome of primary liver transplantation in children with cirrhosis and hepatocellular carcinoma. *Pediatr Transplant* 15:573–579
21. Sevmis S, Karakayali H, Ozcay F et al (2008) Liver transplantation for hepatocellular carcinoma in children. *Pediatr Transplant* 12:52–56
22. Evans AE, Land VJ, Newton WA et al (1982) Combination chemotherapy (vincristine, adriamycin, cyclophosphamide, and 5-fluorouracil) in the treatment of children with malignant hepatoma. *Cancer* 50:821–826
23. Weinblatt ME, Siegel SE, Siegel MM et al (1982) Preoperative chemotherapy for unresectable primary hepatic malignancies in children. *Cancer* 50:1061–1064
24. King DR, Ortega J, Campbell J et al (1991) The surgical management of children with incompletely resected hepatic cancer is facilitated by intensive chemotherapy. *J Pediatr Surg* 26:1074–1080 (discussion 80-1)
25. Czauderna P, Mackinlay G, Perilongo G et al (2002) Hepatocellular carcinoma in children: results of the first prospective study of the International Society of Pediatric Oncology group. *J Clin Oncol* 20:2798–2804
26. Katzenstein HM, Krailo MD, Malogolowkin MH et al (2002) Hepatocellular carcinoma in children and adolescents: results from the Pediatric Oncology Group and the Children's Cancer Group intergroup study. *J Clin Oncol* 20:2789–2797
27. Schmid I, Haberle B, Albert MH et al (2012) Sorafenib and cisplatin/doxorubicin (PLADO) in pediatric hepatocellular carcinoma. *Pediatr Blood Cancer* 58:539–544