Pattern and Outcome of Primary Liver Tumors in Children: Eight–year experience at South Egypt Cancer Institute.

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Abstract

Background: Liver tumors in children are not uncommon account for 0.5-2% of all pediatric neoplasm, they may be primary or secondary, benign or malignant. Hepatoblastoma (HBL) and Hepatocelluar carcinoma (HCC) are the most common primary malignant liver tumors in children.

Objective: To study the pattern and outcome of primary liver tumors in children at South Egypt Cancer Institute (SECI).

Introduction:

Liver is the third-most-common site for intra-abdominal malignancy in children following adrenal neuroblastoma and Wilm's tumor **(1)**. The incidence of primary malignant liver tumors per year is 1-1.5 per million children in the United States. This yields a relative low rate for hepatic tumors about (0.5 - 2 %) of all pediatric neoplasm **(2).** Liver tumors represented 0.8 % of all pediatric tumors diagnosed in South Egypt Cancer Institute (SECI), Assiut University between January 2001 and December 2013 **(3).**

About two-thirds of all pediatric liver tumors are malignant **(4)** and almost 70% of those are hepatocellular in origin, either hepatoblastomas or hepatocellular carcinomas **(5).** Benign lesions may be of mesenchymal or epithelial origin **(6).** Spontaneous regression usually occurs after the first year of life and long term survival is about 70% **(7).**

Hepatoblastoma (HBL) is the most common malignant liver tumor in children accounting for nearly 80 % of all malignant liver tumors, with an incidence of 0.7 to 1 per million children under 15 years of age in Western countries. It comprises 1 % of all pediatric malignancies **(8)**. Most cases are sporadic, however some are associated with genetic cancer syndromes as Edwards's syndrome, Familial adenomatous polyposis and Beckwith-Wiedemann syndrome **(9).** Boys are affected more commonly than girls, with a male: female ratio ranging from 1.2:1 to 3.6:1. The right lobe of the liver is affected more commonly than the left, and in 35 % of patients there is bilateral involvement. Around 20% of patients present with metastasis in the lung at time of diagnosis **(10).**

Diagnosis of HBL by clinical presentation and imaging studies to confirm the origin and size of of the tumor for PRETEXT (Pretreatment Extension of the disease) staging of HBL and tumor markers mainly alpha fetoprotein (AFP)which was elevated in about 90 % of cases also useful for follow up during treatment and after finishing during follow up of cases .

Hepatoblastoma is mainly divided into two histologic types: epithelial, accounting for 56% of the cases, and mixed epithelial/mesenchymal **(11).**The epithelial type can be further divided into fetal (31%), embryonal (19%), macrotrabecular (3%), and small cell undifferentiated subtypes (3%) **(12).** It has been observed that the histologic subtypes have an effect on the prognosis, with the pure fetal type having the most favorable outcome and the small-cell undifferentiated type having the worst **(13, 14).**

Hepatocellular carcinoma (HCC) is the commonest hepatic malignancy of adolescents and often occurs in the presence of underlying liver pathology **(15).**

Complete surgical resection is the corner stone in management of malignant liver tumors, however, combination of chemotherapy, conventional resection, and liver transplantation in management, have improved prognosis where long term survival rates of 70-80% have been reported for HBL, though prognosis is still poor in HCC **(16).** In this study, we aimed to analyze pattern and outcome of primary liver tumors in our center.

Patients and Methods:

We reviewed the records of all children with hepatic focal lesions presented to Pediatric Oncology Department at South Egypt Cancer Institute between January 2012 to December 2020. Data collected included demographic characteristics of the patients, the presenting symptoms and signs, laboratory data (including AFP level), tumor localization, extent of disease and treatment approaches (including chemotherapy, surgical practices and treatment responses) as well as events and outcomes.

Tumor extension within the liver was graded using the PRETEXT system of the International Society of

Pediatric Oncology (SIOP) **(17).** Patients with secondary liver tumors were excluded from the study.

Ethical consideration:

The study was approved by Ethical Committee at South Egypt Cancer Institute and Written informed consent to use the patients′ data, was obtained from the patients′ families.

Statistical analysis:

SPSS version 20.0 for Windows (IBM SPSS, Armonk, NY, USA) was used for data analysis. The frequencies of different parameters were expressed in numbers and/or percentages. Survival tables were used to calculate the median survival rate for hepatoblastoma patients and Kaplan Meier survival analysis was performed to compare overall survival among different study groups. $P<0.05$ was considered to indicate a statistically significant difference.

