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Research Article

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Treatment Outcomes for Hepatoblastoma: 15-Years-Experience of a Single Institution – Sheikh Khalifa Medical City, Abu Dhabi, UAE

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Abstract

Background: *Hepatoblastoma is the most common malignant liver tumor in children. Treatment protocols varies. In our center, we have adopted the Children's Oncology Group (COG) AHEP0731 protocol, in addition to some experimental regimens for relapsed solid tumors.*

Methods: *We aimed to investigate the outcome of the current hepatoblastoma treatment protocol at our center. 15 patients were included between January 2008 and June 2023. A retrospective review was carried to review the clinical presentation, serum α-fetoprotein (AFP) level at diagnosis, histological subtype, treatment, and outcomes.*

Results: *12 patients (80%) were symptomatic at time of diagnosis, with abdominal mass being the most common presenting complaint. Nine patients (60%) presented in stage 3 PRETEXT staging system. Epithelial histopathological subtype was predominant subtype. Thirteen patients have received preoperative chemotherapy, followed by surgical resection; only one patient underwent upfront surgical resection followed by chemotherapy. Preoperative chemotherapy consists of 2 to 4 cycles of Cisplatin, Fluorouracil, Vincristine and Doxorubicin (C5VD), followed by surgical resection. Four of them underwent neoadjuvent experimental chemotherapy utilizing agents such as Pazopanib, Pembrolizumab and Sorafenib. During follow-up, six patients died of progressive disease. The median survival time was 42 months (95% confidence interval: 18–42%). Five-year overall survival was 44.09% (95% confidence interval: 18–42%).*

Conclusions: *The combination of surgery and chemotherapy for hepatoblastoma is an effective approach.*

Utilization of new-targeted therapies and relapsed solid tumors regimens may prolong life in patients who did not respond to standard therapy. Further studies are required to validate its usage on patients with advanced hepatoblastoma.

Keywords: Hepatoblastoma, Chemotherapy, Surgical Resection, Malignancies

1. Main Text

1.1 Background

Hepatoblastoma (HB) is one of the most common malignant liver tumors that occurs in children. It accounts for 50% of all liver tumors and approximately 1.3% of malignant tumors in children [1].

In many cases, hepatoblastoma affects those who are two years of age and younger, and it is rarely seen in those older than 5 years of age. The incidence of hepatoblastoma is found to be twice more in males than in females. Certain syndromes carry a higher risk of genetic predisposition to hepatoblastoma. These include examples such as Beckwith Wiedmann syndrome, Acardia syndrome, trisomy 18, trisomy 21, Li-Fraumeni syndrome, Goldenhar syndrome, type 1a glycogen storage disease (von Gierke disease), and familial adenomatous polyposis [2]. Most patients with hepatoblastoma present with an abdominal mass, that most commonly involves the right lobe of liver than the left. It has been observed that bilobar involvement is seen in 20-30% of patients, while multicentric involvement accounts for 15% [3,4]. Other symptoms of hepatoblastoma can be vague and present like any other liver illness such as anorexia, abdominal pain and weight loss [3]. The serum level of alpha-fetoprotein (AFP) in these cases is almost always elevate, while bilirubin and liver enzymes are usually normal [4]. Approximately 10% to 20% of patients present with distant metastases at diagnosis, with lungs being the commonest site of metastasis. Other rare sites of distant metastasis include the brain and bone. Hepatoblastoma is histologically classified as epithelial (56%) or mixed epithelial/mesenchymal (44%) [5]. Epithelial type is subdivided to pure fetal (31%) which carries the best prognosis, embryonal (19%), macro trabecular (3%) and small-cell undifferentiated (SCU)

(3%) which is the worst in terms of prognosis. Mixed type consists of stromal derivatives and teratoid [6].

The mainstay of curative therapy in children with hepatoblastoma is surgical resection, however, only one-third to one to half of the newly diagnosed patients present with a fully resectable disease. Those patients that undergo surgery have an excellent prognosis (90% event-free survival [EFS]). The main factors that contribute to the clinical outcome in patients with hepatoblastoma depends on two main factors; (1) on the presence or absence of metastatic disease, and (2) tumor resectability [7].

Multiple studies from around the world in the last 3 decades have demonstrated the effectiveness of chemotherapy in increasing rates of surgical resection and survival in initially unresectable patients [8,9].

