Primary liver tumors in children: Hacettepe experience

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SUMMARY: Kutluk T, Yalçın B, Ekinci S, Kale G, Akyüz C, Aydın B, Varan A, Demir HA, Büyükpamukçu M. Primary liver tumors in children: Hacettepe experience. Turk J Pediatr 2014; 56: 1-10.

We aimed to review our experience with the clinical characteristics and outcome in childhood liver tumors. We investigated the clinical, laboratory and pathological characteristics, treatments and outcome in hepatoblastomas (HBL) and hepatocellular carcinomas (HCC). We identified 91 HBL and 42 HCC cases. Distant metastases were detected in 16% of HBLs and 22% of HCCs. PRETEXT stages were I/II in 34% and III/IV in 66% of HBLs and I/II in 16% and III/IV in 84% of HCCs. Most cases received cisplatin + doxorubicin chemotherapy. At a median of 58 months, 90 cases had died, 28 were alive, and 15 were lost to follow-up. Five-year survival rates were 32.4% for all HBLs and 15.6% for HCCs. Five-year survival rates were 47% in HBLs and 22.8% in HCCs diagnosed after 1990. In HBLs, distant metastases and absence of chemotherapy response indicated poor prognosis. Prognosis for childhood liver tumors has improved over the last two decades with preoperative chemotherapy with cisplatin + doxorubicin. Surgical resectability is important for cure. For HCC, more effective chemotherapy approaches are essential.

Key words: primary liver tumors, hepatoblastoma, hepatocellular carcinoma, children, chemotherapy.

Primary malignant liver tumors are uncommon in childhood. Among a variety of histopathological types, the most common are hepatocellular carcinoma (HCC) and hepatoblastoma (HBL). Together, they constitute about 0.5-2% of all childhood malignancies[1,2]. They account for 1.5% of >7,000 cancer cases diagnosed and treated at our center during the last 40 years[3].

These two tumors in children exhibit marked differences in their clinical presentation and course, treatment responses, surgical resectability, and prognosis. HBL is commonly diagnosed in infants and young children, whereas HCC is generally a disease of older children and adolescents. In recent decades, the prognosis for HBL cases has improved significantly; however, in HCC, less than one-third of the cases can be cured.

The aim of this study was to review our institutional experience with the clinical and pathological characteristics and outcome in childhood primary liver tumors over a period of 40 years.

Material and Methods

We reviewed the hospital files of all patients with biopsy-proven HBL and HCC who were younger than 18 years and received treatment and follow-up care at our hospital between 1972 and 2011. Demographic characteristics of the patients, presenting signs and symptoms, physical examination findings, laboratory data including the radiological studies, localization and extent of disease, treatment approaches, surgical practices, treatments and responses, as well as events and outcomes were recorded.

Tumor extension at diagnosis was assessed in patients who had available results of radiological studies, such as abdominal ultrasound and/or computed tomography (CT) and/or magnetic resonance imaging. Lung metastases were identified by chest CT. For our patients, ultrasound was used after 1983, CT after 1986, and mostly MRI after 2000. Tumor extension within the liver was graded using the PRETEXT system of the International Society of Pediatric Oncology (SIOP) (on a scale of I to IV, with

higher grades indicating tumor involvement in more sectors of the liver)[4].

We used a $\chi 2$ test to examine the relationship between pairs of variables. Overall (OS) and event-free (EFS) survival rates were calculated by the Kaplan–Meier method (5), and differences in survival were compared using the log-rank test. For EFS, an event was defined as no response to treatment, local or metastatic relapse of disease, progression of disease under therapy, death irrespective of its cause, or secondary malignancies, whichever came first. For OS analysis, only death was taken into account. Analyses for OS rates were repeated for 86 cases (58 HBL, 28 HCC) diagnosed and treated after 1990 when chemotherapy protocols were more uniformly given as the PLADO regimen (cisplatin + doxorubicin). For survival analyses, time was censored at the last follow-up date if no failure was observed. Using the Cox proportional hazards regression model, multivariate analyses were performed to determine the variables that were independently predictive of prognosis. In every instance, a p value smaller than 0.05 was considered significant.

