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Pattern and Outcome of primary Liver Tumors in Children: A 10 years report from single oncology center in Upper Egypt

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Abstract

Background: Primary malignant liver tumors are uncommon in children with hepatoblastoma (HB) and hepatocellular carcinoma (HCC) are the most common.

Objective: To study frequency, types, clinical presentation and outcome of liver tumors in children at Sohag Cancer Center (SCC).

Materials and Methods: Data were retrieved from files of all cases with hepatic focal lesions presented to Pediatric Oncology Department at SCC from January 2005 to December 2014.

Results: Among 48 children (26 males) presented to SCC with hepatic focal lesions 12 cases were non-neoplastic, 8 were metastatic hepatic deposits and 28 were primary hepatic tumors (20 HB, 3 HCC and 5 cases benign tumors).

Primary liver tumors accounted for 1.55% of all pediatric tumors with HB being the most frequent (41.7%). Median age of HB cases at diagnosis was 2 years (range 1.5-6 years). PRETEXT stage II/III was reported in 17 cases while stages I and IV were reported in one and two cases, respectively. Nearly two-thirds of cases achieved complete or partial response after neoadjuvant chemotherapy. Complete tumor resection was achieved in 40% of cases. The median survival time for HB patients was 63 months with three years overall survival rate of 65%.

Conclusion: Outcome of patients with HB was affected by both stage and histopathologic subtypes. Upfront chemotherapy allows complete surgical resection of initially unresectable primary tumors with improvement of survival outcome in such patients. As a developing country with high prevalence of infectious causes, non-neoplastic hepatic lesions should be taken in consideration during diagnosis of hepatic focal lesions.

Background:

Several hepatic focal lesions can be seen in infants and children, these lesions usually categorized into congenital, infectious and neoplastic masses in addition to lesions that mimic hepatic focal lesions such as focal fatty proliferation and hepatic infarction [1]. Primary hepatic tumors are rare in children, constitute 5-6% of all intra-abdominal masses and nearly 0.5-2% of all pediatric neoplasms, however detection of focal hepatic lesions in children, is still not uncommon event [2][3].

Metastatic disease from various primary malignancies is the most common neoplasm involving the liver in children [3]. It may arise from neuroblastoma, Wilms′ tumor, rhabdomyosarcoma, rhabdoid tumor, non-Hodgkin lymphoma, or adrenal cortical carcinoma [4].

Most primary hepatic lesions are malignant, however one-third of lesions are benign.

Hepatoblastoma (HB) is by far the most frequent malignant hepatic neoplasm in children, which accounts for 1% of all pediatric malignancies [3][4]. Most cases of HB are sporadic, however some are associated with genetic cancer syndromes as Edwards's syndrome, Familial adenomatous polyposis and Beckwith-Wiedemann syndrome [5]. Hepatocellular carcinoma (HCC) is the commonest hepatic malignancy of adolescents and often occurs in the presence of underlying liver pathology [6].

On the other hand, benign liver tumors account nearly for 30% of hepatic tumors and include infantile hepatic hemangioendothelioma (IHH), hepatic adenoma (HA) mesenchymal hamartoma (MH), nodular regenerative hyperplasia (NRH), and focal nodular hyperplasia (FNH) [7].

Although some of hepatic lesions may be discovered incidentally, the majority of patients present with abdominal distension and palpable abdominal mass that

may be associated with pain, weight loss, fever ,and anorexia[1][4]. After physical examination imaging is the next step in evaluation of children with suspected focal hepatic lesions. Abdominal ultrasonography is the initial diagnostic imaging modality, but definitive characterization of the mass requires a computed tomography (CT) or magnetic resonance imaging (MRI) scan. However, definitive diagnosis can be confirmed only through biopsy findings [8]. Alpha - fetoprotein (AFP) is the most important tumor marker for liver tumors which is highly elevated in 80 to 90% of all HB and moderately elevated in 50 % HCC patients [9].

Complete surgical resection is the corner stone in management of malignant liver tumor, however, combination of chemotherapy, conventional resection, and liver transplantation in management, has improved prognosis where long term survival rates of 70-80% has been reported for HB, though prognosis is still poor in HCC[10] . In this study we aimed to highlight the spectrum, pattern, management and outcome of hepatic tumors in infant and children in our locality.

Material and Methods:

We reviewed the hospital files of all children with hepatic focal lesions presented to pediatric oncology department at Sohag Cancer Center between January/2005 to December/2014. Data collected included demographic characteristics of the patients, presenting symptoms and signs, laboratory data (including AFP level), tumor localization and extent of disease, treatment approaches including (surgical practices, treatments and 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) (on a scale of I to IV, with higher grades indicating tumor involvement in more sectors of the liver) [11].

