Clinical and Evolutionary Characteristics of Hepatoblastomas Treated at the Tunis Children's Hospital

Dr ElhemJbebli., Dr Farah Hssine., Dr Sarra Ben Ahmed., Dr Rim Amdouni., Pr Faten Fedhila., Pr Samar Rhayem., Pr Monia Khemiri

Pediatric Oncology Unit, Department of Medicine A, Tunis Children's Hospital, Tunisia

DOI: https://doi.org/10.51244/IJRSI.2024.1108074

Received: 03 August 2024; Accepted: 10 August 2024; Published: 12 September 2024

ABSTRACT

Epidemiological data on hepatoblastoma, the most common malignant liver tumor in pediatrics, are lacking in Tunisia. The objective of this study was to examine the clinical, therapeutic, and evolutionary characteristics of hepatoblastoma in children and to identify factors that influence prognosis.

This was a retrospective analysis of all pediatric patients under the age of 18 who were treated for hepatoblastoma at the pediatric oncology unit of the Tunis Children's Hospital over a period of 18 years.

A total of 18 patients were included in the study. The median age was 22 months [1 month - 7 years]. The primary presenting symptoms were abdominal bloating and general signs (altered general condition, weight loss and anorexia). Mixed histology was the most prevalent type. Twelve patients were classified in the high-risk group, and six in the standard-risk group. The patients were treated in accordance with the SIOPEL3 protocol. A total of 16 patients underwent surgical treatment. A mean follow-up of 6 years [1 - 14 years] yielded an overall and event-free survival at 5 years of 67% and 55%, respectively. The factors influencing survival were diagnostic delay ($p = 0.048$), alpha-fetoprotein level ($p < 0.001$), venous extension ($p = 0.018$), histological type ($p = 0.004$), risk group ($p = 0.048$), and tumor operability ($p < 0.001$). In the multivariate analysis, socioeconomic status (SES) was found to be independently influenced by alpha-fetoprotein level ($p=0.045$ and OR: 46.2) and venous extension ($p=0.035$ and OR: 0.08).

Our management strategy is in accordance with the most recent recommendations. The prognosis of patients classified inthe high-risk group remains poor in the absence of liver transplantation.

Keywords: Hepatoblastoma, Child, Clinical, Treatment, Survival, Prognosis

INTRIDUCTION

Primary liver tumors are uncommon in children, with hepatoblastoma representing the most prevalent type, occurring in a frequency ranging from 0.5 to 1% of all pediatric tumors [1]. The current incidence of hepatoblastoma is estimated at 1/1,000,000 [2]. It mainly affects children under the age of three with no underlying liver disease.

In most cases, the tumor is sporadic. Despite the lack of clarity surrounding its etiopathogenesis, there is evidence to suggest that genetic predisposing factors may contribute to the development of hepatoblastoma. A diagnosis can be readily established through the identification of a liver tumor accompanied by an elevated level of alpha-fetoprotein (AFP). Imaging plays a pivotal role in the diagnosis and therapeutic management of the disease, enabling its classification into risk groups according to the PRETEXT (Pre-Treatment Extent of Tumor) classification system [3]. The treatment plan is based on a combination of chemotherapy and surgical excision. The prognosis of patients classified in the high-risk group has been improved by intensification of chemotherapy and complete excision, sometimes followed by liver transplantation. This has resulted in an overall survival rate of 80% at five years [4].

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue IX August 2024

The subject has been sparsely studied in Tunisia, with only a few clinical cases having been documented. There is a dearth of data pertaining to incidence and prevalence, particularly in the absence of a national childhood cancer registry.

This study aimed to investigate the clinical, therapeutic, and evolutionary features of childhood hepatoblastoma in a Tunisian pediatric population and to ascertain the factors influencing prognosis.

METHODS

This was a monocentric, descriptive, and retrospective study conducted at the Pediatric Oncology Unit (POU) of the Children's Medicine Department A of the Béchir Hamza Children's Hospital in Tunis over an 18-year period (January 2006 to December 2023).

The study population consisted of all children with hepatoblastoma who were retained on suggestive radiological appearance with elevated αFP or histologically confirmed for non-secreting tumors, aged less than 18 years at diagnosis and not previously treated for another cancer.