Chemotherapy enhanced the survival of those patients with unresectable hepatoblastoma, as it increases the chances of rendering the tumor resectable [8]. However, more recent trials in the last decade have failed to significantly improve survival numbers. Therefore, the current EFS for the entire group of patients with non-metastatic, and unresectable hepatoblastoma at diagnosis remains suboptimal (<70%) and warrants novel treatment approaches. The survival of patients with metastatic disease at diagnosis remains poor (20-30%) and also requires consideration of novel therapeutic strategies [7,8].

Cisplatin (CDDP) is known to be the most active agent for the treatment of hepatoblastoma, followed by Doxorubicin (DOXO) [10,11]. Little is known about the efficacy of other single agents such as Ifosfamide (IFOS), Etoposide (ETOP), Vincristine (VCR), 5-Fluorouracil (FU), Cyclophosphamide (CPM), and Carboplatin (CARBO) in the treatment of hepatoblastoma, as most of these agents have been used in combination therapy [8,12]. The decrease of AFP levels after 4 cycles of chemotherapy and prior to surgical resection of the tumor has been shown to have prognostic value [13,14]. However, it is not clear if the initial rate of decline or the magnitude of decline of AFP after each cycle of chemotherapy can be used to guide subsequent therapy. Initial AFP < 100 ng/mL has been associated with an adverse outcome and worse prognosis.

The recent trends of upfront preoperative chemotherapy followed by surgical resection have increase resectability, and decrease surgical morbidity associated with resection, however, it increased the amount of chemotherapy received by the patients and resulted in increased short-term and long-term toxicity.

To minimize surgical risk and associated comorbidities, SIOPEL-1 introduced the pretreatment extent of disease PRETEXT system to define the liver involvement by the tumor [13]. It aims to predict surgical resectability and prognosis.

2. Subjects and Methods

Our objective was to review the experience of a leading tertiary referral center in treating hepatoblastoma in children over the past 15 years.

In Sheikh Khalifa Medical City (SKMC), we have adopted the AHEP0731 protocol that is based on the results of the last 20 years of hepatoblastoma clinical trials and seeks to diminish toxicity and improve survival.

3. Patients

We retrospectively reviewed and analyzed a comprehensive set of data obtained from electronic medical records of children who were admitted with a confirmed diagnosis of Hepatoblastoma in SKMC in Abu-Dhabi, UAE from January 2008 to June 2023.

Eligible subjects were identified using relevant diagnosis based on international classification of disease (ICD-9 and 10) E-codes. The inclusion criterion was children under 16 years of age with newly diagnosed hepatoblastoma who had never received treatment prior to the study period.

Exclusion criteria included patients outside of the specified age range and those diagnosed or managed in a different institute prior being under our care. Out of the 17 patients, diagnosed with hepatoblastoma, only 15 qualified as per our inclusion criteria for this study. Two patients were excluded, as they were diagnosed and managed in another facility, and came for follow up at SKMC.

4. Methods

The initial diagnosis of hepatoblastoma was determined through either a tissue pathology or by clinical diagnosis including elevated AFP level, and tumor evidence by imaging studies. All patients must have had a tissue pathology to confirm the diagnosis of hepatoblastoma, which was confirmed in all 20 patients examined in this study. As per our treatment guidelines, all patients were initially evaluated by a pediatric surgeon and received upfront surgery if the tumor was found to be resectable. For those who had an unresectable tumor, 2-4 courses of neoadjuvant chemotherapy were given before a reevaluation. After surgery, adjuvant chemotherapy was given until the AFP level was reported to return to normal on 2 consecutive occasions, along with evidence of tumor regression observed on radiological imaging.

5. Staging and Histologic Classification

Our cohort was classified according to the Children's Cancer Group (CCG) and the Pre-Text staging system. Table 1 details the different stages. The Histologic subtypes included epithelial (embryonal, fetal, embryonal type, and mixed fetal), mixed epithelial, mesenchymal, and mesenchymal type.

Stage	U.S. Intergroup	SIOP
I	Completely resected	3 adjacent sectors free
II	Microscopic residual	2 adjacent sectors free
III	Macroscopic residual, unresectable or rupture of capsule	2 non-adjacent sectors or 1 sector free
IV	Metastatic	No free sectors

Table 1: Staging of hepatobastoma

All patients that were Stage I pure fetal histology (PFH) hepatoblastoma were classified as very low-risk. These patients underwent full surgical resection only.