Results

The study group included 133 eligible patients (76 males, 57 females; M/F = 1.33). There were 91 HBL and 42 HCC cases. For all cases, the most common presenting complaints were abdominal distension and/or pain, abdominal mass, fever, weight loss, fatigue, and vomiting. The most common physical examination findings were abdominal mass (>90% of cases) and abdominal distension (>50% of cases). Some demographic and clinical characteristics of the patients are given in Table I.

Hepatoblastomas

The median age at diagnosis was 1.4 years (range: 0.01-16.3; male/female: 47/44), and 30% of cases were older than two years. Median time elapsed from the onset of symptoms to diagnosis was 21 days (1 day-6 months). One of the cases had neurofibromatosis type 1 and another had tyrosinemia type 1. Median serum alpha-fetoprotein (AFP) level at diagnosis was 87805 IU/ml (6-765270; in 91%, levels were elevated for age) (Table I). The median blood platelet count was 596,000/mm^3. Serum total bilirubin levels above 2 mg/ml at initial diagnosis were found in 15/75 (20%) HBL cases.

Distant metastases were detected in the lungs in 15.5% of the cases (13/84); metastases in the central nervous system, abdominal wall and omentum, and peritoneum were found in 1 patient each. In the radiological studies (ultrasound ± CT), of 62 patients with available data, 42 had solitary and 19 had multiple lesions and 2 had ascites; involvement of the portal vein was detected in 4/87 cases.

Data for PRETEXT stages were available for 68 patients: 31 had stage IV, 14 stage III, 17 stage II, and 6 stage I disease (Table I). In 45/91 cases, Tru-cut, and in 30, open biopsies were performed for diagnoses; total resections with no residues, total resections with microscopic residues and partial resections of the primary tumors were performed in 7, 2 and 5 patients, respectively.

Histopathological diagnoses were classical HBL in 75, HBL with pure fetal histology in 6, HBL with fetal and embryonal histology in 3, HBL with mixed epithelial and mesenchymal elements in 6, and HBL with small cell undifferentiated histology in 1.

Nineteen patients did not receive chemotherapy for different reasons; 48 received cisplatin and doxorubicin (PLADO), and 17 received vincristine and cyclophosphamide. All but 2 cases treated after 1990 received the PLADO regimen, while only 1 patient received this protocol before 1990.

At initial diagnosis, 10% of the cases underwent total tumor resection. Two-thirds of the cases (36/54) with available data for response evaluation showed complete or partial responses to induction chemotherapies. Twenty-four cases underwent a second surgery after receiving chemotherapy (PLADO), mostly after the mid-1990s; total tumor resection was possible in 83% of them. Two cases underwent liver transplantation, and one had tyrosinemia type 1. Nine cases experienced recurrence of disease: 6 in the liver, 2 in the liver and lungs, and 1 in the brain. At a median follow-up of 58 months (range: 9.8–253 months) for the survivors, 55 cases had died, 23 were alive, and 13 were lost to follow-up.

Hepatocellular Carcinomas

The median age at diagnosis was 10 years

(range: 1.3-17.5; male/female: 29/13), and 7% of cases were younger than two years. The median time elapsed from the onset of symptoms to diagnosis was 30 days (2 days-4 months). As associated findings, 4 patients had cirrhosis of the liver, 1 patient had coloboma of the iris, and 5 patients had tyrosinemia type 1.

The median serum AFP level at diagnosis was 5825 IU/mL (1.2-573899; in 83%, levels were elevated for age). The median blood platelet count was 277,000/mm^3. Serum total bilirubin levels above 2 mg/ml at initial diagnosis were found in 10/40 (25%) HCC cases.