Results:

During the study period, 37 patients presented with hepatic focal lesions. Sixteen patients had secondary liver tumors and were excluded from the study.

Twenty one patients (56.7%) had primary liver tumors representing 1.1 % of all pediatric tumors diagnosed within the same study period. Four patients (19.04%) had benign tumors (all had hemangioendothelioma) and 17 (80.9 %) patients diagnosed as malignant tumors (HBL). Hepatocelluar carcinoma was not diagnosed among our patients.

Among the four patients diagnosed as benign tumors there were one male (25%) and three females (75%).Their median age at diagnosis ranged between 16 day and 90 days, all cases diagnosed as hemangioendothelioma. The main presenting symptoms were abdominal mass (50%) followed by abdominal distention and vomiting (25%) for each. The tumor was unifocal in two patients (50%) and multifocal in the other two (50%). Size of the tumor ranged from 4 to 11.5 cm with a median size of 6.8 ± 4.07cm. Laboratory studies including complete blood picture and liver function tests were normal. The median AFP level was 4546 IU/ml ranged between 37.5 and 1539 IU/ml.

After a median follow up of 31 months spontaneous regression was reported in 3 patients and they continued in follow up. The remaining patient (3 months old) had progressive disease and respiratory distress that reported within 8 months after diagnosis. Surgical excision of the mass was done, however, the patient died within 6 days post-operative due to severe chest infection and septic shock.

Hepatoblastoma was the only malignant primary hepatic tumor reported among the study group. It reported in 17 cases representing 0.9% of the total number of pediatric patients with cancer admitted during the same study period and 45.9% of all hepatic tumors.

The median age of patients with HBL at diagnosis was 14 months (ranged from 7 to 24 months). Eleven patients (64.7%) were males and 6 patients (35.3%) were females, male to female ratio was2:1.

Most of the patients (58.8%) presented with abdominal distention followed by abdominal mass (52.9%) and abdominal pain (41.2%).Total serum bilirubin level above 1.5 mg/ml at initial diagnosis was reported in 2(11.7%) patients. The median serum AFP level was 4546IU/ml (ranged from 410 to 20141IU/ml).

At presentation, 16 patient's diagnosis were confirmed by true cut needle biopsy. In the remaining case; AFP was overshooting and his general condition didn't allow obtaining biopsy of the lesion. Histologically; 13 patients (76.4%) had pure fetal epithelial subtype, one patient (5.9%) had mixed epithelial subtype, one patient (5.9%) had macrotrabecular subtype and one patient (5.9%) had undifferentiated subtype. The tumor was unifocal in 9 patients (52.9%) and multifocal in 8 patients (47.1%).Its size ranged from 5-19 cm3 with a median size of 8.6±3.3cm3.

Tumor extension within the liver using the PRETEXT staging system revealed that 9(52.9%) patients had stage III and 6(35.3%) patients had stage IV. Distant metastasis to the lung was detected in two patients (11.7%).

Sixteen patients received neoadjuvant chemotherapy in the form of 3 cycles of cisplatin and doxorubicin (PLADO), the remaining case (aged 3 months) with PRETEXT stage I disease was subjected for upfront surgery then continued under follow up.

After neoadjuvant treatment, 3 (17.6%) patients achieved very good partial response (VGPR), 8 patients achieved partial remission (PR) and one patient had disease progression. Evaluation was not done in four patients due to early death that reported in three patients after receiving 2 doses of chemotherapy and one patient lost follow up after receiving one dose.

Nine patients (3 with VGPR and (6 out of 8 patients) subjected to surgical excision in form of non anatomical resection of segment of the liver (n=6) or lobectomy (n=3).

After surgery 8 patients achieved complete remission (CR) and under follow up after receiving 3 cycles of adjuvant PLADO .The remaining case was not in CR after surgery and shifted to second line treatment after disease progression .Treatment related toxicity was reported in 3 patients in form of severe neutropenia grade III and IV in two patients and renal failure in one patient.