The data were obtained from the patients' clinical and paraclinical follow-up records. Biological analysis was employed to ascertain whether the tumor was secretory or non-secretory. Radiological findings were employed to ascertain the extent of hepatic involvement in accordance with the PRETEXT classification system, and to delineate the locoregional and metastatic VPEM extension (V=vena cava and hepatic veins, P=portal system, E=extra-hepatic intra-abdominal extension, M=distant metastases). The classification of the tumor was based on the number of tumor-free hepatic sections. The tumor was classified as PRETEXT I if it had three adjacent healthy sections and only one invaded section, as PRETEXT II if it had two adjacent healthy sections and two invaded sections, as PRETEXT III if it had two non-adjacent healthy sections or only one healthy section, and as PRETEXT IV if it had no section free of invasion and all four sections were invaded. Patients were classified into risk groups: standard risk (PRETEXT I, II or III with no extrahepatic extension or metastases) or high risk (PRETEXT IV and/or extrahepatic extension (V, P, E, M) and/or an AFP level at diagnosis<100 µg/l).

Patients were treated in accordance with the SIOPEL 3 protocol, which entailed four courses of Cisplatin administered every 15 days prior to surgery, followed by two courses postoperatively for the standard-risk group (SIOPEL-3 SR-Arm B). For the high-risk group, the protocol involved alternating Carboplatin/Ariamycin and Cisplatin every 15 days (seven preoperative courses and three postoperative courses) (SIOPEL-3 HR).

The data were entered and analyzed using the IBM SPSS® version 25 software program. Categorical variables were expressed as simple frequencies, while quantitative variables were expressed as means with standard deviations. The normality of the quantitative variables was evaluated.

Overall survival (OS) was defined as the time elapsed between the date of diagnosis and the date of the last known contact with the patient or the date of the patient's death. Event-free survival (EFS) was defined as the time elapsed between the date of diagnosis and the date of occurrence of an event corresponding to either locoregional recurrence or metastasis. The Kaplan-Meier method was employed to construct the OS and SES curves. The log-rank test was employed for univariate analysis to facilitate comparisons of survival curves. A multivariate analysis was conducted to ascertain which factors independently influence survival, employing the Cox regression method. The level of statistical significance was set at 0.05.

The anonymity of the patients was respected. We hereby declare that we have no conflicts of interest in relation to this study. Prior to the commencement of this study, approval was obtained from the institutional ethics committee.

RESULTS

A total of 18 patients with hepatoblastoma were managed at the POU between 2006 and 2023. Hepatoblastoma constituted 2% of the total number of tumors managed at the POU during the study period.

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue IX August 2024

The mean age at diagnosis was 22 ± 20.8 months [1 month - 7 years]. In fourteen cases, patients were under three years of age. One patient had a tumor identified antenatally via third-trimester ultrasound. The sex ratio was 1(9 males and 9 females).

The study revealed four cases of consanguinity. Threepatients had a family history of familial adenomatous polyposis (FAP). No patient was known to have a genetic predisposition to cancer. The personal history included two cases of prematurity and two cases of low birth weight.

The average time to diagnosis was 22 days [3 days - 2 months]. The main circumstances of discovery were abdominal bloating (n=11) and general signs (altered general condition, weight loss and anorexia)(n=10). Hepatoblastomas were revealed by the fortuitous discovery of an abdominal mass by the pediatrician in five cases. For Two newborns, the discovery was also fortuitous on an ultrasound scan (investigation of urinary tract infection and prolonged jaundice). Hepatomegaly was present in 15 cases with signs of portal hypertension present in four.

The radiological appearance was suggestive of hepatoblastoma in 15 cases. The right liver was affected in 15 cases and the left liver in three. The affected segmentswere segment VI (n=12), segment V (n=11), segment VII (n=9), and segment VIII (n=8). One patient was assigned to PRETEXT IV, six to PRETEXT III, seven to PRETEXT II, and four to PRETEXT I.

The presence of deep abdominal adenopathy was noted in three cases, vascular invasion in five patients, and invasion of portal structures in eight. Three patients exhibited considerable peritoneal effusion.

In 15 cases, the tumor was observed to secrete αFP. The mean level of αFP at diagnosis was 265,406 µg/L [1 - 925,552 µg/L]. Two patients had αFP levels at diagnosis below 100 µg/L.

The disease was metastatic in seven cases. Lung metastases were diagnosed in five patients, including micronodules (n=4)and balloon-release nodules (n=1). Two patients were diagnosed with pleural nodules.

Six patients were classified within the standard risk group, while the majority (n=12) were classified within the high-risk group.