Distant metastases in the lungs were detected in 22% of HCC cases: in the central nervous system, kidneys, intestines, and right atrium in 1 patient each, and in the peritoneum in 2 cases. In the radiological studies of 36 patients, 10 had solitary and 24 had multiple lesions and 6 had ascites. Vascular involvement of the portal vein was detected in 9 and of the inferior vena cava in 2/41 cases. Data for PRETEXT stages were available for 37 patients: 21 had stage IV, 10 stage III, 4 stage II, and 2 stage I disease. Initial diagnostic interventions were Tru-cut biopsies in 20, open biopsies in 18, total resection in 2 (in 1 with microscopic residue), and partial resection in 1 (Table I). Histopathological diagnoses were HCC in 37, HCC adult type in 1, and HCC fibrolamellar type in 3.

Five patients did not receive chemotherapy for different reasons; 27 patients received PLADO regimen, 5 patients received vincristine, cyclophosphamide, doxorubicin, and 5-fluorouracil (FU), 2 patients received vincristine and cyclophosphamide, and 2 patients received vincristine, cyclophosphamide, and actinomycin-D (Table I).

In HCCs, at initial diagnosis, total resection of the primary tumor could be performed in 1 patient. After receiving chemotherapy, 7/42 HCC cases underwent a second surgery, and in 5 of them, total tumor resection was possible. Four cases with tyrosinemia type 1 underwent liver transplantation. Relapses occurred in 8/42 cases: 6 in the liver, 1 in the lungs, and 1 in the liver and lungs. Thirty-five HCC patients died, 5 cases are alive and under regular follow-up at a median of 103 months (66-202), and 2 were lost to follow-up. A 13-year-old girl with fibrolamellar HCC who rejected further systemic chemotherapy following hepatic lobectomy experienced recurrence of disease five years after the operation and died 6.5 years following the initial diagnosis.

Survival Analyses

Survival analyses were calculated with the univariate method for subgroups of patients. The results are documented in Table II. Five-year OS rates were 32.4% and 15.6% for all HBL and HCC cases, which increased to 47%

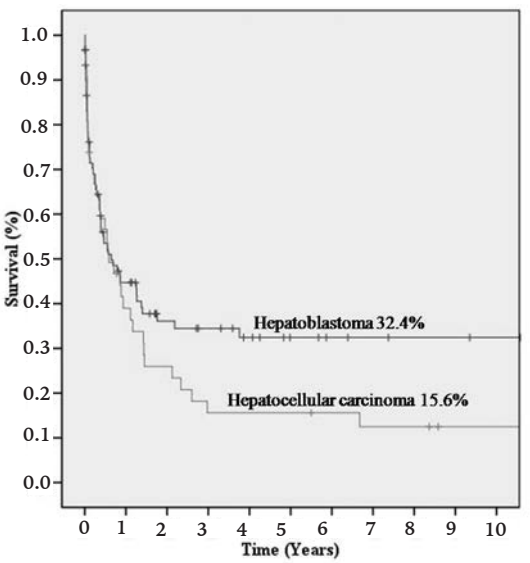

Fig. 1. Overall survival in children with primary liver tumors, 1972-2011.

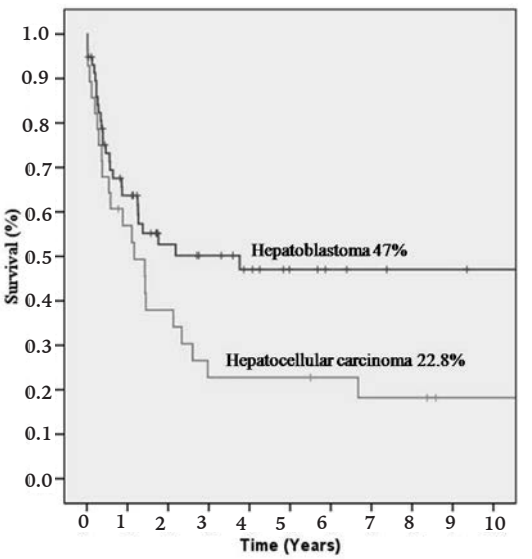

Fig. 2. Overall survival in children with primary liver tumors, after 1990.

