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REVIEW ARTICLE

Management of Hepatoblastoma: ICMR Consensus Document

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Abstract Dramatic advancement has been made in the management of children with hepatoblastoma (HB) over the past 3 decades owing to the improvement in diagnostic imaging, new chemotherapeutic agents, better surgical care and availability of liver transplantation. These advances are the end results of contributions from 4 major study groups across the globe including International Society of Pediatric Oncology – Liver Tumor Strategy Group (SIOPEL), Children's Oncology Group (COG), German Pediatric Hematology Oncology Group (GPOH) and Japanese Pediatric Liver Tumor Study Group (JPLT). The current manuscript is written with the objective of developing a consensus guideline for practitioners at a National level. Based on literature and personal experience over last 3 decades, the Indian Council of Medical Research (ICMR) Expert group has made recommendations for management of children with HB in resource-challenged nations including India.

Keywords Hepatoblastoma · Diagnosis · Treatment · Indian context

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Introduction

The current manuscript is written with the objective of developing a consensus guideline for practitioners at a National level.

This document on consensus guidelines for management of Hepatoblastoma was arrived at after an initial round of meetings with National experts in the field of Pediatric Hematology Oncology. Thereafter, an exhaustive review of literature of National and International data was undertaken and the manuscript was drafted. This was then presented in a second round meeting with the experts till a final consensus was obtained after mutiple rounds of discussion. The final consensus document was once again sent to all the authors for proofing and then submitted.

In the past three decades, availability of highly effective chemotherapeutic agents, better understanding of the surgical anatomy of liver, better anaesthetic and post-operative care and the availability of liver transplantation (LTx) for patients with hepatoblastoma (HB) has improved outcome in these children dramatically. However, in developing countries including India, many children present late. Associated co-morbidities

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including malnutrition further compromise treatment outcomes. To overcome these issues, an attempt has been made by the International Society of Pediatric Oncology – Liver Tumor Strategy (SIOPEL) group (SIOPEL-RCN, described later) to cater to the needs of resource-challenged nations (RCN).

Existing Guidelines

The existing guidelines are based on the recommendations of one of the following cooperative groups:

- International Society of Pediatric Oncology – Liver Tumor Strategy Group (SIOPEL)
- Children's Oncology Group (COG)
- German Pediatric Hematology Oncology Group (GPOH)
- Japanese Pediatric Liver Tumor Study Group (JPLT)

SIOPEL guidelines for staging, diagnostic work-up and management are the ones that are most extensively followed. Within SIOPEL, a SIOPEL-RCN group has been formed with the aim of providing simple, effective and affordable treatment to children with HB in RCN and to offer an easy data collection system [1]. International group CHIC (Children's Hepatic Tumors International Collaboration) has incorporated data into a common database, which now includes the retrospective data of all children treated in eight separate multicenter HB trials performed between 1985 and 2008 (1605 patients) [2–11].

Staging

COG Staging System (Table 1) is a surgico-pathologic staging (post-operative) while SIOPEL system (PRETEXT grouping and risk based staging) (Table 2) is a pre-operative system based on radiological assessment. The GPOH and JPLT have been using the SIOPEL system for several years. The COG is utilizing the SIOPEL system for defining patients who should be taken up for upfront resection. *PRETEXT Staging System* is based exclusively on imaging at diagnosis and, thus, before (surgical) therapy, divides the liver into four parts called sectors. The left lobe of the liver consists of a lateral (Couinaud segments 2 and 3) and medial sector (segment 4), whereas the right lobe is divided into anterior (segments 5 and 8) and posterior sectors (segments 6 and 7) [12]. Couinaud segment 1 is identical with the caudate lobe and is not included in this division. Over the years, the PRETEXT staging system has proven to be prognostically highly relevant. It has proven to be useful not only for risk stratification but also for establishing a common language for the description of pre-operative radiological findings in patients with liver tumors and for comparison of results across various studies. **Risk stratification** for management as well as prognostication has been adopted by all the study groups as tabulated (Table 3).

Management

In the United States, the protocol of the current COG study AHEP 0731 recommends a primary resection for HB limited to PRETEXT I and II tumors with at least 1 cm of clear margin, whereas those tumors with larger extension (PRETEXT III, IV), vascular invasion or distant metastases are treated with neo-adjuvant chemotherapy. The result of primary surgery determines the tumor stage according to the COG system. All patients are treated with adjuvant chemotherapy except patients with a completely resected (Stage I) HB with pure fetal histology. Thus, the COG study AHEP 0731 stratifies patients into four different risk groups, reducing the intensity of chemotherapy in approximately 30% of patients.