A total of 17 patients received neoadjuvant chemotherapy. One patient underwent immediate diagnostic and therapeutic surgery for a tumor rupture with intraperitoneal massif hemorrhage.

Six patients were treated according to SIOPEL-3SR protocol. Two of them required two additional neoadjuvant curses of cisplatin to achieve operability.

Twelvepatients were treated according to SIOPEL-3HR protocol. Six HR grouppatients required a mean number of 4 additional neoadjuvant cures to achieve operability [1-6 cures]. Two patients succumbed died during neoadjuvant treatment.

Sixteen patients had undergone surgery. They were belonging to SR group in six cases and HR group in ten cases. One patientunderwent immediate surgery for a ruptured tumor in the peritoneum with life-threatening internal bleeding and 15 patients underwent secondary surgical procedures. The mean interval between the final neoadjuvant chemotherapy cure and the surgical procedure was 21days [12 - 34 days]. The surgery was a right hepatectomy in six cases, a left hepatectomy in four cases, right segmentectomy in five cases and a III hepatic segmentectomy.

A pathological examination was conducted prior to the administration of chemotherapy for the three patients who underwent radioguided liver biopsy for non-secreting tumors. A histological study of the surgical specimen, conducted on 16 patients, revealed pure epithelial hepatoblastoma in seven cases and mixed histology (epithelial and mesenchymal) in nine. The fetal contingent was the most frequent (n=8), followed by the embryonic contingent (n=6). The microscopic limits of surgical resection were healthy in 10 cases and tumoral in six cases. The three patients with a family history of FAP had epithelial tumors.

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue IX August 2024

Two patients underwent surgical excision of pulmonary metastases. It was a complete resection in one case and an incomplete resection in the other case.

Twelvepatients received adjuvant chemotherapy. The mean time between surgery and adjuvant chemotherapy was 15 days [8 - 60 days]. The mean number of cures was 2 [1 - 6 cures]. The patient who underwent surgery first had received four curses of chemotherapyand subsequently died. Two patients died of rapid tumor progression postoperatively without adjuvant treatment.there was no significant difference in clinical characteristics between males and females, according to the secretory or non-secretory nature of the tumor or according to the family history of FAP.

At the end of treatment, eleven patients achieved complete remission, two achieved partial remission, two experienced tumor progression and three patients died.

Two patients had relapsed. The interval between the end of treatment and recurrence was two and three months, respectively. The recurrence was locoregional in both cases. One patient was treated with a combination of Vincristine, Temozolomide, and Irinotecan, and the second with Etoposide and Cyclophosphamide. At the time of the study, eleven patients were in first complete clinical remission, one patient was in second complete remission after an early relapse, and six patients died.

A mean follow-up of six years [1 - 14 years] revealed an OS of 67% at 2 and 5 years [Figure 1], with an EFS of 55% at 2 and 5 years [Figure 2]. The main prognostic factors influencing survival were diagnostic delay (p=0.048), αFP level(p<0.001), venous extension (0.018), histological type (p=0.004), high-risk group (p=0.048), tumor operability (p<0.001) [Table I]. On multivariate analysis, no independent prognostic factors were identified for OS, whereas EFS was independently influenced by αFP level<100 µg/l (p=0.045 and OR: 46.2) and venous extension (p=0.035 and OR: 0.08).