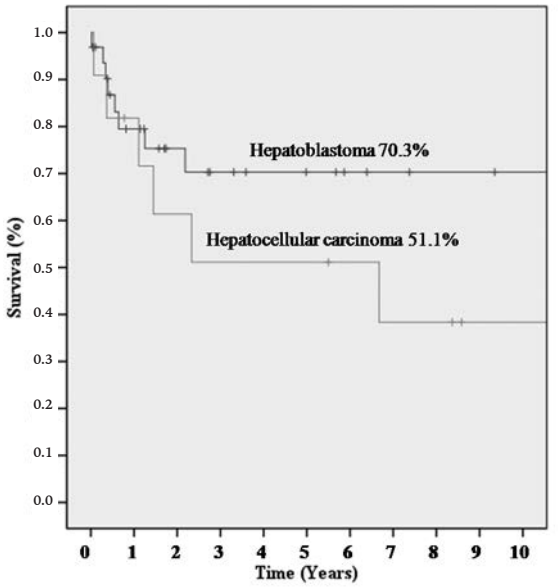

Fig. 3. Overall survival in children with primary liver tumors, after 1990 (PRETEXT I/II/III, no distant metastases).

and 22.8%, respectively, after 1990 (Figs. 1, 2).

Cases without distant metastases had higher survival rates, though not significant. For both HBL and HCC, no significant differences were found in survival rates between the cases with normal or elevated levels of platelets. For HCC cases, male gender was significantly related with lower survival rates (Table II). Among patients with normal AFP levels, 4/6 HBLs died and 2/6 were lost to follow-up, and 3/5 HCCs died, 1/5 was lost to follow-up and 1/5 was alive without disease.

Cases with PRETEXT I/II/III disease or who received PLADO regimens had significantly higher OS rates. OS rates were significantly higher for HBL patients who had complete or partial responses to initial chemotherapy. Such a difference could not be shown for HCC.

Five-year OS rates increased to 70.3% and 51.1%, respectively, for HBL and HCC cases with PRETEXT I/II/III disease without distant metastases who were treated after 1990 (Fig. 3).

In the multivariate Cox model, cases treated more uniformly after 1990 were selected, and PRETEXT stages, presence of distant metastases, and response to chemotherapy were analyzed for OS.

In HBLs, 48 cases with a complete set of data were included in this analysis (19 events, 29 censored), and presence of distant metastases ($p= 0.049$, relative risk [RR]: 2.6; 95% confidence interval [CI]: 1.006-6.75) and absence of response to chemotherapy ($p<0.001$, RR: 7.7; 95% CI: 2.5-23.8) were significant adverse prognostic factors. In HCCs, the number of cases was not sufficient to perform Cox regression analyses.

Discussion

Primary malignant liver tumors are relatively uncommon in children. Presenting a single center's long-term experience, our series contributes to the pediatric liver tumor literature. This is a retrospective review, and for example, the histology, PRETEXT and systemic staging were products of chart review and not reviewed centrally.

Children with primary liver tumors most commonly present with an abdominal mass, swelling and pain[6-10]. Presenting signs and symptoms of our patients were consistent with those of previous reports. Occasionally, HBL cases may present with physical signs of precocious puberty, which is a result of beta-human chorionic gonadotropin production by the tumor[6,7,10] . We did not have any case with such findings.

The median age of our HBL cases was 1.4 years, which was similar to previous reports[8,11-13]; 10 (9%) cases were older than 4 years.

Alpha-fetoprotein (AFP), the most important tumor marker for liver tumors, was elevated in the majority of our cases. In several multicenter trials, AFP level <100 was reported to indicate worse prognosis[14,15]. In a series of 43 HBL cases from Korea, low AFP levels at diagnosis were associated with shorter survival[15]. We could not perform such an analysis for AFP due to limited number of cases with low serum levels.