In contrast, the SIOPEL and GPOH group do not recommend upfront surgery. This is followed in Europe, South America and most of Asia-Pacific region. These recommendations are based on the response rate of approximately 90% for these tumors to neo-adjuvant therapy, which not only makes them smaller and less risky to resect but potentially can also suppress occult micro-metastases without delay. Finally, the GPOH group observed that hepatic surgery alone with induction of liver regeneration may also promote the growth of residual tumor and metastases not pre-treated with chemotherapy by secretion of so-called liver growth factors [13]. Therefore, neo-adjuvant chemotherapy is recommended for more or less all HB.

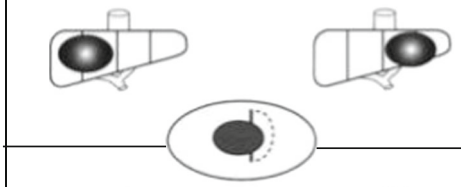
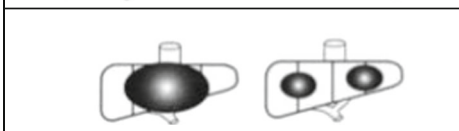
Chemotherapy

The evolution of various chemotherapy regimens for the treatment of HB has been governed by differing

Table 1 COG staging system (Evans' staging) [2]

Stage I	Complete gross resection at diagnosis with clear margins
Stage II	Complete gross resection at diagnosis with microscopic residue at margins of resection
Stage III	Biopsy only at diagnosis
	Gross total resection with lymph nodal positivity
	Pre-operative tumor spillage or rupture
	Incomplete resection with gross residue
Stage IV	Distant metastatic disease at diagnosis

Table 2 PRETEXT staging system (sectoral involvement) [3]

PRETEXT staging system		
	PRETEXT I	Three adjoining sectors free of tumor
	PRETEXT II	Two adjoining sectors free of tumor
	PRETEXT III	Only one sector free of tumor
	PRETEXT IV	All sectors involved (none free)
In addition any group may have the following additional criteria: + V: Ingrowth into venacaval or all three hepatic veins involved + P: Ingrowth into portal vein, portal bifurcation involved + E: Extrahepatic contiguous tumor + C: Involvement of caudate lobe + M: Distant metastases + N: Nodal involvement + H: Tumor rupture		

principles over time. The identification and development of new prognostic stratifications has led to novel treatments for high-risk patients and treatment reduction for low-risk patients, who do not need therapy intensification but need to avoid the delayed effects and unnecessary toxicities associated with treatment. That HB is a chemosensitive tumor was realised in the early 1970's when good response was observed to a combination of cyclophosphamide, vincristine, 5-fluorouracil and actinomycin-D [14]. Introduction of cisplatin and doxorubicin containing regimens in the 1980's had a major impact on survival. Over 30 y later, cisplatin still remains the backbone of chemotherapy regimens [15, 16]. Doxorubicin is the second most commonly administered agent. Table 4 tabulates the current chemotherapy recommendations of the various HB study groups. The current COG trial AHEP 0731 is testing whether a reduction in therapy from 4 to 2 cycles can maintain the excellent outcome with less acute toxicity and lower cost. The COG 9645 used observation alone for the upfront resected tumors with pure fetal histology. An event free survival (EFS) and overall survival (OS) of 100% was seen for this sub-group and hence it was concluded that surgical resection alone with follow-up was sufficient treatment for this group, thereby avoiding the chemotherapy-related morbidity [17]. In contrast, tumors with small cell undifferentiated histology (SCUD) had worse outcomes and warranted intensive chemotherapy regimen.

In the SIOPEL-3 study, high-risk patients received cisplatin alternating with carboplatin/doxorubicin for a total of 10 cycles [18]. Patients with standard-risk HB were randomized to receive cisplatin alone *vs*. cisplatin/doxorubicin [4]. Three-year EFS for both these random groups was similar at 83% *vs*. 85%. Hence, it is now recommended to use cisplatin monotherapy for those with standard-risk with less potential for side effects, particularly ototoxicity. Sodium thiosulfate has demonstrated otoprotective effects, as well as potential tumor protective effects, and is being studied in the SIOPEL-6 trial and in a COG trial for several solid tumor types treated with cisplatin.

Surgery

Complete surgical resection provides the only realistic chance of long-term disease-free survival in children with HB, yet

Table 3 Current risk stratification systems of different study groups

Study group	Risk group	
COG	Very low-risk	Stage I, PFH
	Low-risk	Stage I, non PFH/non SCU
		Stage II, non SCU
	Intermediate-risk	Stage I/II + SCU
		Stage III
	High-risk	Stage IV
		Any stage + αFP < 100 ng/ml
SIOPEL/GPOH	Standard-risk	PRETEXT I/II/III + αFP > 100 ng/ml + no additional criteria
	High-risk	PRETEXT IV
		Any PRETEXT + αFP < 100 ng/ml
		Any PRETEXT + additional criteria (E,V,P,M,N,H)
JPLT	PRETEXT I, no additional criteria	
	PRETEXT II, no additional criteria	
	PRETEXT III/IV or any PRETEXT + additional criteria (E,V,P,M,H,N)	