Patients were followed up for a median of 43.4 months (ranged from 30.3 to 64.6 months). Nine (52.9%) patients are alive and under follow up in complete remission. Early death during chemotherapy was reported in three cases due to severe neutropenia associated with septic shock in one case and severe chest infection. Two patients with disease progression died due to neutropenia and septic shock after aggressive second line treatment in one patient and severe chest infection with respiratory failure in the second patient.

Table (1) characteristic and outcome of patients diagnosed as hepatoblastoma included in the study

Variable	No (%)
Age:	
- <6 months	7(41.2%)
- >6 months	10 (58.8%)
Sex:	
- Male	11(64.7%)
- Female	6(35.3%)
- Male : female ratio	2:1
Clinical presentation:	
- Abdominal mass	9(52.9%)
- Abdominal pain	7(41.2%)
- Abdominal distention	10 (58.8%)
- Pallor	4 (23.5%)
- Jaundice	0 (-)
- Diarrhea	2 (11.8%)
- Fever	4 (23.5%)
Histopathology (16 patients)	
- Fetal epithelial type	13 (76.4%)
- Mixed epithelial type	1 (5.9%)
- Macrotrabecular type	1 (5.9%)
- Undifferetiated type	1 (5.9%)
Stage:	
- I	1 (5.9%)
- II	1 (5.9%)
- III	9 (52.9%)
- IV	6 (35.3%)
Bilirubin:	
- Less than 1.5 mg/ml	15 (88.2%)
- More than 1.5 mg/ml	2 (11.7%)
AFP:	
- High	15 (88.2%)
- Normal (< 0.9 IU/ml)	2 (11.7%)
Outcome :	
- Alive	9 (52.9%)
- Died	8 (47.05%)

Survival analysis:

Five-year OS for the patients with hepatoblastoma was 52.9%. Figure 1. 5-year DFS was 52.9%. Figure 2. The 5 year EFS was 59.7%. Figure 3.

Stage of the disease was the only factor that significantly affected OS (p= 0.033) and DFS (p=0.025) among our patients. Children with low stages HB had a significantly better overall and disease free survival rates compared to patients with high disease stages.

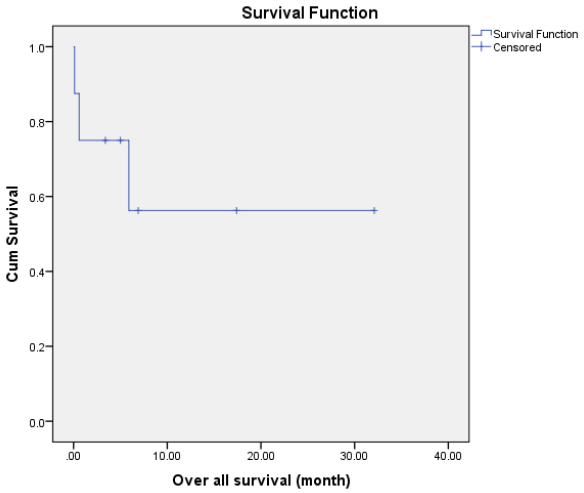

Figure (1) Five-year Overall survival of the patients with hepatoblastoma in this study

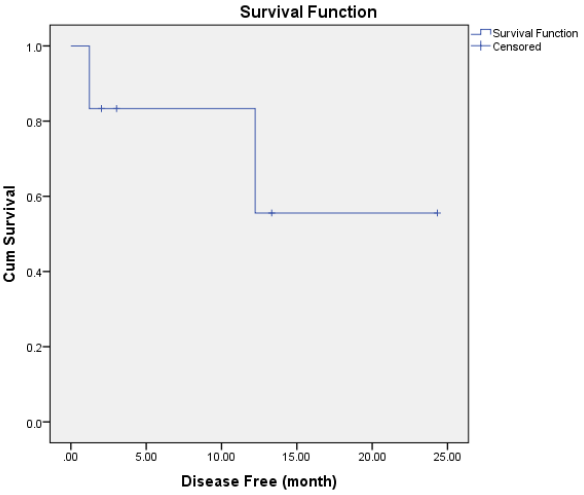

Figure (2) Five-year Disease free survival of the patients with hepatoblastoma in this study