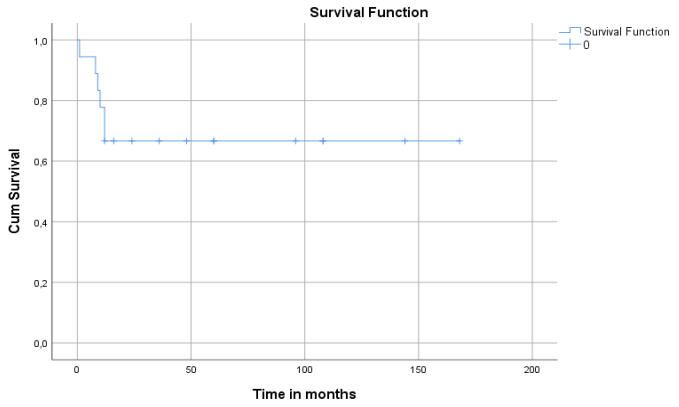

Figure 1: Overall survival of children with hepatoblastoma

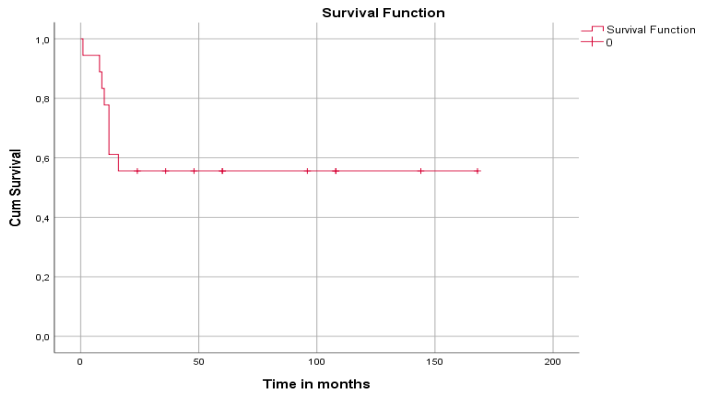

Figure 2: Event free survival of children with hepatoblastoma

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue IX August 2024

DISCUSSION

To our knowledge, this is the first national study to examine the clinical and evolutionary profiles of childhood hepatoblastoma, as well as its prognostic factors. All cases of this rare pathology were collected over an 18-year period. The length of the study also enabled us to take a long view.

The results of this study will serve as a starting point for a better understanding of the disease in this age group and for planning other, larger studies. In fact, the retrospective, monocentric nature of the study made it difficult to fill in some missing data, and the small sample size leads us to interpret the results with caution.

Table I: Factors Influencing Survival of Hepatoblastoma in a Tunisian Pediatric Population.

Factors influencing survivor		**5-yearsOS[a]**	**P[b]**	**5-years EFS[c]**	**P**
Gender	Male	55%	0.26	55%	0.74
	Female	78%		55%	
Age at diagnosis	<12 months	62%	0.62	50%	0.84
	12-36 months	83%		68%	
	>36 months	50%		50%	
Diagnostic delay	<10 days	100%	**0.048**	83%	**0.05**
	≥10 days	50%		41%	
Initial αFP[d]level	<100 µg/L	0%	**<0.01**	0%	**<0.01**
	≥100 µg/L	75%		62%	
Pre-surgerysecretorystatus	Negative	87.5%	0.32	62.5%	0.9
	Positive	62%		62.5%	
Venous extension	Yes	20%	**0.018**	0%	**<0.01**
	No	85%		76%	
Portal extension	Yes	62%	0.78	38%	0.26
	No	70%		70%	
Metastasis	Yes	58%	0.54	28%	0.11
	No	72%		72%	
Risk stratification	Highrisk	100%	**0.048**	100%	**0,014**
	Standardrisk	50%		33%	
Histological type	Epithelial	70%	**<0.01**	58%	**<0.01**
	Mixed	78%		68%	

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue IX August 2024

Tumoroperability	Operable	75%	**<0.01**	62%	**<0.01**
	Operable	75%		62%	

[a]Overall survivor, [b] p value, [c] Event free survivor, [d] alpha fetoprotein

Hepatoblastoma accounted for 2% of all tumours treated at the POU. Hepatoblastoma is the most common primary malignant liver tumor in young children, accounting for 0.8% to 2% of all pediatric malignancies and approximately 1% to 4% of all solid tumors [5]. In Europe, the number of new cases was estimated at 1-1.9 per million population per year between 1995 and 2002 [6]. It accounts for 91% of livertumors in children[7]. La fréquence de l'hépatoblastome a été estimée à 3,6 % au Niger [8] et à 5,9 % en République démocratique du Congo [9]. In patients between five and nine years of age, the incidence was estimated to be 0.1 cases per million children [11]. The disease was diagnosed prenatally in one patient. Approximately 52 cases of congenital hepatoblastoma have been reported in the literature between 1970 and 2012 [12]. In the literature, the incidence of hepatoblastoma is significantly higher in boys than in girls [13]. However, in our cohort, the sex ratio was 1.

Little is known about the etiopathogenesis of hepatoblastoma. No genetic predisposition to hepatoblastoma was found in our cohort. The tumor was sporadic in most cases. A review of the literature identified 109 cases of children with hepatoblastoma and a family history of FAP with the APC mutation [14]. In three of our patients, there was a strong suspicion of FAP in the family without genetic data on the APC mutation. Beckwith-Wiedmann syndrome (BWS) is closely associated with hepatoblastoma, with 56 cases reported between 1970 and 2012 [15]. The association between hepatoblastoma and trisomy 18 has also long been described [16].

