RESEARCH ARTICLE

The outcome of liver resections for hepatoblastoma in children: a 10-year experience from cancer dedicated institute

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Abstract

Objective: To review the comprehensive experience of surgical and oncological management of paediatric hepatoblastoma with 5-year survival outcome.

Method: The retrospective study was conducted at the Department of Surgical Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data from 2011 to 2020 of primary hepatoblastoma patients aged up to 18 years. Demographic details, size and site of the primary hepatic mass, tumour markers, radiological findings, PRE-Treatment Extent of tumour staging, treatment provided, histopathological and surgical details, and outcomes were assessed. Disease-free survival and overall survival were focussed upon. Data was analysed using SPSS 20.

Results: Of the 60 patients with mean age 2.0+1.54 years, 32(53%) were inoperable. The remaining 28(47%) patients underwent liver resection with a mean operative time of 270±118.41 minutes. Right hemi hepatectomy was performed in 14(50%) patients and the most common histology was epithelial foetal type in 16(57.1 %) patients. The five-year disease-free survival was 62%, while the five-year overall survival was 82%.

Conclusion: The survival rate of paediatric hepatoblastoma patients who underwent liver resections was within the acceptable range.

Key Words: Hepatoblastoma, Liver resection, Children, Outcome.

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Introduction

Paediatric hepatoblastoma is the most common primary hepatic malignancy, and its incidence has increased considerably in the last two decades with the prevalence being 1 per 1,000,000 population.[1] This upward trend was observed due to an increased survival rate among low-birth-weight (LBW) and premature infants.[2] A significantly raised alpha-fetoprotein protein (AFP) and radiologically confirmed hepatic lesion is enough for the clinical diagnosis in age ranging from 06 to 36 months. However, an image-guided core needle biopsy is more helpful in tissue diagnosis and management across age groups.[3]

Additionally, the development of a multidisciplinary approach and a combination of surgical resection, cisplatin-based chemotherapy, and adjuvant therapy provide standard-risk patients with a 5-year overall survival (OS) of >90%.[4] Surgery remains the mainstay of treatment, but a liver transplant combined with chemotherapy is the ultimate option for unresectable and PRE-Treatment Extent of tumour (PRETEXT) stage IV disease with a 10-year disease-free survival (DFS) of >80%.[5] Moreover, trans-arterial chemoembolisation (TACE) only, or combined with high-intensity focussed ultrasound, is another option for non-resectable tumours and those not responding to neo-adjuvant chemotherapy (NAC) and unsuitable for liver transplantation.[6]

Various studies proposed excellent long-term survival of paediatric hepatoblastoma after liver resection.[7,8] Moreover, a retrospective review proposed satisfactory results of liver resection for hepatoblastoma with 2-year event-free survival (EFS) and OS >90%.[9] Another cohort of 443 paediatric patients reported that liver transplant was not ominously associated with better OS in contrast to liver resection combined with adjuvant chemotherapy.[10]

Advanced cancer stage, treatment abandonment, and limited access to liver transplantation are the major challenges found in developing countries. Data is scarce regarding the management and outcomes of paediatric hepatoblastoma, especially in the underdeveloped world. Therefore, the current study was planned to review and assess the experience of surgical and oncological management of paediatric hepatoblastoma with their 5-year DFS and OS.

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Materials and Methods

The retrospective study was conducted at the Department of Surgical Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised patient data from 2011 to 2020. After approval from the institutional ethics review board, data of all individuals aged up to 18 years with hepatoblastoma diagnosis was retrieved from the hospital information system (HIS). Variables, including demographic details, size and site of the primary hepatic lesion, baseline tumour markers, radiological findings, PRETEXT staging, treatment provided, histopathological and surgical details, and outcomes were noted using a pre-designed proforma.

After completion of the initial workup and confirmation of diagnosis based on imaging and an elevated AFP level, the patients were discussed in the multidisciplinary tumour board, and cisplatin-based NAC in line with the International Childhood Liver Tumours Strategy Group (SIOPEL) guideline, was instituted for all the patients.[11] The patients with resectable disease on reassessment scan underwent surgical resection of the residual tumour intending to obtain clear margins, and received adjuvant treatment (Figures 1-2). The patients who has irresectable disease were sent for second opinion for transplantation at the institutional transplant centre, but only one child had liver transplant. Other modalities, like stereotactic body radiation therapy (SBRT) and radiofrequency ablation (RFA), were not considered because of their unavailability for paediatric cases at the study site.