PFH Pure fetal histology; *SCU* Small cell undifferentiated histology; *E* Extrahepatic contiguous spread; *V* Vena cava or all 3 hepatic veins involvement; *P* Portal vein bifurcation, main portal vein or both portal veins involvement; *M* Distant metastasis; *N* Positive lymph nodes; *H* Tumor rupture; *COG* Children's Oncology Group; *SIOPEL* International Society of Pediatric Oncology – Liver Tumor Strategy Group; *GPOH* German Pediatric Hematology Oncology Group; *JPLT* Japanese Pediatric Liver Tumor Study Group; *αFP* Alpha feto protein

less than 50% of patients with HB have resectable tumors at diagnosis [19]. SIOPEL has defined complete surgical resection as - 'Total macroscopic removal of the tumor as reported by the surgeon and pathologist'. SIOPEL advocates at least 4 courses of neo-adjuvant chemotherapy followed by re-assessment of tumor extent and delayed resection/LTx.

COG (AHEP-0731) recommended surgical guidelines:

1. Lobectomy or segmentectomy at diagnosis for PRETEXT I and II if a margin-free resection is anticipated. If not, percutaneous, laparoscopic, or open biopsy is performed.

Table 4 Current chemotherapy recommendations for the HB study groups

Study group	Risk group	Neo-adjuvant chemotherapy	Adjuvant chemotherapy
COG	Very low-risk	Nil	Nil
	Low-risk	Nil	C5V × 2
	Intermediate-risk	C5V-Doxo × 4–6	C5V-Doxo × 2
	High-risk	VCR-Irino × 2 + C5V-Doxo × 6	
SIOPEL	Standard-risk	CDDP × 4	CDDP × 2
	High-risk	CDDP × 4 alternating with Carbo/Doxo × 3	CDDP × 1 alternating with Carbo/Doxo × 2
GPOH	Standard-risk	PLADO × 2–3 or IPA	PLADO × 1
	High-risk	CDDP × 4 alternating with Carbo/Doxo × 3 or Carbo/Etoposide	CDDP × 1 alternating with Carbo/Doxo × 2
JPLT	PRETEXT I	–	CITA × 4 (50% dose)
	PRETEXT II	CITA × 2	CITA × 4 (50% dose)
	PRETEXT III/IV or EVPH+	CITA × 4	CITA × 2
	M+	CITA × 4 + high dose Etoposide/ Carbo/Melphalan +/− HACE	CITA × 2

C5V Cisplatin + 5-fluorouracil + vincristine; *CDDP* Cisplatin; *Carbo* Carboplatin; *Doxo* Doxorubicin; *PLADO* Cisplatin + doxorubicin; *CITA* Cisplatin + pirarubicin; *EVPHM E*xtrahepatic/venous involvement/portal vein invasion/tumor rupture/metastasis; *IPA* Ifosphamide/cisplatin/doxorubicin; *HACE* Hepatic artery chemo-embolisation; *COG* Children's Oncology Group; *SIOPEL* International Society of Pediatric Oncology – Liver Tumor Strategy Group; *GPOH* German Pediatric Hematology Oncology Group; *JPLT* Japanese Pediatric Liver Tumor Study Group; *VCR* Vincristine; *Irino* Irinotecan

2. Lobectomy or trisegmentectomy after neo-adjuvant chemotherapy for POST-TEXT II or III which do not have macroscopic venous involvement.
3. Extreme/complex resection or LTx after neo-adjuvant chemotherapy for POST-TEXT III with macroscopic venous involvement or POST-TEXT IV. Only in the setting of an experienced surgical liver team with transplant capability should the decision to perform an extreme/complex resection rather than a LTx be made [20–22].

Incomplete tumor resection and macroscopic tumor residual has been associated with a worse outcome. If a resection free margin obtained safely and without danger to the inflow/outflow vasculature cannot be anticipated with a high degree of confidence, LTx is preferred. Atypical, non-anatomic or wedge resections are not recommended. Adding additional chemotherapy or alternate chemotherapy if also, usually is of no use.

Role of Liver Transplantation

Recently, the study groups COG, SIOPEL, and GPOH have developed common guidelines for LTx in HB [23–25]. These indications are:-

1. Multifocal HB in all 4 liver sectors (PRETEXT IV)
2. Patients with solitary PRETEXT IV HB that are not clearly down staged to PRETEXT III
3. HB with portal vein involvement
4. HB with involvement of all 3 hepatic veins (V3)
5. Central HB (if a conventional resection does not seem feasible)

General indications for referral to a centre for LTx also include (1) insufficient tumor regression after a variable number of cycles of neo-adjuvant chemotherapy to render the tumor resectable as determined by imaging; (2) attempted unsuccessful resection by a surgeon; or (3) recurrence in the native liver after initial resection. Pulmonary extension of disease at time of initial diagnosis is not a contraindication for LTx as long as it is considered resolved with either surgical resection or chemotherapy before transplant.