Patients with Stage I non-PFH, SCU hepatoblastoma or with Stage II non-SCU hepatoblastoma were classified as low-risk. These patients were treated with Regimen T with 2 adjuvant cycles of cisplatin, vincristine (C5V), and 5-flouorouracil. Patients with Stage I SCU, Stage II SCU, or any Stage III hepatoblastoma were classified as intermediate-risk, and were treated with Regimen F. Regimen F includes 6 cycles of C5V plus Doxorubicin, and this was followed by surgical resection of the tumor. Surgical resection was intended after 4 cycles for intermediate-risk therapy. Any patient with Stage IV hepatoblastoma, as well as patients with any stage of hepatoblastoma and had an initial AFP of <100 ng/mL, were classified as high-risk. High risk patients were treated with the novel combination of Vincristine, Irinotecan in regimen H which consists of 2 cycles of "up-front" Vincristine, and Irinotecan in the initial 6 weeks of therapy. Patients that responded to Vincristine/Irinotecan (VI) continued to receive this combination. Serum AFP and imaging studies including abdominal ultrasonography and/or computed tomographic scan were regularly examined to evaluate treatment response. Heart echocardiogram and hearing test were examined to detect any possible sequelae. Temsirolimus was not utilized for Regimen H patients, as it was not available in our institution.

6. Statistical Analysis

Overall survival (OS) was defined as the time between the diagnosis date and the latest follow-up or death. EFS was defined as the time between the date of diagnosis and the first unfavorable event (death or recurrence) or the most recent follow-up. Kaplan-Meier analysis was used to examine OS and EFS. To estimate survival, 95% confidence intervals (CIs) were computed.

This study was approved by the Ethics Committee of the Faculty of Pediatrics at SKMC (COA number Si.592/2013).

P Values <0.05 were statistically significant.]

7. Results

A cohort of 15 children with hepatoblastoma was managed in our institution between January 2008 and June 2023. There were 7 male (46.7%) and 8 female (53.3%) children with a median age of 23.27 months at diagnosis in our institution. The youngest patient in our cohort was diagnosed at 16 days of age.

We reviewed the clinical presentation, treatment, outcomes, serum AFP level at diagnosis, and histological subtype of all patients (Table-2). One patient had Edward syndrome and another patient had severe common immunodeficiency (SCID). Two of our patients had a history of transaminitis prior to their diagnosis, and only one patient had significant family history of malignancy. The remaining patients were previously healthy to our knowledge.

Median age at diagnosis in months, range	**23 (0.52 – 64)**
Gender n(%) Male Female	 7 (46.7) 8 (53.3)
Median follow-up time in years, range	**3.7 (0.2-5.9)**
AFP level n(%) <10 000 IU/ML >10 000 IU/ML	 7 (46.7) 8 (53.3)
COG staging n (%) Stage I Stage II Stage III Stage IV	 1 (6.7) 2 (13.3) 9 (60) 3 (20)
Initial metastasis n(%) Lung Bone No metastasis	 2 (13.3) 0 13 (86.7)

Pathological results n(%)	
Mixed epithelia and mesenchymal type	2 (13.3)
Pure fetal type	11 (73.3)
Embryonal type	2 (13.3)
Radiological findings of tumor location n(%)	
Right lobe	9 (60)
Left lobe	2 (13.3)
Unspecified	4 (26.7)

Table 2: Demographic, clinical, radiological and pathological characteristics of study cohort

Of the 15 patients, 12 patients were symptomatic at time of diagnosis. The presence of an abdominal mass was the most common presenting complaint in 35% (Fig. 1). The median AFP level at diagnosis was 10000 ng/mL. Nine patients (60%) presented in stage 3 PRETEXT staging system. Two patients were stage 4 with lung metastases. The right lobe of the liver was the commonest site of affection in 9 patients, and epithelial type, and epithelia mixed were the predominant histopathological subtypes in 11 patients 73.3%.