After treatment, the patients were followed up regularly in physical and tele-clinics, with AFP, chest radiography, and ultrasound of the abdomen every 3 months for local recurrence or metastasis for 2 years, and every 6 months

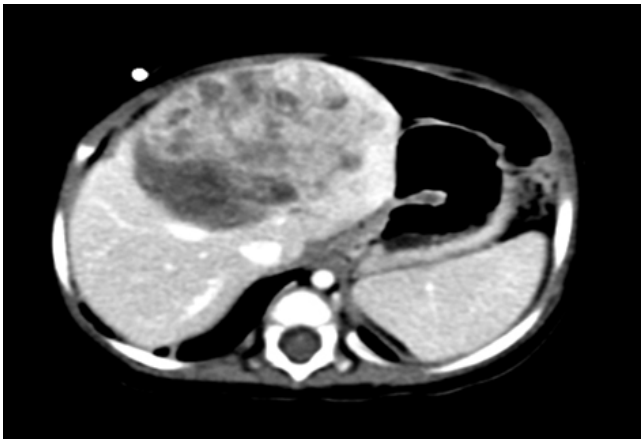

Figure-1: Contrast-enhanced computed tomography (CT) scan showing a large heterogeneously enhancing soft tissue mass centred in the left hepatic lobe with internal areas of necrosis.

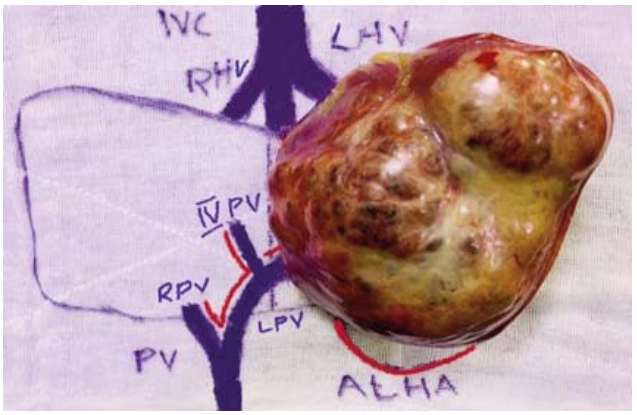

Figure-2: Post-resection left lobe of the liver containing the tumour

thereafter up to 5 years as per the hospital protocol.

In case of disease recurrence or progression (clinically or on scans), the patients were restaged and received second-line therapy until local control was achieved, or patients with inoperable disease or multi-organ involvement were sent for palliative care. The resection of recurrent or metastatic disease after primary surgery or second-line chemotherapy was individualised based on multi-specialty board decisions.

Data was analysed using SPSS 20. Mean +/- standard deviation were used to express continuous variables, whereas frequencies and percentages were used for categorical variables. Kaplan-Meier curve was used for survival analysis in terms of DFS and OS.

Results

There were 60 patients with mean age 2.0+1.54 years, who were treated with pre-operative chemotherapy, and all 60(100%) had baseline AFP levels >30,000ng/ml. There were 58(80.8%) patients who reported abdominal mass at presentation, and 17(31.7%) patients had metastatic disease. After NAC, 32(53%) were found to be inoperable (Table 1).

The remaining 28(47%) patients underwent liver resection with a mean operative time of 270±118.41 minutes. Right hemi hepatectomy was performed in 14(50%) patients and the most common histology was epithelial foetal type 16(57.1%).

Furthermore, 4(14.2%) patients decompensated postoperatively and were managed conservatively. The mean expected volume of blood loss was 216.9±182.52ml, the volume of red blood cells transfused was 106.6±104.42ml, and the mean length of hospital stay (LOS) was 8.7±2.83 days.

Following surgery, 22(78.5%) patients received adjuvant

Table-1: Demographic, clinical and radiological characteristics of the patients.