In this study, 60% of HBL cases had elevated platelet levels at the initial diagnosis. Thrombocytosis is believed to be a paraneoplastic syndrome due to overproduction of thrombopoietin by the tumors[16,17]. Thrombocytosis is reported to be related with advanced disease and worse prognosis in malignant liver tumors[8]. However, we did not show any relation with disease stage or any prognostic significance. Some other studies also reported that a high platelet level was not a significant indicator of outcome[3,18].

Table I. Clinical and Laboratory Characteristics of 133 Children with Primary Liver Tumors

		Hepatoplastoma			Hepatocellular carcinoma	
		n	%		n	%
Gender	Male	47	51.6		29	69
	Female	44	48.4		13	31
	Total	91	100		42	100
	p			*0.06*		
Age group	≤ 2 years	64	70.3		3	7.1
	> 2 years	27	29.7		39	92.9
	Total	91	100		42	100
	p			*<0.001*		
AFP	Normal for age	6	9.5		5	16.6
	Elevated	57	90.5		25	83.4
	Total	63	100		30	100
	p			*0.32*		
HBs	Negative	56	96.6		15	46.9
	Positive	2	3.4		17	53.1
	Total	58	100		32	100
	p			*<0.001*		
*Platelets	Normal-Low	19	40.4		15	78.9
	Elevated	28	59.6		4	21.1
	Total	47	100		19	100
	P			*0.005*		
Lung metastases	Negative	71	84.5		32	78
	Positive	13	15.5		9	22
	Total	84	100		41	100
	p			*0.45*		
PRETEXT stages	I+II+III	37	54.4		16	43.2
	IV	31	45.6		21	56.8
	Total	68	100		37	100
	p			*0.11*		
**Response to chemotherapy	Yes	36	66.6		12	46.1
	No	18	33.4		14	53.9
	Total	54	100		26	100
	p			*0.3*		
**Chemotherapy regimens	PLADO	48	68.5		27	73
	Others	22	31.5		10	27
	Total	70	100		37	100

AFP: Alpha-fetoprotein. HBs: Hepatitis B surface antigen. * Normal-low platelets: <500,000/mm3, elevated platelets: >500,000/mm3. ** Complete or partial responses. *** PLADO: Cisplatin and doxorubicin. Others: Chemotherapy regimens containing combinations of vincristine, actinomycin-D, cyclophosphamide, 5-fluorouracil, adriamycin.

Tablo II. Overall Survival Rates in Children with Hepatoblastoma and Hepatocellular Carcinoma (Univariate Analyses)

		All Cases (1972-2011)				Cases Diagnosed after 1990			
		Hepatoblastoma		Hepatocellular carcinoma		Hepatoblastoma		Hepatocellular carcinoma	
		n	5-year(%)	n	5-year (%)	n	5-year (%)	n	5-year (%)
All cases		91	32.4	42	15.6	58	47.0	28	22.8
Gender	Male	47	31.6	29	7.3	31	42.3	17	11.8
	Female	44	34.5	13	34.6	27	54.8	11	40.9
	p		*0.58*		*0.01*		*0.77*		*0.032*
Age	≤ 2 years	64	33.7	3	None alive at 7 mo.	40	47.8	1	Died at 3. mo
groups	>2 years	27	31.1	39	13.4	18	47.5	27	23.6
	p		*0.74*		*0.035*		*0.61*		*<0.001*
Platelets*	Normal-low	19	38.4	15	33.3	18	34.3	15	33.3
	Elevated	28	59.3	4	None alive at 25 mo.	28	59.3	4	None alive at 25 mo.
	p		*0.32*		*0.36*		*0.24*		*0.36*
PRETEXT	I+II+III	37	62.3	16	37.9	34	64.9	12	46.9
stages	IV	31	23.3	21	4.8	21	30.2	16	6.3
	p		*0.001*		*0.036*		*0.01*		*0.03*
Distant metastases	Yes	13	16.7	9	11.1	9	22.2	8	12.5
	No	71	40.1	32	17.4	47	56.2	20	26.9
	p		*0.3*		*0.47*		*0.07*		*0.14*
Chemotherapy	PLADO	48	47.1	27	23.6	48	47.1	26	24.5
regiments**	Others	22	5.5	10	None alive at 25 mo.	1	Died at 2nd mo.	1	Died at 2nd mo.
	p		*<0.001*		*<0.001*		*0.001*		*0.008*
Response to	Yes	37	68.8	12	16.7	35	69.8	11	18.2
chemotherapy***	No	18	8.9	14	8.6	13	13.5	10	12.5
	p		*<0.001*		*0.087*		*<0.001*		*0.26*