This suggests an etiologic rather than a coincidental association between these two conditions. However, the incidence of hepatoblastoma in children with trisomy 18 is unknown and difficult to estimate given the high mortality in infancy. Epidemiologic studies have highlighted the association between prematurity and low birth weight with the subsequent development of hepatoblastoma [17]. The risk was 20 times higher in children with a birth weight <1500 g.

Data from the Children's Oncology Group (COG) [18] and the International Childhood Liver Tumor Strategy Group (SIOPEL) [19] have identified several factors that influence survival in children with hepatoblastoma. In our study, the mean age was 22 months, and age did not correlate with OS or EFS, whereas several authors considered it an important predictor of hepatoblastoma prognosis.

Maibach et al [20] found that the higher the age at diagnosis of children with hepatoblastoma, the worse the prognosis. In another study of 606 children by Allan et al [21], survival was highest in children diagnosed at less than 5 years of age, reaching 63% at 5 years and 59% at 20 years after diagnosis.

The majority of hepatoblastoma working groups have concluded that an age-normal or slightly elevated αFP level (<100 ng/mL) is a poor prognostic factor [12,22]. In our study, OS and EFS were significantly lower when αFP levels were below 100µg/l. This level was found to be an independent factor significantly influencing EFS. Several authors have noted that pure fetal hepatoblastoma has an excellent prognosis compared to other histologic types, being amenable to exclusive primary surgery without recurrence. Indeed, COG studies have shown that completely resected pure fetal hepatoblastoma is associated with a low risk of death [23]. A study conducted in China in 2015 showed that the 5-year EFS was better for the epithelial type, estimated at 71.8% compared with the other types (35.5%) [24]. In our univariate study, we found that, on the contrary, the pure epithelial type was associated with significantly lower OS and EFS than the other histologic types. The multivariate study did not confirm that epithelial histology was an independent factor influencing survival. The landmark SIOPEL1 studies showed that five-year EFS was significantly impaired in patients with multifocal tumors (40%) compared to those with unifocal tumors (72%) [25]. Qiao et al. demonstrated that tumor multifocality was a risk factor independently associated with poor prognosis, with a 5-year EFS of 68.8% for unifocal tumors and 25.9% for multifocal tumors [26]. The prognostic value of the PRETEXT system has been extensively validated by SIOPEL [20]. In a study conducted in China by Zhi et al. in 2021, the

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue IX August 2024

five-year EFS rates of patients with PRETEXT I, II, III, and IV hepatoblastoma were 100%, 97.8%, 69.4%, and 28.6%, respectively ($p<0.01$) [27]. Tumor invasion of all four hepatic regions at diagnosis has always been considered an unfavorable clinical feature due to limited options for radical surgical resection. However, the prognosis of PRETEXT IV tumors could be improved with intensive preoperative chemotherapy and liver transplantation [28]. In our study, the influence of PRETEXT classification on survival could not be demonstrated. Due to the small size of the cohort, the difference was not statistically significant. In the absence of a technical platform for liver transplantation currently available in Tunisia, the prognosis for patients classified as PRETEXT IV remains poor. Vascular invasion involving the portal vein, its two main branches, the hepatic veins, or the inferior vena cava was also a significant predictor of hepatoblastoma survival. In the study conducted by Shi et al. in 2017, a significant difference in 3-year OS was found between patients who had no pathological vascular invasion, estimated at 95% versus 61% in patients who had pathological vascular invasion ($p=0.02$) [29]. In this study, we found that OS and EFS were both correlated with venous extension. OS and EFS at 1 year were 20% and 0%, respectively ($p=0.018$), when vein extension was present, and 84% and 77%, respectively, when it was not ($p=0.005$). However, the association between survival and portal extension was not significant. The presence of pulmonary metastases has been recognized as a poor prognostic factor. Allan et al. had shown that patients with local hepatoblastoma achieved a survival rate of 80% at 5, 10 and 20 years after diagnosis, while patients with hepatoblastoma with distant metastases had survival rates close to 40% at all three time points [21].

CONCLUSIONS

This study has enabled us to gain insight into the clinical, therapeutic, and evolutionary aspects of hepatoblastoma in a Tunisian pediatric population, which had previously been under-researched, and to identify the factors affecting survival.

Our management approach is fully in line with the latest recommendations regarding classification, surgery and chemotherapy. However, it is important to note that the prognosis of patients in the high-risk group remains poor without liver transplantation.

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