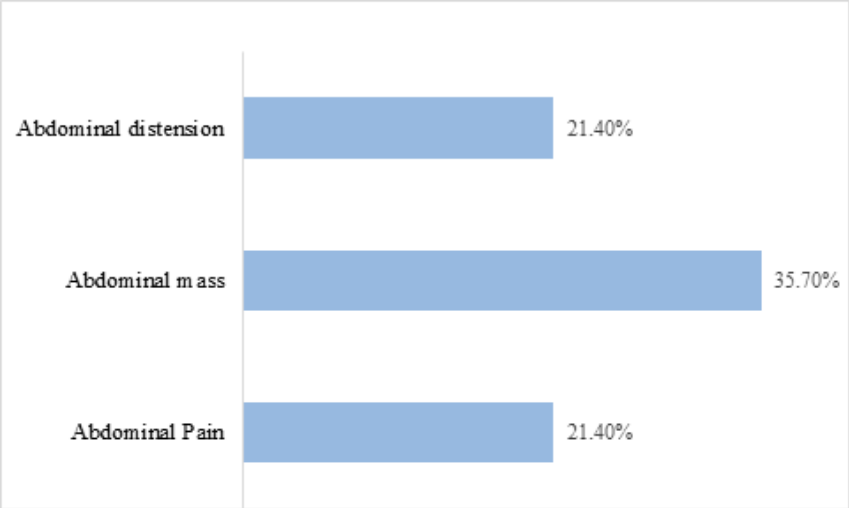

Figure 1: Most common clinical presentation

Thirteen patients have received preoperative chemotherapy, followed by surgical resection. Only one patient underwent upfront surgical resection followed by chemotherapy.

The one patient with an underlying diagnosis of Edwards Syndrome was only in for observation as the tumor showed spontaneous regression. One patient underwent liver transplant. 13 patients underwent the recommended treatment protocol which utilizes 2-4 cycles of C5VD, followed by surgical resection. Four of the patients who showed progression while on therapy in the form of distant metastases, or failure of primary tumor regression was not considered amenable to surgical resection, underwent other modalities of therapies, including the use of the relapsed solid tumor regimen which consists of Gemcitabine 1000 mg/m2 IV, Bevacizumab (Avastin) 5-10 mg/kg IV on Day 1 of each cycle, and Oxlaliplatin 100 mg/m2 IV on Day 2. This was a 14-day cycle.

Liposomal Doxorubicin was not available at our institution, so Doxorubicin was tried on 2 patients. One of these patients developed a reaction to it in the form of skin rash and respiratory distress, so it was discontinued.

Criteria of eligibility to start such therapy included, evidence of disease progression by both imaging studies and AFP level, a good performance scale using the Lansky or KARNOFSKY PERFORMANCE STATUS SCALE of more than 70%, hematological count recovery with absolute neutrophil count above 750, and a platelet count above 75,000, before each cycle. This was well tolerated with no major side effects. All patients received more than 6 months of this regimen, with acceptable performance.

Three out of the four patients did receive their planned chemotherapy on time, except one who had delayed count recovery, mainly thrombocytopenia.

All 4 patients had shown stable disease while on this regimen. One patient went into apparent remission and travelled abroad where he received a live donor liver transplant. He was kept on Sorafenib post-transplant, but unfortunately, he relapsed after 3 months with disease progression and died.

Other neoadjuvant experimental chemotherapy utilizing agents, such as Pazopanib, Pembrolizumab and Sorafenib, was used on one patient. She was stable for almost 6 months, before she progressed, and her condition deteriorated and died.

During follow-up, six patients died from progressive disease. Five of them had pulmonary metastases, and one had brain

metastases. Only one patient underwent liver transplant, that was well-tolerated, however he later died due to tumor recurrence. The remaining patients are in remission until now.

The median survival time was 42 months (95% confidence interval:18–41%). Five-year overall survival was 44.09% (95% confidence interval:18–41%) (Fig. 2)

