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Original Article

Clinical Outcomes of Hepatoblastoma: An Experience of 37 Cases

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Abstract

Background: **Hepatoblastoma is the most common malignant liver tumor occurring in young children. Results of the treatment have continuously improved with increasing 5-year survival rates.**

Objective: **The aim of this study was to review clinical outcomes of hepatoblastoma in 11-year period.**

Materials and Methods: **A retrospective study was conducted including 37 patients with hepatoblastoma treated at Queen Sirikit National Institute of Child Health between 2003 and 2013. Patients' data were reviewed including demographics, clinical presentations, investigations, staging, histopathological reports and treatment outcome. Clinical information was expressed as percentage, range, mean, median, standard deviation and analyzed with Chi-square test.**

Results: **Thirty-seven patients with hepatoblastoma, 20 males and 17 females, were treated during the study period. Mean age at the operation was 23.0 ± 28.2 months (ranged from 2 months to 12 years). Abdominal mass and abdominal distension were the principal complaints. Investigations by ultrasonography and computed tomography scan were performed in 14 (37.8%) and 31cases (83.8%), respectively. Alpha-fetoprotein level at the time of diagnosis ranged from 627 to 484,000 ng/ml and it returned to normal after the treatment in 15 of the 33 patients (45.5%). Of the 37 patients, 9 (24.3%) were noted to have distant metastasis at the time of diagnosis. The tumor sites were located in the right, left and bilateral hepatic lobes in 21 (56.8%), 11 (29.7%) and 5 cases (13.5%), respectively. Primary tumor resection was performed in 9 patients (24.3%). The 28 remainders underwent liver biopsies. After chemotherapy, the residual tumors were completely resected in 12 cases. The histological types were epithelial (59.5%), mesenchymal (37.8%) and undifferentiated cell type (2.7%). Four patients (10.8%) died due to serious immediate post operative complications; massive intraabdominal bleeding due to tumor rupture (2 cases), hepatic failure (1case) and pneumonia (1case). Of the 33 survived patients, 12 (36.4%) were alive over 2 years and 9 (27.3%) were doing well over 5 years after the first operation with the longest follow-up of 9-year period.**

Conclusion: **Hepatoblastoma was mostly found in children younger than three years. Only one-fourth of the patients could undergo primary tumor resections, while the residual tumors could be resected after chemotherapy in one-third of the remainders. The survival rates at 2 and 5 years were 36.4% and 27.3,%, respectively.**

Keywords: **Hepatoblastoma, tumor resection, chemotherapy, survival rate**

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Introduction

Hepatoblastoma is the most common primary malignant liver tumor and accounts for 79% of all liver tumors[1]. Most hepatoblastomas develop before 3 years of age with a median age at 18 months[1,2]. Since 1999, cisplatin, vincristin and 5-FU have been administered as the new chemotherapy regimen for neoadjuvant and adjuvant therapy at our institute. Cisplatin is the main drug of all current chemotherapy regimens and increases the overall survival rate to 75%[1,3-8]. The authors herein reviewed their experiences with clinical outcomes of hepatoblastoma during a 11-year period comparing with the previous study reported in 2002[9].

Materials and Methods

After the proposal was approved by the Institutiona[l] Review Board (Document No. 57-020), the medical records of all children with liver tumors who were admitted at the Department of Surgery, Queen Sirikit National Institute of Child Health, during January 2003 to December 2013, were reviewed. The final diagnosis was based on histopathology results obtained either from biopsy or tumor resection. This study focused on 37 patients with hepatoblastoma. Patients' data were reviewed including demographics, clinical presentations, investigations, staging, histopathological reports and results of the treatment. Clinical information was expressed as percentage, range, mean, median, standard deviation and analyzed with Chi-square test.

Results

During 2003 to 2013, 52 patients with liver tumors were treated at our institute. Benign and malignant liver tumors were noted in 13: 39 cases (ratio 1:3). Of the 39 malignant tumors, 37 (94.9%) were hepatoblastoma and 2 (5.1%) were hepatocellular carcinoma.

Amongst these 37 cases of hepatoblastoma, male to female ratio was 1.2:1 (20:17 cases). Age at clinical presentation ranged from 2 months to 12 years (mean 23.0 ± 28.2 months, median 12 months). Two-third of the patients (27/37 cases) were lower than 3 years of age (Figure 1). Birth weight ranged from 700 to 4,000 grams (mean 2705.8±890.0 grams). Four cases (10.8%) were born premature with the birth weight less than 2500 grams. All of the patients had no associated congenital anomalies. Abdominal distension and palpable abdominal mass were the most common clinical presentation.