Characteristics	(n= %)
Gender	
Male	44 (73.3)
Female	16 (26.7)
Age (mean)	2.0 ± 1.54 years
Clinical Presentation	
Abdominal mass	40 (70.4)
Abdominal mass +Pain	18 (10.4)
Asymptomatic	02 (19.1)
Site of primary Tumour	
Right lobe	25 (41.7)
Left lobe	10 (16.6)
Bilateral / Central	25 (41.7)
PRETEXT Stage	
I	01 (1.7)
II	16 (26.7)
III	25 (41.7)
IV	18 (30)
Site of metastasis (n=18)	
Lung	17 (28.3)
Extra hepatic extension	01 (1.7)
Brain	01 (1.7)
Reasons for Irresectibily (n=32)	
Major vascular involvement (P + V)*	17 (28.3)
Death during treatment	10 (16.7)
Consent not given for surgery	05 (8.4)

PRETEXT: PRE-Treatment Extent of tumour, V: Hepatic vein invasion, P: Portal vain invasion.

Table-2: Surgical and oncological outcomes.

Characteristics	(n= %)
Liver resection	
Right hemihepatectomy	14 (50)
Left hemihepatectomy	12 (42 .8)
Bisegmentectomy	02 (7.1)
Histological sub-types	
Epithelial foetal	16 (57.1)
Epithelial embryonic	02 (7.1)
Mixed epithelial foetal and mesenchymal with teratoid features	01 (3.5)
Mixed epithelial foetal and mesenchymal without teratoid features	08 (28.5)
Small cell undifferentiated	01 (3.5)
Surgical margins	
Positive (RI)	06 (21.5)
Negative (R0)	22 (78.5)
Lymph node status	
Positive	10 (35.7)
Negative	18 (64.2)
Tumour Focality	
Unifocal	23 (82.1)
Multifocal (single lobe)	05 (17.8)
Oncological outcome	
Complete remission	21 (75)
Recurrence	04 (14.2)
Death	03 (10.7)
Baseline tumour size (mean ± SD) cm	10.0 ± 3.61
Post-chemotherapy tumour size (mean ± SD) cm	8.3 ± 1.92
Mean length of hospital stay (days)	8.7 ± 2.83

SD: Standard deviation.

chemotherapy, including those who had positive margins (R1) and lymph node (LN) disease, and 10(35.7%) patients underwent video-assisted thoracoscopic surgery (VATS) due to residual lung nodules. With a median follow-up of 63.5 months (IQR= 21-31.75), 21(75%) patients survived with complete remission, 4(14.2%) had disease recurrence, and 3(10.7%) died. All 4(100%) patients with recurrence received second-line chemotherapy, followed by surgery l segmentectomy in 2(7.1%) patients, VATS in 1(3.5%), and 1(3.5 %) patient was sent for palliative care due to multi-organ involvement (Table 2).

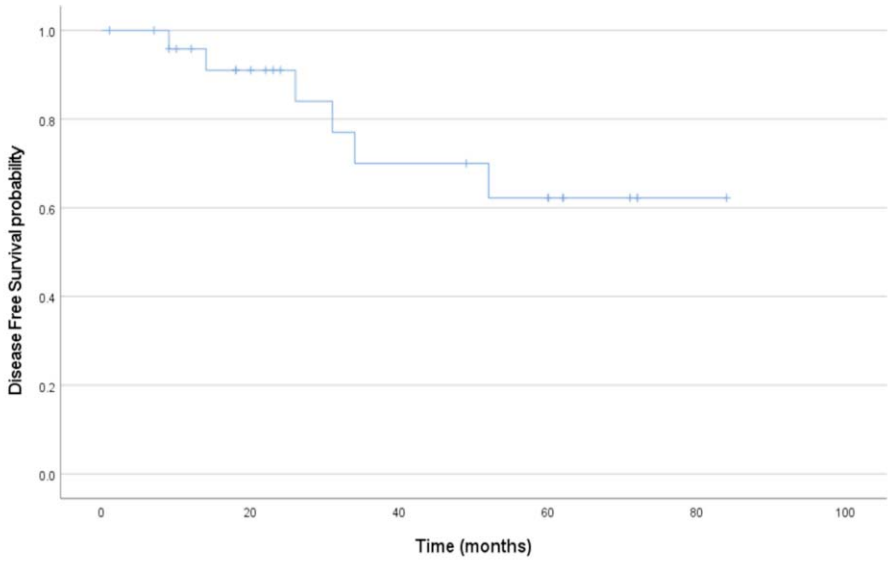

Figure-3: Disease-free survival (DFS).