Rescue LTx for recurrent HB after previous resection has a poor survival outcome. In one series, children who received these so called “rescue transplants” had a 1-year survival rate of only 25% compared with 90% survival in those whose hepatectomy and transplant constituted the first hepatic resection. To learn more about children with LTx for liver tumors, an international electronic registry, the Pediatric Liver Unresectable Tumor Observatory (PLUTO) has been established, which collects detailed clinical data of these patients [26].

Surgery for Lung Metastases

Recent data confirm that in patients with HB presenting with initial lung metastases and locally resectable hepatic tumor, reasonable survival can be achieved with cisplatin-based chemotherapy and aggressive surgery of the metastatic lesions [27]. Lung metastases generally respond sufficiently to initial chemotherapy leading in most cases to complete disappearance of the lung disease. In few cases, however, some residual disease remains visible in the lungs making surgical removal necessary. When metastatic tumors become refractory to chemotherapy, their active removal should be attempted, rather than administration of further chemotherapy. Subsequent to successful pulmonary metastectomy, hepatic tumor resection must be completed.

There is no clear limit to the number of metastases that is reasonable and justified to attempt to resect. Despite adequate imaging, manual lung palpation is indispensable for detection of metastases during the operation. Not infrequently, the number of metastases detected manually can be higher than shown by imaging studies and therefore, open thoracotomy is preferred over thoracoscopic approach. Wedge resection is a preferred technique for the removal of pulmonary deposits.

Alternative Therapies

The most promising alternative approach is hepatic artery chemoembolization (HACE, also called transarterial chemoembolization—TACE). Most of the liver (75–80%) derives its supply from the portal vein whereas the tumor derives its supply from the hepatic artery. The dual blood supply of liver makes it an appropriate site for intra-arterial drug treatment. Different cytotoxic drugs, mostly cisplatin and doxorubicin, have been mixed either with water-soluble radiographic contrast media or with ethiodized oil (Lipoidol). The procedure is completed by embolization of the feeding arteries of the tumor with gelatine foam or stainless steel coils. The rate of complications is substantial with pain, nausea, and fever in most patients, sometimes tumor lysis syndrome or lipoidol embolization into the lungs, which may be fatal. Taken together, indications for HACE would be:-

1. To increase resectability in tumors which remain unresectable even after neo-adjuvant chemotherapy, thereby decreasing need for LTx.
2. As a bridge to LTx.
3. Palliation in unresectable tumors in children who are unfit as LTx candidates.

Percutaneous tumor ablation with radiofrequency, ethanol injection, cryoablation, laser or microwave ablation, which are commonly applied in adults, are rarely indicated for HB.

Outcomes

Outcomes of children with HB in India were analysed in a comprehensive review of the published literature (Table 5) [28]. Tata Memorial Hospital, Mumbai reported on their experience with 18 patients giving a resectability rate of 88.8% and disease-free survival of 67% [29]. Similar report from Kidwai Memorial Institute of Oncology, Bengaluru, on their experience with 12 cases, reported a resection rate of 75% and a survival rate of 100% for all those who underwent resection [30]. The experience at AIIMS, New Delhi, on 36 children showed that 83.3% could undergo resection with the overall survival among PRETEXT II, III & IV stages being 82.6%, 42.9% and 16.7% respectively. The 5 year OS and EFS for standard-risk HB was 85% and 80% and that for high-risk was 37.5% and 20% respectively [31].

Table 5 Outcomes of various International cooperative trials

	No. of patients	Stage	Survival rate
SIOPEL-1 (3-y EFS)[34]	6	PRETEXT I	100
	52	PRETEXT II	83
	45	PRETEXT III	56
	39	PRETEXT IV	46
	31	Metastatic disease	28
SIOPEL-2 (3-y EFS)[7]	6/36/25	PRETEXT I/II/III	73
	21	PRETEXT IV	48
	25	Metastatic disease	36
SIOPEL-3 (3-y EFS) [4, 19]	126	Standard-risk	83
	129	High-risk	65
	70	Metastatic	57
SIOPEL-4 (3-y EFS)[35]	61	High-risk	76
GPOH HB-89 (3-y EFS) [36]	21	I	100
	6	II	50
	38	III	71
	7	IV	29
GPOH HB-94 (4-y EFS) [8]	27	I	89
	3	II	100
	25	III	68
	14	IV	21
GPOH HB-99 (3-y EFS) [37]	58	Standard-risk	90
	42	High-risk	52
COG INT-0098 (4-y EFS) [2]	26	I/II	88
	45	III	60
	21	IV	14
COG P9645 [38]	55	I/II	84
	38	III	63
	10	IV	50
JPLT-1 (5-y OS) [6]	9	I	100
	32	II	76
	48	IIIa	50
	25	IIIb	64
	20	IV	77
JPLT-2 (5-y OS) [5]	95	I	100
	95	II	89
	100	III	93
	48	IV	63
	46	Metastatic disease	32