Laboratory investigations revealed thrombocytosis (platelet over 500,000/μl) in 24 cases (64.9%). Serum alpha-fetoprotein (AFP) level at the time of diagnosis ranged from 627 to 484,000 ng/ml (mean 150,811.8 ± 170,420.7 ng/ml). Bone marrow study was obtained in 18 cases (48.7%) but only one had tumor cell infiltration in the bone marrow. Imaging studies were performed by ultrasonography in 14 cases (37.8%) and computed

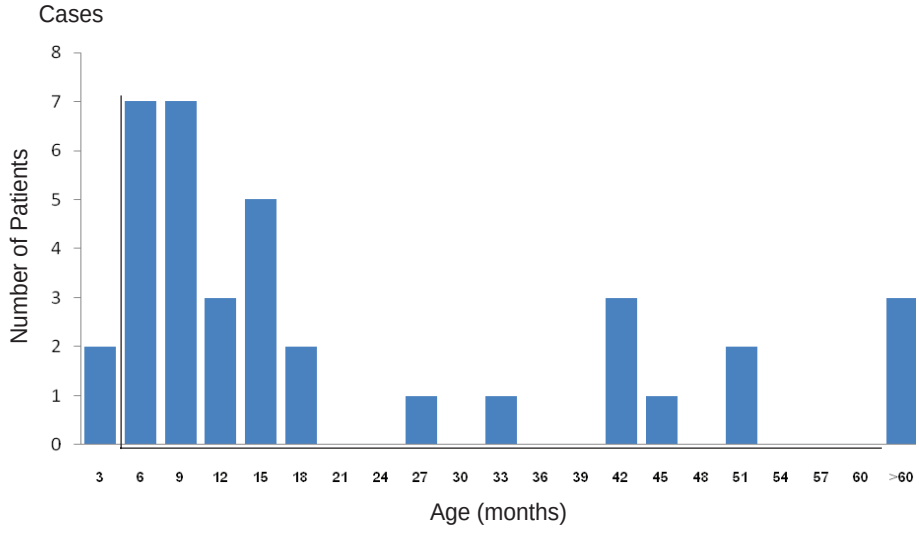

Figure 1 Age distribution of the 37 patients with hepatoblastoma.

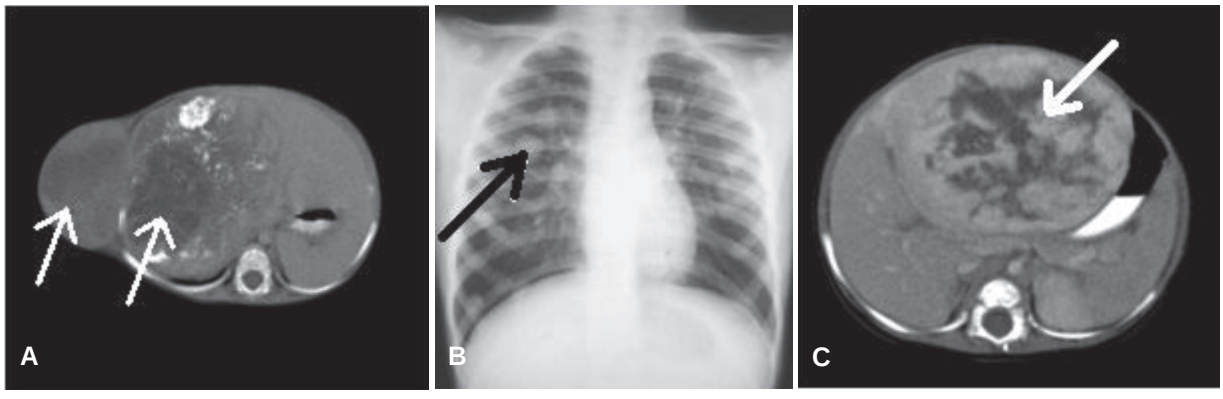

Figure 2 A. a 7-month-old girl with calcified hepatoblastoma in the right lobe and tumor seeding to the abdominal wall after needle biopsy, B. tumor metastasis to the lung after needle biopsy, C. a 18-month-old boy with calcified hepatoblastoma in the left lobe.

tomography (CT) scan in 31 cases (83.8%). There were calcification of the tumor and lung metastasis in eight cases each detected by CT scan (Figure 2). Locations of the tumors based on imaging and operative findings were noted at the right lobe 21 cases, left lobe 11 cases and bilobes 5 cases (56.8% : 29.7%: 13.5%) (Table 1).