Patients who had a significant response to adjuvant chemotherapy and underwent resections had better outcomes with 5-year DFS of 62%, while the 5-year OS was 82% (Figures 3-4). Factors that adversely affected patients with hepatoblastoma were delayed presentation, inoperability, poor chemotherapy response, disease progression and pulmonary metastasis, however all the factors were statistically insignificant.

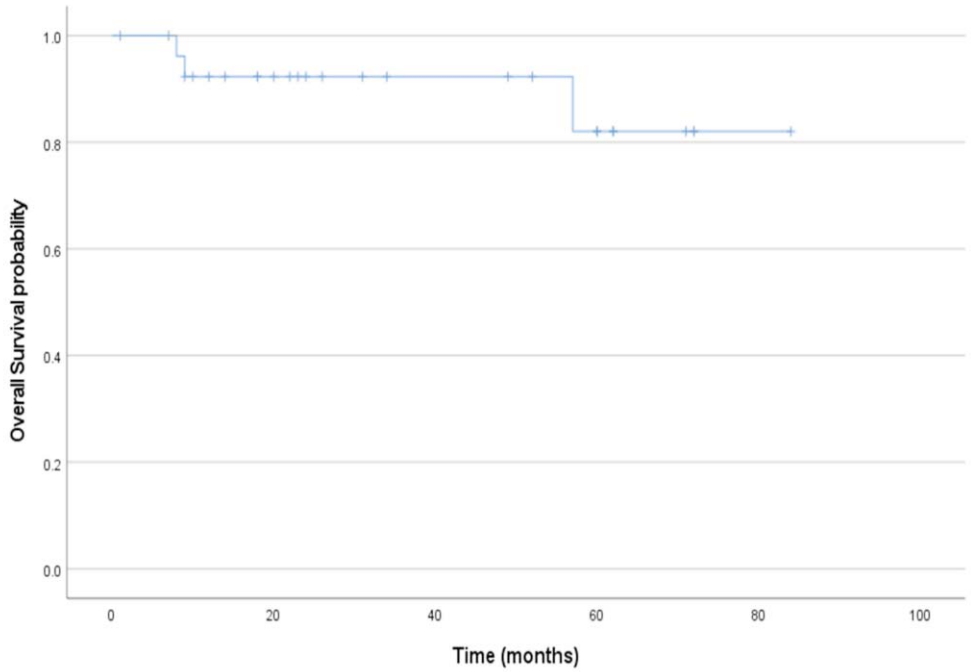

Figure-4: Overall survival (OS)

Discussion

The management of paediatric hepatoblastoma poses substantial challenges, and a multitude of factors influence survival outcomes, including clinical presentation, tumour burden, surgical approaches, and oncological treatment. Preceding epidemiological studies of paediatric hepatoblastoma have largely relied on data from the Surveillance, Epidemiology and End Results (SEER) programme and the National Cancer Institute's (NCI) surveillance that covers <30% of the United States population.[12,13] In the meantime, liver tumours only constitute 1% of childhood cancers, and the reported incidence of hepatoblastoma is >60% of paediatric hepatic malignancies in the US. SEER also reported a male-to-female ratio of 1.6,[12] but data from large trials in the US and Europe have reported a higher male-to-female ratio, ranging 1.6-3.6.[14]

A population-based registry from Taiwan on hepatoblastoma showed an age distribution in line with the SEER data, but a higher male-to-female ratio of 2.9.[15] Another Japanese cohort indicated that hepatoblastoma was more likely to develop in individuals with LBW.[16] Furthermore, evidence suggests an increased risk of hepatoblastoma associated with familial adenomatosis polypus (FAP), Beckwith-Weidemann syndrome (BWS) and hemihypertrophy, but this association is challenging to establish due to the scarcity of such tumour.[17]

The demographic features of the patients in SIOPEL are also comparable with the literature related to the incidence in younger age, and male predominance with elevated biomarkers, like AFP levels and thrombocytosis.[18] The current study had 60 patients treated based on a standardised SIOPEL protocol. Comparable to the SIOPEL study, the current patients also reflected a male predominance (73.3%) and a mean age of 2.0±1.54 years with raised AFP levels and predominantly right lobe involvement.[18]

In contrast to the SIOPEL, where the majority of children presented with a PRETEXT stage II, the current subset presented most with PRETEXT III (41.7%). Overall, 32 tumours were unresectable, and 17(28.3%) of them had major vascular involvement, 10(16.7%) could not survive chemotherapy, and 5(8.4%) children's guardians did not give consent for treatment.