COG Children's Oncology Group; *SIOPEL* International Society of Pediatric Oncology – Liver Tumor Strategy Group; *GPOH* German Pediatric Hematology Oncology Group; *HB* Hepatoblastoma; *JPLT* Japanese Pediatric Liver Tumor Study Group; *EFS* Event free survival; *OS* Overall survival

Recurrent Disease

Very little definitive data exist regarding treatment for relapsed HB. The SIOPEL group have segregated their data on children with relapsed HB (defined as recurrence after complete remission with normal αFP values for at least 4 wk after completion of treatment) from SIOPEL 1, 2 & 3 studies [2]. Out of a total of 695 children, 59 had recurrent disease (8.4%). The median time from the initial diagnosis to relapse was 12 mo. The site of relapse was most commonly lung followed by liver, both liver and lung and others. All but 9 patients had an αFP level > 10 ng/ml at the time of relapse. Overall, 52% achieved a second remission. Three-year EFS and OS were 34% and 43% respectively. The best available data indicate that doxorubicin, if not given during initial treatment, and irinotecan are the most active agents in recurrent HB. A multi-centre, prospective, phase II trial of SIOPEL group evaluated the clinical activity of irinotecan as single drug in children with refractory or recurrent HB [32]. In 30% of the patients, a tumor free status was achieved. Patients with recurrent disease had a better response rate than those with refractory/progressive disease. No patients with low αFP level showed response.

Recommendations of the ICMR Expert Group

Laboratory Evaluation

Appropriate laboratory evaluation for suspected HB includes total blood counts, liver function tests, and αFP. Several investigators have shown that most HB's with low αFP levels (<100 ng/ml) are aggressive and associated with a poor prognosis. In neonates, the interpretation of αFP measurements is more difficult because of the naturally high serum levels in infants (Table 6) [33]. αFP is used in disease monitoring to identify poor treatment responders, relapse, or metastatic disease, indicating the need for change in treatment strategy.

Table 6 αFP values in normal term babies [33]

Age (in months)	Mean αFP (ng/ml)	αFP (95% range) (ng/ml)
0	41,687	9120–190,546
1	36,391	7943–165,959
2	31,769	6950–144,544
3	27,733	6026–125,893
4	24,210	5297–109,648
5	21,135	4624–96,605
6	18,450	4037–84,334
7	16,107	3524–73,621
18–14	9333	1480–58,887
15–21	3631	575–22,910
22–28	1396	316–6310
29–45	417	30–5754
46–60	178	16–1995
61–90	80	6–1045
91–120	36	3–417
121–150	20	2–216
151–180	13	1,25–129
181–720	8	0.8–87

Imaging

Abdominal ultrasound is the technique of choice as the initial diagnostic modality for suspected liver tumors. Contrast enhanced computed tomography (CECT) of the chest and abdomen is essential for the evaluation of pulmonary metastases and can further assess the primary liver tumor and the lymph node status. Here, a triple phase CECT with intravenous contrast that can assess arterial, venous, and portal systems is the radiological investigation of choice today. The value of FDG-PET/CT (fluorodeoxyglucose-positron emission tomography/computed tomography) in diagnosis and staging of childhood liver tumors is not yet established.

Tumor Biopsy

For histologic confirmation of the diagnosis, a core needle biopsy or Fine-needle aspiration cytology (FNAC) is usually performed. Children 6 mo to 3 y of age with a highly elevated serum-αFP (>1000 ng/ml) are typically diagnosed based on radiology and a raised αFP and treated as HB [13] without a histological diagnosis.

Chemotherapy

Definite advantages of neo-adjuvant chemotherapy, especially in the Indian context, where the tumor burden is high, lead us to recommend neo-adjuvant chemotherapy for all patients of HB. Either the well established SIOPEL-3 guidelines for chemotherapy or the COG guidelines could be followed. The recommendation is for cisplatin monotherapy 3-weekly for standard-risk (SR) and PLADO (cis**pla**tin + **do**xorubicin) 3-weekly for HR HB (high risk hepatoblastoma) (Fig. 1). However, centres may opt for super PLADO for HR HB. All patients are recommended to get atleast 4 courses of neo-adjuvant chemotherapy. The SIOPEL recommendation for administration of cisplatin is as 80 mg/m^2 continuous infusion over 24 h when given as monotherapy or as a part of PLADO. However, several centres in India have been administering 25 mg/m^2 daily for 3 consecutive days, as a 6 h infusion every day in daycare uneventfully. The administration of doxorubicin is as continuous infusion of 60 mg/m^2 over 48 h (according to SIOPEL). This has instead been done as a one to six hour infusion daily of 20 mg/m^2 for consecutive 3 d in many centres. In sick, malnourished patients, even with HR HB, the first course can be of cisplatin monotherapy instead of PLADO. If the patient tolerates the therapy, the general condition is likely to improve and the subsequent courses could then include doxorubicin as well.