* Normal-low platelets: <500.000/mm^3, elevated platelets: > 500.000/mm^3. ** PLADO: Cisplatin and doxorubicin. Others: Chemotherapy regimens containing combinations of vincristine, actinomycin-D, cyclophosphamide, 5-fluorouracil, adriamycin. *** Complete or partial responses.

Hepatoblastoma (HBL) mostly appears as a large multinodular expansile mass, usually unifocal[11,13,19]. There is higher frequency of multiple nodules and multifocality in HCC[9,20]. Tumor distribution within the liver is a significant prognostic indicator[21,22]. In this study, most HBL cases had unifocal solitary tumors. Tumor invasion into the inferior vena cava, portal vein and/or hepatic veins puts the patients into the high-risk group[9,12,22]. In the International Society of Pediatric Oncology Epithelial Liver Tumors (SIOPEL) studies, major hepatic vascular involvement was reported to be around 10% in HBLs[20,22].

PRETEXT staging was developed for the first prospective liver tumor study by the SIOP[4] based on the number of liver segments involved as determined by preoperative imaging studies. Results of SIOPEL studies have indicated that the system has very good reproducibility and predictive value as regards prognosis[4,12,20,23,24]. In primary liver tumors, PRETEXT IV disease carries a poorer prognosis since complete tumor resection becomes very difficult. As to the PRETEXT stages, one-third of our HBL cases had stage I/II disease. In our study, nearly half of all cases had PRETEXT IV disease. In the SIOPEL studies, 60% of HCC cases had advanced (III/IV) PRETEXT stages[12,19,25].

The improvements in survival over the decades have been largely contributed by standardized chemotherapy regimens that reduce tumor size and enable complete tumor excision, as clearly experienced in several cooperative study groups[11,12,21,24,25,27]. Some tumors that could not be resected primarily may become resectable after shrinkage by chemotherapy, which also results in downstaging of the PRETEXT stage[12,13,20,23,25].

In the last three decades, chemotherapy regimens have progressively been more effective for liver tumors, and have mostly included cisplatin, doxorubicin, 5-FU, and vincristine. HBLs are chemosensitive tumors, and most of the initially unresectable tumors become amenable to complete surgical resection following the current preoperative chemotherapy regimens, mostly with cisplatin and doxorubicin.

Response to chemotherapy was achieved in two-thirds of our HBL cases, and 24 cases underwent a second surgery following chemotherapy. Complete removal of the tumor was possible in <10% of our HBL cases at initial diagnosis. With delayed or second-look surgery following preoperative chemotherapy with PLADO, the complete resection rate improved with less intensive liver resections. The rate of complete tumor resection has been even higher in the last two decades.

The overall prognosis in HBL depends on many clinical or histopathological factors. Among these, the most important are resectability of the primary tumor and presence of distant metastases[8,12,13,25-27]. Some other important adverse prognostic factors are reported as an initially low AFP (<100), presence of vascular invasion, lymph node metastases, and small-cell undifferentiated histology[9,12,13,23,26]. In this retrospective series, presence of distant metastases and absence of response to chemotherapy were the independent poor prognostic indicators for HBLs.

Hepatocellular carcinoma (HCC) is the most common hepatic malignancy of adolescents [6,8,10,20,28]. Only 3 (7%) of our HCC cases were younger than two years. A male predominance is reported in children with liver tumors, especially for HCC[8,12,13,21], for which the reason remains unclear. The male predominance in our cases was more significant for HCC, similar to an adult HCC series from our country[29].