Ethical consideration

The protocol of the study was approved by Ethical Committee at Sohag Cancer Center. 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 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:

Data of 48 children with hepatic focal lesion(s) presented to Sohag Cancer Center between January/2005 and December/2014, were retrieved for this retrospective study; including 22 females and 26 males. The patients` ages at presentation ranged between 1 and 16 years with a median age of 5 years.

Laboratory and radiological studies revealed criteria of non-neoplastic lesions in one quarter of cases including six cases of pyogenic liver abscess, four cases of hydated cyst, one case of glycogen storage disease and one case of inflammatory pseudo-tumor. Furthermore, eight cases (16.7%) were diagnosed as metastatic liver deposits from either neuroblastoma (n=6) or Non-Hodgkin`s lymphoma (n=2). Both non-neoplastic and metastatic liver lesions were excluded from further analysis. Final diagnoses of the cases presented with hepatic focal lesions at Sohag cancer center between 2005-2014 were summarized in Table 1.

Table 1: Final diagnoses of the cases presented with hepatic focal lesions at Sohag cancer center between 2005-2014

Final diagnosis	Freq-uency	%
Non-neoplastic hepatic lesions:		
- Pyogenic liver abscess	6	12.5
- Hydatid cyst	4	8.3
- Inflammatory pseudotumor	1	2.1
- Glycogen-storage disease	1	2.1
Metastatic hepatic deposits:		
- Neuroblastoma	6	12.5
- Non-Hodgkin`s lymphoma	2	4.2
Primary hepatic tumors:		
- Liver cell adenoma	1	2.1
- Infantile heamangioendothelioma	1	2.1
- Vascular Hamartoma	2	4.2
- Mature teratoma	1	2.1
- Hepatoblastoma	20	41.7
- Hepatocellular carcinoma	3	6.2
Total	**48**	**100.0**

Primary hepatic tumors were reported in 28 patients representing 1.55% of all pediatric tumors and 7.8% of pediatric solid tumors diagnosed within the same study period. Five patients (17.9%) had benign tumors (Table 1). The median age at diagnosis of patients with benign tumors was 7 months and all patients had been subjected to surgical resection and followed up for a median duration of 31 months.

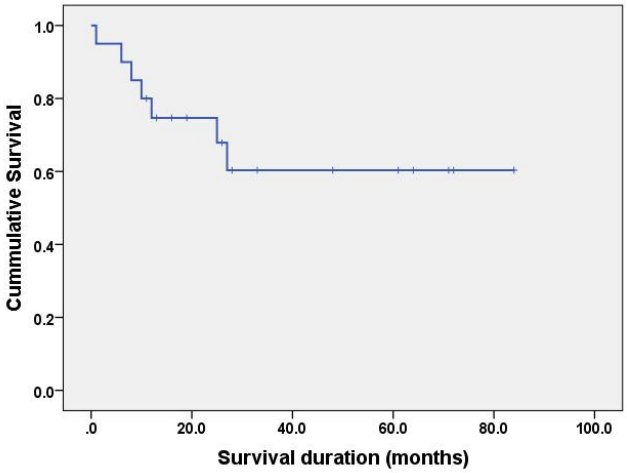
Among primary hepatic tumors, HB was reported in 20/28 cases (71.4%); of which 16 were confirmed by true-cut needle biopsy. In the remaining cases; AFP was over shooting and their general condition didn't allow obtaining biopsy of the lesions. The median age at diagnosis was two years (range 1.5-6 years) with no specific sex predilection (male to female ratio 1:1.05). Most of cases (75%) presented with hepatomegaly associated with jaundice in 3 cases and abdominal pain in 2 cases. The median serum alpha-fetoprotein (AFP) level at diagnosis was 117.75 IU/ml (range 23-453120 IU/ml).Total serum bilirubin level above 1.5mg/ml at initial diagnosis was reported in three (15%) patients. Histologically; 11 cases had pure fetal HB and the

remaining cases were mixed subtypes. Distant metastases to the lung were detected in two (10.5%) patients. Radiological studies revealed solitary lesions in 14 (70%) cases, multiple lesions in five (25%) cases and diffuse hepatic involvement in the remaining case. Tumor extension within the liver using the PRETEXT staging system revealed that one case had stage I disease, seven cases had stage II, 10 cases had stage III and two cases had stage IV.