Response Evaluation

This should be done during neo-adjuvant chemotherapy with αFP monitoring in conjunction with the age-related nomogram available (Table 6) [33]. Inadequate response may help upgrading from monotherapy to PLADO. Response evaluation by imaging is recommended with ultrasound of the abdomen following 2 courses of neo-adjuvant chemotherapy. Mild rise in αFP is sometimes observed with the onset of chemotherapy and is not to be mistaken for progression. Major increase in αFP, no decrease in tumor size on CT is taken as inadequate response. The ultrasound should look for reduction in tumor volume, status of inferior vena cava (IVC) or portal vein, particularly if these were involved earlier. Immediate pre-operative evaluation should include serum αFP level, triple phase CECT of the chest and abdomen to clearly delineate the extent of resection required and the vascular anatomy, echocardiography to evaluate the cardiac function, complete blood counts, prothrombin time, liver and renal function tests.

Surgery

An anatomical surgical resection is recommended in all cases of HB. Non-anatomical resections should be avoided. If anatomical resection is not feasible, one must consider the possibility of LTx. Patients with pulmonary metastases at the end of 4 courses of neo-adjuvant chemotherapy should undergo resection of these pulmonary metastases before liver resection is undertaken. Liver resection is only useful if the patient achieves a CR (complete remission) at the end of the surgical treatment.