Hepatocellular carcinoma (HCC) often occurs in the presence of underlying liver disease and cirrhosis[11,20,30]. In children, cirrhosis is less common, while congenital or acquired disorders of the liver, such as inborn metabolic diseases, are common[9,11,20,28]. Patients with tyrosinemia are particularly at high risk. In our series, five HCC cases had hereditary tyrosinemia type 1.

Similar to adults, there is a clear association of pediatric HCC with hepatitis B virus infection [11,28,31,32]. In the SIOPEL study, 33% of HCC cases presented with disease associated with hepatitis B and cirrhosis[20,33]. In a report from our country, of 221 adult HCC cases, 44% had hepatitis B and 21% hepatitis C positivity, and 71% had cirrhosis[29]. Half of our HCC cases were positive for hepatitis B. Vaccination programs against hepatitis have led to a significant decrease in the incidence of HCC worldwide[8,32,34].

In HCC, serum AFP is also useful as a prognostic indicator; survival rates are significantly lower

in cases with high levels[29,35-37]. Mitsuhashi et al.[37] reported that the poor prognosis of HCC associated with high AFP level is due to high cell proliferation, high angiogenesis and low apoptosis. We could not perform an analysis for the prognostic significance of AFP due to limited number of cases with normal serum levels.

Involvement of the major hepatic vessels was detected significantly more often in HCCs in our study. Furthermore, intraabdominal disease spread and ascites were more frequently detected in HCC cases, which all indicated poorer prognosis. In most similar series, the presence of lung metastases at diagnosis is reported as an independent indicator of worse prognosis[12,13,22,26]. Distant metastases in the lungs at initial diagnosis were detected in 15% of HBLs and 22% of HCCs in this study, which is consistent with previous reports[6-8,12,13,20].

In our series, female HCC patients had higher survival rates, which has been reported in several similar studies and might be due to the receptor of sex hormones[29,35,36]. In our HCCs, positivity for hepatitis B was related with lower survival rates. Qin et al.[35] reported that longer disease-free survival is found in patients without active hepatitis, which is related with good liver function reservation.

As clearly seen in our study group, HCC cases frequently presented with multifocal advanced-stage disease, chemotherapy agents were less effective, and complete resection rates were much lower. The overall improvement in prognosis has been much less impressive in HCC, and survival rates are still below 30% in most studies[9,20,28,32,38,39]. New multi-center prospective studies with novel chemotherapy approaches in children with HCC are required for better results.

Liver transplantation has become an important option for the treatment of primary liver tumors in children whose primary tumors cannot be completely resected[40-42]. In our series, two cases with HBL and four with HCCs with underlying tyrosinemia underwent liver transplantation[43]. The case with tyrosinemia type 1 and HBL died. The other five cases are disease-free and under follow-up. Liver transplantation should be considered as an option for children with unresectable liver tumors, which can provide a significant chance of survival in selected cases.

In our series, throughout the study period, the results were poor due to the advanced stage of most tumors at diagnosis as concerned PRETEXT grouping, presence of distant metastases and multifocality, and the low rates of complete excision. The prognosis of both HBL and HCC has improved over time through advances in radiologic imaging, chemotherapy and surgery. The introduction of combined chemotherapy regimens including cisplatin and adriamycin either before or after surgery and advances in hepatobiliary surgery have made it possible to perform liver resections more safely[6,7,12,19,26,36-38]. In our HBL and HCC cases with PRETEXT I/II/III disease without distant metastases, five-year OS rates increased to 70.3% and over 51.1%, respectively.

In conclusion, our study has indicated that a marked improvement has occurred over the last four decades in our center in the outcome of cases with HBL. Although survival rates also improved for HCC, prognosis is still poor. Advances in diagnostic and surgical techniques, as well as implementation of effective combined chemotherapy regimens, have all contributed to this improvement. There are still challenges to be overcome, especially for HCC.

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