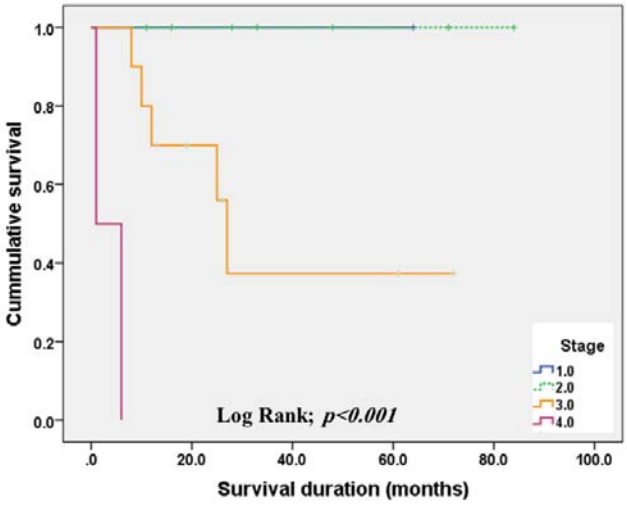
Nineteen patients received neoadjuvant chemotherapy in form of cisplatin and doxorubicin (PLADO), the remaining case with PRETEXT I disease had undergone upfront surgery with complete resection of the tumor followed by adjuvant chemotherapy. Data of response evaluation were available for 17 patients; it revealed return of AFP to normal levels in most (77.8%) patients. Radiologically, complete remission (CR) was achieved in one case (5.6%) with complete disappearance of the tumor, nine (50%) cases had achieved partial response (PR) and four (22.2%) cases had stationary disease (SD) while disease progression (DP) was reported in three (16.7%) cases. Ten cases were operable; complete resection was achieved in seven patients, while the other three patients had residual.

The patients were followed up for a median of 74 months. Local recurrence was reported in one out of the ten patients who had achieved CR. Early death during chemotherapy was reported in two cases due to neutropenia and septicemia in one case and progressive liver cell failure in the other case. Three cases died due to disease progression and two cases lost follow up. According to life tables, the median survival time for HB patients was 63 months with three years overall survival (OS) rate of 65% (Figure 1A). Children with low stages HB and pure fetal histologic subtype had a significantly better survival rate compared to patients with high disease stages or other histologic subtypes ($p<0.001$, $p=0.012$ respectively) as shown in both (Figure 1B) (Figure 1C).

HCC was reported in three cases; they were 15, 7 and 9 years old at time of diagnosis. All of them presented with hepatomegaly associated with jaundice in two of them and liver cirrhosis was reported in one case; however screening for hepatitis B or C markers was negative. The median serum level of AFP was 67.53IU/ml. Radiological studies revealed presence of solitary lesion in one and multiple lesions associated with ascites in two cases, lung metastasis was detected in one case. As regard PRETEXT stage, one case was stage IV while the other two were stage III, histopathologic examination proved the presence of fibrolamellar variant in one case. All patients received three courses of PLADO with stable disease in two case and disease progression and death in the third case. After another two courses of chemotherapy, death was reported in both cases due to disease progression in first one and severe neutropenia associated with septicemia after aggressive chemotherapy in the other.



(A)



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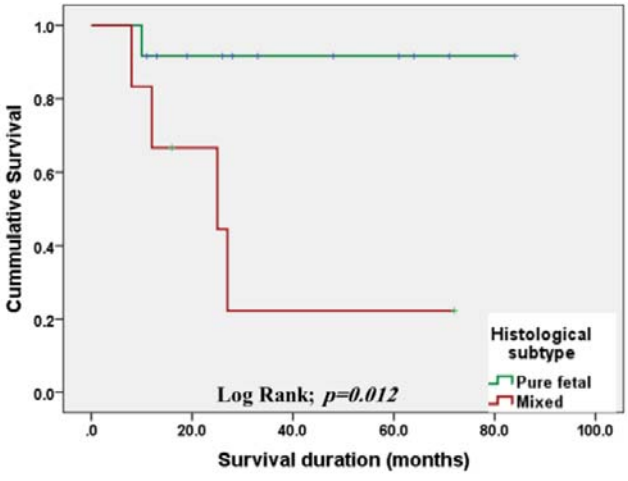

(C)

Figure 1: Overall survival of the investigated hepatoblastoma cases (A) and comparative survival rates of stages (B) and histological subtypes (C) for patients with hepatoblastoma.

Discussion:

Primary liver tumors are rare in children and constitute 0.5-2% of all pediatric neoplasms. They represent the third most common intra-abdominal neoplasm after neuroblastoma and Wilms' tumor [2]. In this study, primary hepatic tumors were identified in 28 patients representing 1.55% of all pediatric tumors and 7.8% of solid tumors diagnosed in our center during the study period.

Non-neoplastic hepatic lesions, mostly of infectious etiology, were diagnosed in one quarter of the referred cases to our center. This came in agreement with El-Karaksy et al.,[12] who reported infectious lesions in 29% of children with focal hepatic lesions investigated in Children Hospital, Cairo university. This can be explained by high prevalence of bacterial and parasitic infections in developing countries.