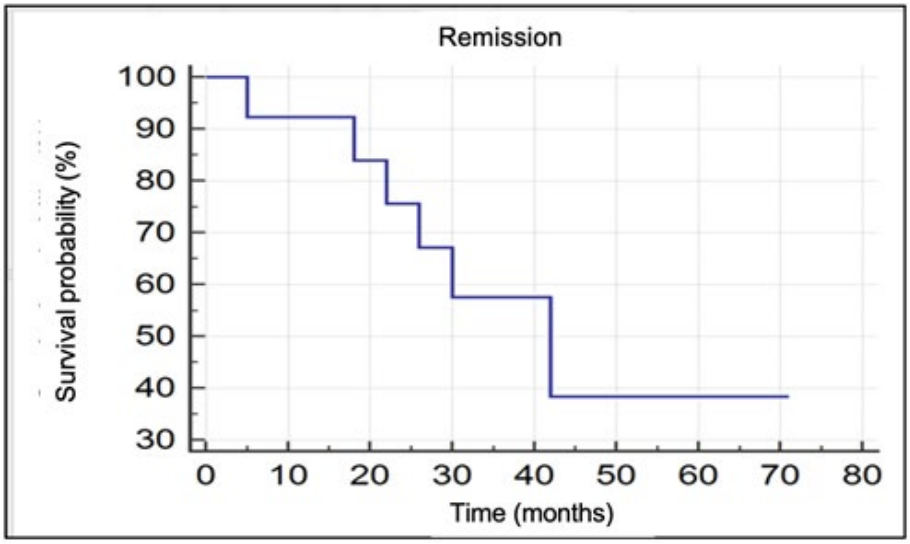

Figure 2: Kaplan-Meier survival analysis in months

8. Discussion

In most cases, hepatoblastoma can be diagnosed without the need for tumor biopsy, except in patients who are younger than 6 months or older than 3 years. However, in our center we opted to biopsy patients with high AFP levels, as previous studies have shown that elevated AFP could be linked to other diagnosis [5].

The mainstay of treating hepatoblastoma varies widely between centers. Neoadjuvant chemotherapy followed by resection has become the mainstay in the treatment of hepatoblastoma. Very effective preoperative chemotherapy for hepatoblastoma may shrink the tumor enough to allow for partial hepatectomy.

Total hepatectomy and liver transplantation has emerged as an effective treatment for the small proportion of children with unresectable hepatoblastoma that is limited to the liver [7]. A 5-year survival rate of 70% can be achieved in such cases.

Neoadjuvant chemotherapy, however, is the only treatment that can downstage unresectable hepatoblastoma tumors in order to make them resectable.

It is noteworthy that patients in our group had observable positive outcomes at the earliest possible follow-up. Any method that increases the resection rate of the tumor will increase survival because complete tumor resection is a requirement for cure. Hepatoblastoma excision during surgery is never simple, and even with skilled surgeons, resection-related deaths may still happen.

Increasing the use of chemotherapy in the neoadjuvant setting has improved the percentage of surgical resections. Our findings also point to a significant role for preoperative neoadjuvant chemotherapy in cases where the tumor is inoperable or unlikely to be completely removed at the time of diagnosis [15].

Data from our study showed that, in general, tumors of a lower stage had better 5-year EFS and OS rates than tumors of a higher stage; this was like the results of previous reports.

It is known that tumor metastasis, the outcomes of surgery, the initial AFP level and the pathological subtype are the important prognostic factors for hepatoblastoma.

In our study, we also observed that patients who had complete tumor removal without microscopic residual disease had better survival, indicating the importance of radical surgery in treating hepatoblastoma.

Several reports have shown that a tumor with a pure fetal histology (PFH) had a better outcome, especially for those patients whose tumor could be completely resected.
Despite having different treatment approaches or using different chemotherapy regimens, the patients in our study had 5-year EFS and OS rates comparable to those reported in studies from North America and Europe [9,16-19].

9. Conclusion

The cornerstone of treatment for hepatoblastoma and the only way to get the best clinical outcome is a thorough surgical resection. Despite this, standardized chemotherapy has contributed to the increases in survival over the past three decades by shrinking tumors and enabling total tumor removal, especially in cases where the tumor was initially incurable or had spread to other organs.

In our study, chemotherapy has been shown to be successful as a neoadjuvant and adjuvant treatment. It reduces the tumor tendency to hemorrhage, distinguishes the tumor from the surrounding healthy parenchyma and vascular structures, and makes resections easier. Doxorubicin, Cisplatin, Vincristine, and 5-FU are the types of chemotherapy that HB is sensitive to.

In addition, in advanced stages, HB may show sensitivity to other forms of chemotherapy, like the regimen utilized on our patients who failed the conventional one. Targeted therapies also may have a role in prolongation life expectancy for those children with advanced disease.

Further studies are needed on the new-targeted therapies to be able to validate the current data, in the hope to integrate it in the future as part of standard therapies for advanced stages of hepatoblastoma.

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