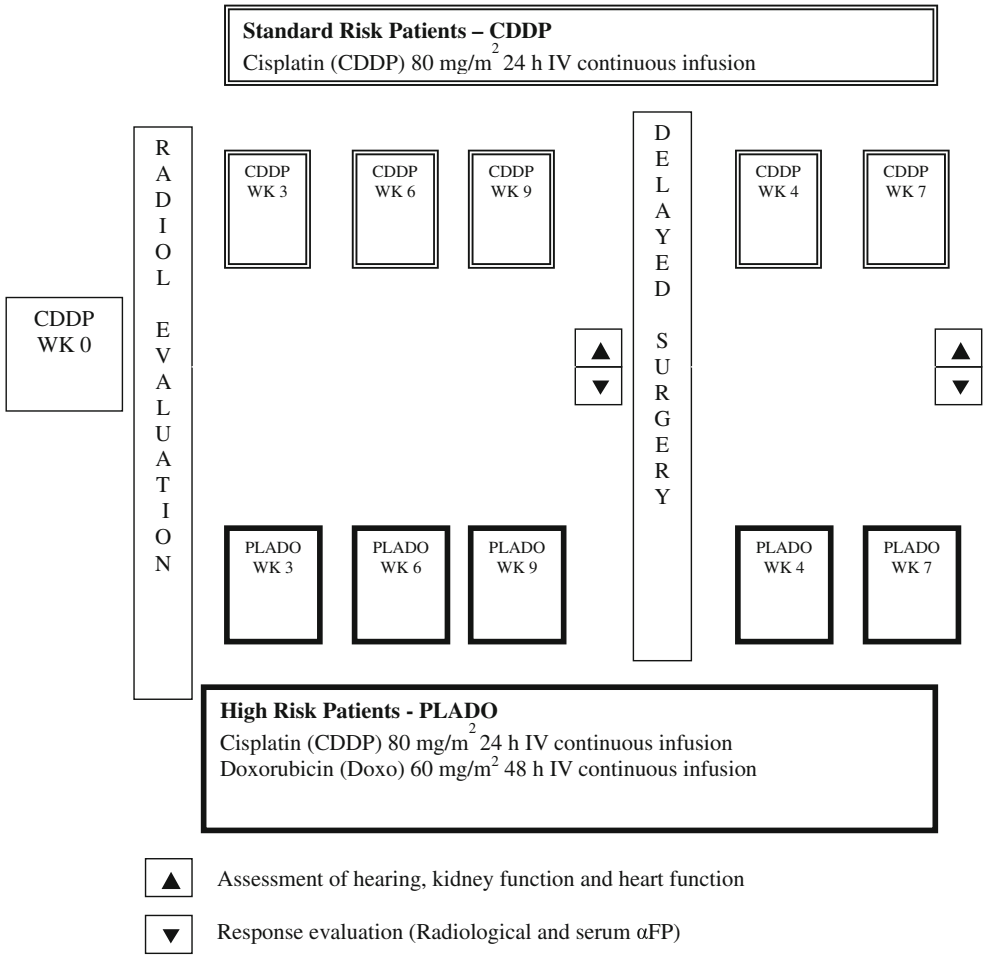


Fig. 1 Chemotherapy plan: • Week 0: This could either be PLADO or CDDP alone (even for HR HB). • PLADO: Administration could be changed to daily administration of 25 mg/m^2 of CDDP as IV infusion with adequate hydration over 6 h + 20 mg/m^2 of Doxo IV infusion over 1 h for 3 consecutive days. This could then be done as day care case. • Response evaluation: Every 3 weekly with serum αFP. Ultrasound evaluation (or CECT chest and abdomen) at 8th wk • Preoperative evaluation: Triple phase CECT chest and abdomen, echocardiogram, αFP, complete blood counts, prothrombin time, liver and renal function tests. • Post-operative evaluation prior to starting adjuvant wk 4 chemotherapy: CECT scan (to assess for residual disease), αFP, complete blood counts, liver and renal function tests. *PLADO* Cisplatin+doxorubicin; *HR HB* High risk hepatoblastoma

Radiotherapy

Radiotherapy has very little defined role in the management of HB. However, some centres have occasionally used adjuvant RT in cases with positive surgical margins. It has also been described for non-responsive unresectable HB.

Follow-Up

The follow-up (FU) protocol, subsequent to completion of all treatment, should include monthly αFP for the first 6 mo, a CECT of chest and abdomen at 3 mo and an ultrasound abdomen at 6 mo. Subsequently, 3-monthly radiological evaluation and αFP levels for at least 1 y. It is important to evaluate the chest as most of the recurrences take place in the lungs (besides the local recurrences). After the first year of FU, the frequency of these evaluations should be reduced to 6-monthly intervals for at least 2 more years and then annually. The survivors should also be evaluated for long term adverse effects such as ototoxicity by pure tone audiometry, nephrotoxicity by a radio-nuclide glomerular filtration rate (GFR) estimation, and cardiotoxicity by echocardiogram or a MUGA (Multiple gated acquisition) scan.

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Compliance with Ethical Standards