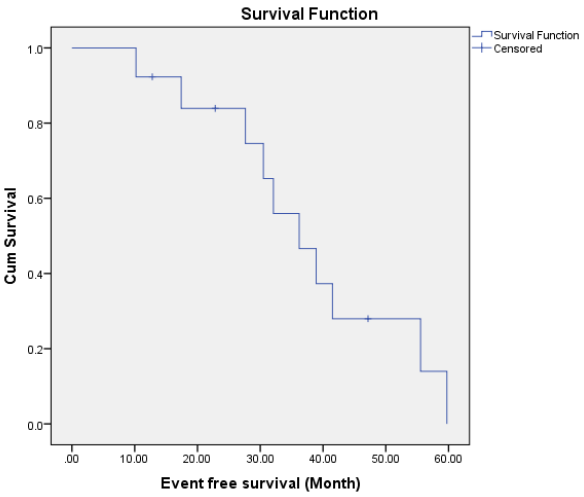

Figure (3).Five-year Event free survival of the patients with hepatoblastoma in this study

Discussion:

The incidence of primary malignant liver tumors per year is 1-1.5 per million children in the United States. This yields a relative low rate for hepatic tumors (about 0.5-2%) of all pediatric neoplasm (2). In this study, we reported nearly similar rate for primary liver tumors representing 1.1 % of all pediatric tumors diagnosed within the same study period. A slightly higher result was reported by Abou-Taleb et al., 2017 where primary liver tumors represented (1.5%) of all pediatric tumors diagnosed in nearby Sohag cancer center within ten years (4). Hepatic tumors represented 0.8 % of all pediatric tumors diagnosed in South Egypt Cancer Institute (SECI), Assiut University between January 2001 and December 2013 as reported by Amany et al., 2016 (3).

Benign lesions in children represent 30% of hepatic tumors and are most commonly vascular in origin (eg, hemangiomas) (18). Benign hepatic tumors in this study represented 19 % of primary hepatic tumors which is comparable to 18.7% reported by Zaman et al., 2011 (19) and lower than (32.3%) that reported by Geramizadeh et al., 2010 (20).

Hemangioendothelioma is a subtype of hemangioma that is typically found in infants. A female predilection for hemangioendothelioma is noted, with a female-to-male ratio of 4.3:1 to 2:1 (13). In this study, all patients with benign lesions were infants (their age ranged between 16 day and 90 days), and diagnosed as hemangioendothelioma. Also a female predilection was noted with male to female ratio of 1:3. Laboratory abnormalities associated with this tumor include anemia, elevated aspartate transaminase levels, hyperbilirubinemia, and occasionally an elevated α-fetoprotein (AFP) level (13). We reported shooting levels of AFP in most cases otherwise; no other laboratory abnormalities were reported. The natural history for hemangiomas is spontaneous regression in the first 2 years of life; however, treatment is required if cardiac failure or platelet consumption occurs (21), among our cases three out of four achieved spontaneous regression.

Hepatoblastoma is the most common primary hepatic malignancy in childhood, accounting for 43% of all pediatric liver tumors (16) and nearly two- thirds of malignant liver tumors in children (22). In this study, HB represented 45.9% of all hepatic tumors and 51.5% of malignant liver tumors. Hepatoblastoma is most frequently diagnosed in children less than 5 years of age (23).

The median age of patients with HB in our study at diagnosis was 14 months (ranged from 7 to 24 months) with male predominance. This is comparable to result reported by Hartely et al., 1990 (10). Although genetic syndromes are associated with approximately 15% of HBs. None of our cases reported to have any genetic abnormalities.

Markedly elevated serum level of AFP can be detected in HB, yolk sac tumor, and HCC. Certain histological variants of HB like small cell type do not produce AFP. Complete excision of the HB causes the serum AFP levels to return to normal level in 4-6 weeks (24). The median serum alpha-fetoprotein level at diagnosis at our data was 4546IU/ml (ranged from 410 to 20141IU/ml) that returned to normal values in the majority of HB cases after chemotherapy. This finding in line with previous data ensures the reliable validity of AFP as a marker of response to treatment in addition to its role in initial diagnosis.

Histologically HB is classified into epithelial (56%) and mixed epithelial/mesenchymal (44%). Epithelial HB is subdivided into pure fetal (31%), embryonal (19%), macrotrabecular (3%) and small- cell undifferentiated (3%). The most common mesenchymal elements are osteoid and cartilage (25). In our study, 76.4% of patients with HB had pure fetal epithelial subtype, 5.9% had mixed epithelial subtype, 5.9% had macrotrabecular subtype and 5.9% had undifferentiated subtype.