Table 1 Demographic data of 37 patients with hepatoblastoma

Patient characteristics	Number	Percentage
Gender		
Male	20	54.0
Female	17	46.0
Age (months)		
Range	2 -144	
Mean	23 ± 28.2	
Median	12	
Serum alpha-fetoprotein at diagnosis (ng/ml)		
Range	627 - 484,000	
Mean	150,811.8 ± 170,420.7	
Median	60,500	
Imaging modality		
Ultrasound	14	37.8
CT scan	31	83.8
Location of primary tumor		
Right lobe	21	56.8
Left lobe	11	29.7
Bilobes	5	13.5
Location of metastasis		
Lung	7	18.9
Lung and bone	1	2.7
Bone marrow	1	2.7

Nine cases (24.3%) underwent primary tumor resections (right or left lobe hepatectomy) and followed by adjuvant chemotherapy. The remaining 28 cases (75.7%) underwent only tumor biopsies. Five patients (13.5%) developed severe immediate post-operative complications including subdiaphragmatic abscess with sepsis and developed tumor seeding of the abdominal wall (one case and survived), massive hemorrhage due to tumor rupture before operation (2 cases and both died), hepatic failure and pneumonia (both died).

The 33 patients who survived received chemotherapy with 1 of the 2 regimens; 1. cisplatin and doxorubicin (PLADO) or 2. cisplatin, 5-FU and vincristin (VCR). The patients were followed-up by monitoring serum AFP and serial CT scan. After chemotherapy, 15 of the 33 patients (45.5%) had normal AFP level and 12 cases with initial tumor biopsy could undergo complete tumor resection (Figure 3).

Histological cell types and tumor staging[10] were shown in Table 2. There were no statistical difference of the survival rates of patients with epithelial or mesenchymal cell types (59.1% VS 57.1%, $p = 0.96$). The patients with tumor staging of I, III and IV had the survival rates of 100%, 52.6%, and 22.2%, respectively. There was no patient with stage II disease.

Despite the 4-immediate postoperative deaths, long-term follow-up of the remaining 33 patients showed that 10 cases (30.3%) died and 2 cases were lost to follow-up (Figure 3). Eight cases had progressive distant metastasis to lung, bone and bone marrow. Approximately 64% (21/33 cases) had 2- and 5-year survival rate of 36.4% and 27.3%, respectively. The

Table 2 Summary of histological types and tumor staging in relation to patient survival rate

Tumor characteristics	No (Percentage)	Metastasis	Results of treatment	
			Survival	Death
Histological cell type				
Epithelial	22 (59.5)			
Fetal subtype	14	Lung and bone (1) Lung (5)	8	6
Mmixed fetal-embryonal subtype	8	Lung (1)	5	3
Mesenchymal	14 (37.8)			
Without teratoid features	8	Bone marrow(1)	4	4
With teratoid features	6	Lung (1)	4	2
Undifferentiated	1 (2.7)		0	1
Tumor staging*				
I	9	-	9	0
II	0	-	-	-
III	19	-	10	9
IV	9	Lung (7)	2	5
		Lung and bone (1)	0	1
		Bone marrow (1)	0	1

*based on Children's Oncology Group[10] : stage I complete resection, II microscopic residual tumor, III macroscopic residual tumor or nodal involvement or tumor spillage or tumor biopsy, IV metastasis