The rate of benign hepatic tumors in this study was 17.8% of primary hepatic tumors which was comparable to a previous report by Zaman et al.(18.75%)[13] and lower than the rate reported by Geramizadeh et al. (32.3%)[14] . The most frequent benign tumor was hamartoma in the three studies.

Two-thirds of liver tumors in children are malignant. In adults, the most common histopathology is HCC, whereas HB constitutes the dominant primary pediatric liver tumor (two-thirds of malignant liver tumors in children)[15] .This was in agreement with its incidence in our results (71.4%).

In our study, among primary hepatic tumors, HB was reported in 20/28 cases (71.4%). Similar to literature, the median age at diagnosis was two years (range 1.5-6 years) with no specific sex predilection (male to female ratio= 1:1.05) [13][14][16].

The triad of a liver tumor, thrombocytosis, and high level of serum AFP in a child between 6 months and 3 years age, is diagnostic of HB [17]. Markedly elevated serum level of AFP can be detected in HB, yolk sac tumor, and HCC. Also serum AFP levels can be elevated in certain benign tumors like mesenchymal hamartoma, focal nodular hyperplasia and infantile haemangioendothelioma. On the other hand 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 [18]. The median serum alpha-fetoprotein level at diagnosis in our data was 117.75 IU/ml (range 23-453120 IU/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 [19].

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 [20][21]. In our study, eleven cases had pure fetal HB and the remaining cases were mixed subtypes.

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 [11] [22][23].In primary liver tumors, PRETEXT IV disease carries a poorer prognosis since complete tumor resection becomes very difficult. In our study, using the PRETEXT system, one case had stage I disease, seven cases had stage II, 10 cases had stage III and two 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 [24] .We detected distant metastases to the lung in two (10.5%) patients.

Although complete surgical resection is considered the most important factor predicting patients who would achieve cure, yet response to chemotherapy is another paramount factor affecting survival in those patients[25][26]. 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 [24][25][26]. In this study, after upfront chemotherapy, ten out of nineteen cases were rendered operable; complete resection was achieved in seven patients, while the other three patients had residual. On the other hand, one case with PRETEXT I had undergone upfront surgery with complete resection of the tumor followed by chemotherapy.

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[16].Unfortunately, both doxorubicin and cisplatin are associated with the potential for significant side effects, cardiac toxicity with doxorubicin and nephro- and ototoxicity with cisplatin. Intra-arterial chemo-embolization has the potential for helping to avoid these systemic adverse effects in selected cases of HB. This allows for exposure of tumor cells to high concentrations of drugs, which cannot be achieved by the same dose of systemically administered agents [27]. None of our cases treated with chemo-embolization

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 [22][28]. Some other important adverse prognostic factors are reported as an initially low AFP , vascular invasion, lymph node metastases, and small-cell undifferentiated histology[7][28]. In this series, the reported three years overall survival rate in patients with HB treated with intent to cure was 65%. Both stage and histologic subtypes had significantly affected the outcome of our patients. Children with low stages HB and pure fetal histologic subtype had a significantly

better survival rate compared to patients with high disease stages or mixed subtype ($p < 0.001$ and $p=0.12$ respectively).

HCC and HB in children exhibit marked differences in their clinical presentation, course, treatment responses, surgical resectability, and prognosis. HB 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 HB cases has improved significantly; however, in HCC, less than one-third of the cases can be cured [29]. The three HCC cases in this series presented with late stage disease and had a progressive course. This limited number of HCC cases didn′t allow comparison with others.

Conclusion:

Outcome of patients with HB was affected by both stage and histopathologic subtypes. Upfront chemotherapy allows complete surgical resection of initially unresectable primary tumors with improvement of survival outcome in such patients. As a developing country with high prevalence of infectious causes, non-neoplastic hepatic lesions should be taken in consideration during diagnosis of hepatic focal lesions in children.

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List of Abbreviations:

AFP	Alpha –fetoprotein
CR	Complete remission
CT	Computed tomography
DP	Disease progression
FNH	Focal nodular hyperplasia
HA	Hepatic adenoma
HB	Hepatoblastoma
HCC	Hepatocellular carcinoma
IHH	Infantile hepatic hemangioendothelioma
MH	Mesenchymal hamartoma
MRI	Magnetic resonance imaging
NRH	Nodular regenerative hyperplasia
OS	Overall survival
PRETEXT	Pretreatment extent of disease
PR	Partial response
SCC	Sohag Cancer Center
SD	Stationary disease
SIOP	International Society of Pediatric Oncology

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