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References

1. Aronson DC, Czauderna P, Maibach R, Perilongo G, Morland B. The treatment of hepatoblastoma: its evolution and the current status as per the SIOPEL trials. J Indian Assoc Pediatr Surg. 2014;19:201–7.
2. Ortega JA, Douglass EC, Feusner JH, et al. Randomized comparison of cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: a report from the children's cancer group and the pediatric oncology group. J Clin Oncol. 2000;18:2665–75.
3. Pritchard J, Brown J, Shafford E, et al. Cisplatin, doxorubicin, and delayed surgery for childhood hepatoblastoma: a successful approach–results of the first prospective study of the International Society of Pediatric Oncology. J Clin Oncol. 2000;18:3819–28.
4. Perilongo G, Maibach R, Shafford E, et al. Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. N Engl J Med. 2009;361:1662–70.
5. Hishiki T, Matsunaga T, Sasaki F, et al. Outcome of hepatoblastomas treated using the Japanese study Group for Pediatric Liver Tumor (JPLT) protocol-2: report from the JPLT. Pediatr Surg Int. 2011;27:1–8.
6. Sasaki F, Matsunaga T, Iwafuchi M, et al; Japanese Study Group for Pediatric Liver Tumor. Outcome of hepatoblastoma treated with the JPLT-1 (Japanese Study Group for Pediatric Liver Tumor) Protocol-1: a report from the Japanese Study Group for Pediatric Liver Tumor. J Pediatr Surg. 2002;37:851–6.
7. Perilongo G, Shafford E, Maibach R et al. International Society of Paediatric Oncology-SIOPEL 2. Risk-adapted treatment for childhood hepatoblastoma. final report of the second study of the International Society of Paediatric Oncology-SIOPEL 2. Eur J Cancer. 2004;40:411–21.
8. Fuchs J, Rydzynski J, Von Schweinitz D, et al; Study Committee of the Cooperative Pediatric Liver Tumor Study HB 94 for the German Society for Pediatric Oncology and Hematology. Pretreatment prognostic factors and treatment results in children with hepatoblastoma: a report from the German cooperative pediatric liver tumor study HB 94. Cancer. 2002;95:172–82.
9. Häberle B, Bode U, von Schweinitz D. Differentiated treatment protocols for high- and standard-risk hepatoblastoma–an interim report of the German Liver Tumor Study HB99. Klin Padiatr. 2003;215:159–65.
10. Katzenstein HM, Rigsby C, Shaw PH, et al; Novel therapeutic approaches in the treatment of children with hepatoblastoma. J Pediatr Hematol Oncol. 2002;24:751–5.
11. Katzenstein HM, Chang KW, Krailo M, et al. Children's Oncology Group. Amifostine does not prevent platinum-induced hearing loss associated with the treatment of children with hepatoblastoma: a report of the Intergroup Hepatoblastoma Study P9645 as a part of the Children's Oncology Group. Cancer. 2009;115:5828–35.
12. Couinaud C. Liver lobes and segments: notes on the anatomical architecture and surgery of the liver. Presse Med. 1954;62:709–12.
13. von Schweinitz D. Management of liver tumors in childhood. Semin Pediatr Surg. 2006;15:17–24.
14. Evans AE, Land VJ, Newton WA, Randolph JG, Sather HN, Tefft M. Combination chemotherapy (vincristine, adriamycin, cyclophosphamide, and 5-fluorouracil) in the treatment of children with malignant hepatoma. Cancer. 1982;50:821–6.
15. Black CT, Cangir A, Choroszy M, Andrassy RJ. Marked response to preoperative high-dose cis-platinum in children with unresectable hepatoblastoma. J Pediatr Surg. 1991;26:1070–3.
16. Douglass EC, Green AA, Wrenn E, Champion J, Shipp M, Pratt CB. Effective cisplatin (DDP) based chemotherapy in the treatment of hepatoblastoma. Med Pediatr Oncol. 1985;13:187–90.
17. Malogolowkin MH, Katzenstein HM, Meyers RL, et al. Complete surgical resection is curative for children with hepatoblastoma with pure fetal histology: a report from the Children's oncology group. J Clin Oncol. 2011;29:3301–6.
18. Zsíros J, Maibach R, Shafford E, et al. Successful treatment of childhood high-risk hepatoblastoma with dose-intensive multiagent chemotherapy and surgery: final results of the SIOPEL-3HR study. J Clin Oncol. 2010;28:2584–90.
19. Katzenstein HM, London WB, Douglass EC, et al. Treatment of unresectable and metastatic hepatoblastoma: a pediatric oncology group phase II study. J Clin Oncol. 2002;20:3438–44.
20. Meyers RL, Tiao GM, Dunn SP, Langham MR Jr. Liver transplantation in the management of unresectable hepatoblastoma in children. Front Biosci (Elite Ed). 2012;4:1293–302.
21. Lautz TB, Ben-Ami T, Tantemsapya N, Gosiengfiao Y, Superina RA. Successful nontransplant resection of POST-TEXT III and IV hepatoblastoma. Cancer. 2011;117:1976–83.
22. Guérin F, Gauthier F, Martelli H, et al. Outcome of central hepatectomy for hepatoblastomas. J Pediatr Surg. 2010;45:555–63.
23. Meyers RL, Aronson DC, von Schweinitz D, et al. Pediatric liver tumors. In: Pizzo PA, Poplack DG, editors. Principles and Practice in Pediatric Oncology. Philadelphia, PA: Wolters Kluwer, Lippincott. Williams Wilkins; 2011. p. 838–60.
24. Meyers RL, Otte J-B. Liver transplantation for unresectable liver tumors in children. In: Zimmermann A, Perilongo G, Malogolowkin M, von Schweinitz D, editors. Pediatric liver tumors. Heidelberg: Springer; 2011. p. 133–52.
25. Gupta AA, Gerstle JT, Ng V, et al. Critical review of controversial issues in the management of advanced pediatric liver tumors. Pediatr Blood Cancer. 2011;56:1013–8.
26. Otte JB, Meyers R. PLUTO first report. Pediatr Transplant. 2010;14:830–5.
27. Meyers RL, Katzenstein HM, Krailo M, McGahren 3rd ED, Malogolowkin MH. Surgical resection of pulmonary metastatic lesions in children with hepatoblastoma. J Pediatr Surg. 2007;42:2050–6.
28. Arora RS. Outcomes of hepatoblastoma in the Indian context. Indian Pediatr. 2012;49:307–9.
29. Shukla PJ, Barreto SG, Qureshi SS, et al. Hepatoblastoma: a single institutional experience of 18 cases. Pediatr Surg Int. 2008;24:799–802.
30. Singh T, Satheesh CT, Appaji L, et al. Hepatoblastoma: experience from a single center. Indian J Cancer. 2010;47:314–6.
31. Agarwala S, Bakshi S, Bajpai M, et al. Validation of PRETEXT staging system and risk categorization for prognostication and outcome in hepatoblastoma- results from AIIMS-HB94 trial [abstract]. Pediatr Blood Cancer. 2007;49:401–2.
32. Zsíros J, Brugières L, Brock P, et al. Efficacy of irinotecan single drug treatment in children with refractory or recurrent hepatoblastoma–a phase II trial of the childhood liver tumour strategy group (SIOPEL). Eur J Cancer. 2012;48:3456–64.
33. Blohm ME, Vesterling-Hörner D, Calaminus G, Göbel U. Alpha 1-fetoprotein (AFP) reference values in infants up to 2 years of age. Pediatr Hematol Oncol. 1998;15:135–42.