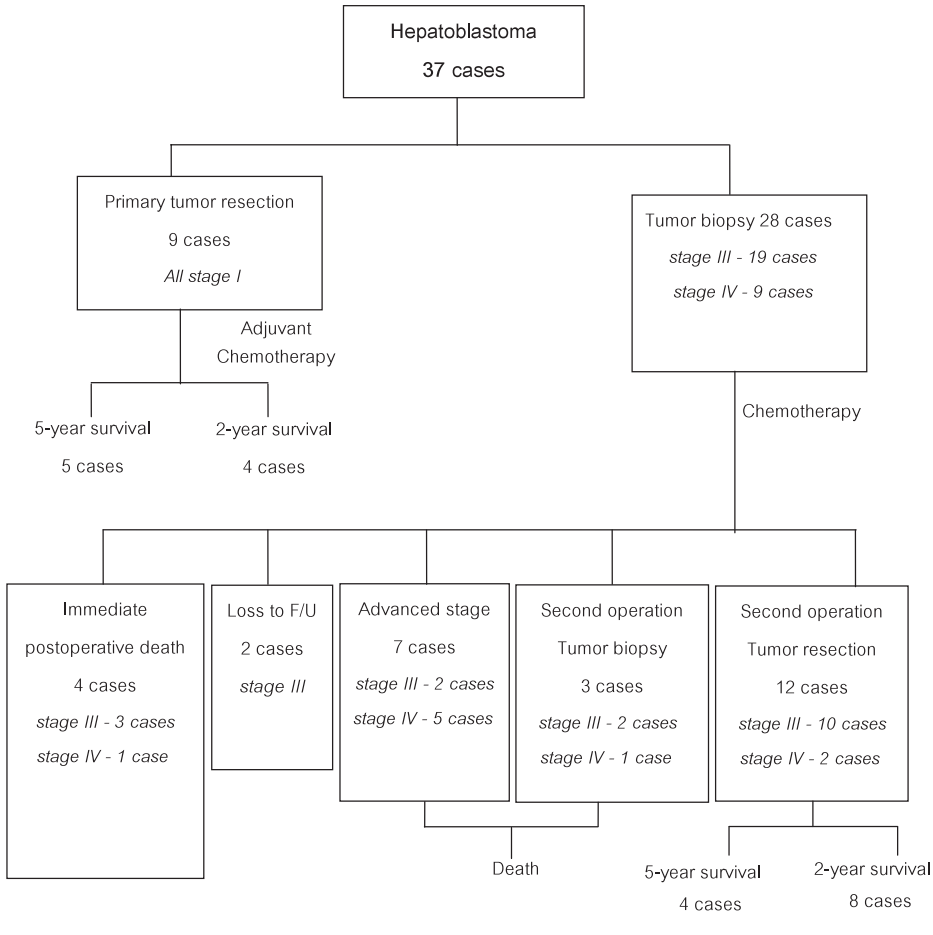

Figure 3 Schematic diagram for the treatment outcomes of 37 patients with hepatoblastoma

longest follow-up period was 9 years.

Discussion

The occurrences and demographic data of patients with hepatoblastoma at our institute comparing with the previous study (1987-2000)[9] have not changed. Hepatoblastoma accounted for 71% (37/52 cases) of primary hepatic tumors. Seventy-three percent of the patients were younger than three years. There were approximately three new cases per year. However, the results of the treatment have significantly improved between the two studies. In the previous study, total tumor resection could be performed in only 33% of cases (13/39 cases) and overall survival rate was 20.5%[9], whereas total tumor resection was performed in 56.8% of cases (21/37 cases) and overall survival rate was 51.5% in the present study. Improved outcomes also might be the results from better chemotherapeutic agents which had changed from VCR, cyclophosphamide and 5-FU in the previous period to the 2-new regimens including 1. PLADO and 2. cisplatin, VCR and 5-FU.

Concerning the treatment modality, resectability was the most important prognostic factor for survival. Nine patients, who could undergo primary resection plus adjuvant chemotherapy, had 100% survival rate (Figure 3). As for the primary unresectable cases, tumor biopsy followed by chemotherapy until the tumor size reduces enough for delayed resection[8,11-13]. Post-chemotherapy, the tumor is more solid which is less prone to bleeding and has more clear demarcation from the surrounding healthy liver parenchyma, these components facilitate the complete resection[14]. Our 12 of 22 cases with huge hepatoblastoma (stage III or IV) could undergo delayed tumor resection safely. It is noted that many authors recommend that chemotherapy administration to reduce the size of unresectable hepatoblastoma should be given not more than three cycles because of the possibility of developing resistance to the drugs[4,5,15-17].

As mentioned in the literature, histological cell types of the hepatoblastoma determines the response of the treatment which affects the outcome. The epithelial-pure fetal subtype is considered to be favorable histology opposite to the undifferentiated subtype which is unfavorable histology known to have poor response to treatment[18]. Also, the survival rate of patients with epithelial, mesenchymal and mixed epithelial-mesenchymal histology are better than the undifferentiated subtype[19]. In our study, we had only one patient with undifferentiated histology and died. There was no difference of the survival rates of patients with epithelial or mesenchymal histology.

Conclusion

Hepatoblastoma is mostly found in children younger than three years of age. Primary tumor resection could be performed in approximately one-fourth of the patients. After chemotherapeutic treatment, primary unresectable tumors could be completely excised in one-third of the remainders. Tumor resectability is the most important factor for survival of patients with hepatoblastoma. The outcomes of hepatoblastoma treatment in this era has improved more than in the past. The survival rates at 2 and 5 years were 36.4% and 27.3% from the present study.

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