In literature, merely 30% of hepatoblastoma patients were amenable to primary surgical resection. However, the contemporary utilisation of cutting-edge imaging modalities and refined surgical approaches suggests that the success rate now hovers at an estimated 50%. This implies that, at the point of diagnosis, 50% of the tumours remain categorised as unresectable. However, half of these malignancies can be rendered resectable through the application of contemporary pre-operative chemotherapy. This notable progress in tumours can be primarily attributed to the favourable response to systemic chemotherapy, which effectively diminishes tumour volume. In essence, this advancement signifies that ultimately, a total of 75% of all tumours can be surgically excised.[19]

Advanced disease with disseminated unresectable metastasis which does not respond to chemotherapy, progression of disease whilst on chemotherapy, vascular invasion, vascular malformation at portal triad, and multiple satellite lesions are a few of the factors reported in the literature that categorise hepatoblastoma as unresectable.[20]

Other factors associated with poor prognosis reported in the literature include age >3 years at diagnosis, and metastatic disease.[21] In a recent hepatoblastoma patients within the SIOPEL and other networks were analysed to categorise patients into risk groups as per the various defining characteristics.[18,22] The findings revealed that metastatic disease, as well as advanced age at diagnosis (8 years or older for PRETEXT I-III and 3 years or older for PRETEXT IV), were identified as factors that lead to less favourable outcomes, irrespective of the PRETEXT staging.[18]

A potential explanation for the poorer outcomes observed in older children diagnosed with hepatoblastoma could be attributed to the tendency among these older subjects to exhibit mixed hepatocellular carcinoma-hepatoblastoma histology which holds for the adult population.[22] Nevertheless, the current sample showed 8 patients with mixed epithelial foetal and mesenchymal without teratoid features, and only 1 patient had mixed epithelial foetal and mesenchymal teratoid features.

There were 28 children who underwent liver resection after cisplatin-based chemotherapy as per the SIOPEL protocol[11] followed by adjuvant treatment in the current cohort. Moreover, it often has been observed that chemotherapy helps in the down-staging of tumours, making them more solid, easier to handle, and with reduced bleeding. Subsequently, dissection/excision of the tumour becomes more feasible in a well-demarcated lesion from the surrounding liver parenchyma.[23] The tumours in the current sample responded to chemotherapy with an interval decrease in size from 10.0±3.61cm to 8.3±1.92 cm. In the SIOPEL trial where patients treated with delayed surgery and chemotherapy had a median size of tumour 6.8cm at diagnosis, exact change in dimensions was not reported except a holistic down-staging of 28% (32/115) patients which referred to metastatic as well as local PRETEXT.[18]

Unifocal, foetal epithelial-type tumours were predominant. We were able to achieve negative margins in 22(78.5%) patients compared to 87% of patients in the SIOPEL trial.[18] This highlights the fact that modern treatment strategies with NAC have dramatically improved the resection rate.

With the median follow-up of 63.5 months, 75% patients were in complete remission, and only 3 children succumbed to death. The SIOPEL trial reported a 13% overall mortality with surgical mortality of 5%. An American study showed a 5-year survival of 77% which is comparable to the current finding, and a 90-day mortality of 3.1%.[24,25]

The current study is one of the few from lower- and middle-income countries (LMICs), like Pakistan, that have detailed analysis of variables and prognostic factors for a rare tumour, and its impact on survival outcomes. The current study also has several limitations. Its retrospective design meant poor clinical controls and objectivity. Besides, it was conducted at a single centre with a small sample size based on readily accessible medical records.

Conclusion

Survival outcomes of hepatoblastoma patients who underwent liver resections were favourable. NAC had a significant effect on tumour size. However, late presentation, tumour burden, and abandonment of treatment were common findings that had a negative impact on survival outcomes.

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Conflict of Interest: None.

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AUTHOR'S CONTRIBUTION:
SA: Concept, design, data acquisition, analysis, interpretation, drafting, revision, review and final approval.
UA & MAS: Data acquisition, analysis, interpretation, review and final approval.
AMS: Drafting, revision, review and final approval.
TL: Concept, design, review and final approval.