Multiple staging systems are used worldwide. In the United States, staging of tumors is based on the extent of tumor and outcome of surgical resection as critical criteria. Pretreatment extent of disease (PRETEXT) staging was developed by the International Society of Pediatric Oncology (SIOPEL) 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 (26). In primary liver tumors, PRETEXT IV disease carries a poorer prognosis since complete tumor resection becomes very difficult. In this study, using the PRETEXT system, most cases (35.3%) had stage III and stage IV (52.9%) and (35.3%) respectively, Abou-Taleb et al., 2017 in their study reported that 10 (50%) cases had stage III and only two (10%) cases had stage IV.

Distant metastases at the time of diagnosis occur in 10%-20% of HB patients, with the lung being the predominant site of metastases both at presentation and relapse, while other sites of metastases are rare and usually occur in the setting of relapsed disease (22). We detected distant metastases to the lung in two (11.7%) patients comparable to Abou –Taleb et al., 2017 (4).

Complete surgical resection is the most important factor predicting patients who would achieve cure, yet response to chemotherapy is another paramount factor affecting survival in those patients (27).

Two main strategies for approaching resection of the tumor are noted. In the United States, the bias is towards early resection of tumor at diagnosis with an opportunity to delay resection until after neoadjuvant therapy is observed in patients with stage III and IV tumors. In contrast, the SIOPEL group advocates neoadjuvant therapy in all patients (13). Also, HBs 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 (28). Chemotherapy causes the tumor not only to shrink in size but also to become more clearly

defined and less friable which is reflected in safer surgery with reduced blood loss (29).

In this study, Nine patients (3 with VGPR and (6 out of 8 patients) who achieved partial response (PR) were rendered operable and subjected to surgical excision in form of non anatomical resection of segment of the liver (n=6) or lobectomy (n=3). On the other hand, one case with PRETEXT I had underwent upfront surgery with complete resection of the tumor followed by chemotherapy.

Survival outcomes have greatly improved over the past four decades (30). With advances in surgical management and chemotherapy, the 5-year OS rate for children with hepatoblastoma has increased to more than 80% (31). Pham et al., 2015 reported 10-year disease-free survival and OS rates of 82% and 84%, respectively (32). In another SEER study including 318 hepatoblastoma patients undergoing surgery, McAteer et al., 2013 found that the overall 5-year disease-specific survival rate was 85.7%, and the rates for patients undergoing resection and transplantation were essentially equivalent (85.6% vs. 86.5%, P = 0.66) (33) . Feng et al., 2019, reported that patients in their study who underwent liver resection (n = 341) and liver transplantation (n = 84) had 10-year OS rates (89.3% vs. 90.1%, P = 0.891) (31) .Survival rates in these studies are very high compared to our results (5-year OS was 52.9%). Although number of patients can partially explain this high difference, the progress in surgical techniques and use of liver transplantation in management of their patients can present the main explanation.

The overall prognosis in HB depends on many clinical and histopathological factors. Among these, resectability of the primary tumor and presence of distant metastases are the most important factors (34). Some other important adverse prognostic factors are reported as an initially low AFP, vascular invasion, lymph node metastases, and small-cell undifferentiated histology (35). Feng et al., 2019 reported that surgery was a strong predictor of OS of their patients (31). Stage of disease was the only factor that significantly affects 5-year OS in this study. Children with low stages HB had a significantly better survival rate compared to patients with high disease stages (p=0.025) that is nearly similar to (0.001) reported by (Abou-Taleb et al., 2017) (4)

Conclusion:

In our center, upfront chemotherapy allowed complete surgical resection of initially unresectable tumors in patients with hepatoblastoma with improvement of their outcome. As a rare disease, further multiceneric study with large number of patients is recommended to reach more significant conclusion.

List of Abbreviations:

AFP	Alpha –fetoprotein
CR	Complete remission
CT	Computed tomography
DFS	Disease Free Survival
EFS	Event Free Survival
HBL	Hepatoblastoma
HCC	Hepatocellular Carcinoma
MRI	Magnetic resonance imaging
OS	Overall Survival
PLADO	Platinol and doxorubicin
PR	Partial response
PRETEXT	Pretreatment extent of disease
SECI	South Egypt Cancer institute
SIOP	International Society of Pediatric Oncology

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