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Original Article

Clinical and Pathological Spectrum of Hepatoblastoma with Emphasis on Treatment-Induced Changes: Experience from Tertiary Care Center

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Abstract

Introduction Hepatoblastoma is a rare pediatric liver tumor. Advances in imaging/surgical techniques and use of neoadjuvant chemotherapy (NACT) in recent times have resulted in improved survival of children with hepatoblastoma. Yet it has dismal prognosis in some children. Unlike other pediatric malignant tumors, pathological tumor regression grading in hepatoblastoma following NACT is not in routine practice. Assessing tumor-induced maturation and delineating it from non-neoplastic liver at resection margin are often challenging in this setting.

Objective We aim to describe the clinicopathological spectrum of hepatoblastoma encountered in our center with emphasis on exploring the role of grading the therapy-induced changes by correlating with existing prognostic factors and patient survival.

Materials and Methods All cases of hepatoblastoma having undergone resection after NACT over 9 years were included. Pathology slides (hematoxylin and eosin/immunohistochemistry) were reviewed. Therapy-related changes were scored and compared with pretreatment extent (PRETEXT)/posttreatment extent (POSTTEXT) staging, alpha fetoprotein (AFP) levels, and patient survival.

Results A total of 15 children diagnosed with hepatoblastoma were included in the study. The median age of diagnosis was 10 months. PRETEXT III was the commonest stage and fetal variant was the commonest histological subtype. Fibrosis, necrosis, maturation, calcification, and ductular reaction were the therapy-induced changes encountered in 93, 80, 60, 53 and 33% cases, respectively. Higher percentage of therapy-induced changes was associated with good prognosis and better survival. Glypican-3 positivity delineated tumor-induced maturation from the non-neoplastic liver.

Keywords
- hepatoblastoma
- child
- liver neoplasm
- neoadjuvant therapy
- immunohistoche–mistry
- prognosis

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Conclusion This study describes the spectrum of hepatoblastoma at a single center and emphasizes that grading therapy-induced changes may have a significant role in patient prognosis and guide further treatment interventions for effective management of patients. Glypican-3 eases microscopic assessment of resection margins in the presence of therapy-induced maturation.

Introduction

Liver malignancies account for 1% of pediatric cancers. Hepatoblastoma (HB) is the most common primary pediatric malignancy of the liver, affecting 1.5 cases per million population annually.[1] Most HBs (>90%) present with markedly elevated serum alpha-fetoprotein (AFP), which plays a major role in the diagnosis, monitoring response to therapy, and patient follow-up.[2] Complete resection of the tumor is critical for cure. However, approximately 60 to 80% of these patients present with unresectable tumor at diagnosis.

Introduction of cisplatin-based neoadjuvant chemotherapy (NACT) has facilitated downsizing of tumor and greatly improved resectability and hence the survival.[3] Currently the 5-year survival rate of HB is up to 80% as compared with 30% 30 years ago.[4] Therapeutic approaches and patient management across the globe largely rely on the risk stratification by international organizations for pediatric malignancies such as Children's Oncology Group (COG), Childhood Liver Tumors Strategy Group (SIOPEL), and Children's Hepatic tumors International Collaboration (CHIC), which are largely based on radiological pretreatment extent (PRETEXT)/posttreatment extent (POSTTEXT) staging, and AFP levels at diagnosis.[5–7] Although controversial, NACT followed by surgical resection is the mainstay of treating[6] HB at most centers. Prognostication and treatment modification based on response to NACT, as adopted for other pediatric malignancies such as neuroblastoma and nephroblastoma, has not been adopted for HB. Various aspects of histological assessment of treatment-induced changes in HB are not well documented in the literature. The phenomenon of therapy-induced maturation of tumor cells in HB poses significant difficulty in accurate assessment of surgical margins.[8] A reliable marker to distinguish tumor cells from normal hepatocytes at the margins is warrantied.

Currently, the role of histological assessment and grading of therapy-induced changes as prognostic/predictive marker in HB is not well established and is not in routine practice.

In this study, we aim to describe the clinicopathological spectrum of HB encountered at our center and emphasize the role of assessing the therapy-induced changes by correlating with known prognostic factors and patient survival.

Materials and Methods

Study Design and Setting

The present study is a retrospective, descriptive study on a cohort of patients diagnosed with HB.

Children diagnosed with HB based on imaging and/or serum AFP levels and who have undergone NACT followed by surgical resection between 2011 and 2019 (9 years) were included in the study. Cases determined as non-HB on histology were excluded. Patient details such as demography, history, AFP levels (at diagnosis, postchemotherapy, postsurgery, and at last follow-up), radiological tumor size (at diagnosis and post-NACT), PRETEXT staging, chemotherapy regimen, and follow-up details were obtained from the hospital database and cancer registry. It was a time bound, retrospective study including all patients diagnosed as HB between 2010 and 2019; the sample size obtained was 15.

Pathological Assessment

Hematoxylin and eosin (H&E) and immunohistochemistry (IHC) slides of all the cases were reviewed, blinded to the original reports. Viable and nonviable areas of the tumor were scored as percentage of the total tumor tissue. Tumor regression grading (TRG) was done as follows.

- **TRG** I: greater than 75% nonviable areas.
- **TRG** II: greater than 25% and ≤75% nonviable areas.
- **TRG** III: ≤25% nonviable area.

The percentages of fibrosis, necrosis, and therapy-induced maturation seen in the tumor were scored separately. Therapy-induced calcification/ossification and ductular reaction were also noted. When no viable tumor cells were seen, it was called pathological complete regression (PCR). Viable tumor areas were classified based on morphology as fetal, embryonal, mixed fetal and embryonal, mixed epithelial and mesenchymal, teratoid, and small cell undifferentiated (SCUD). Margin clearance of less than 1 mm was considered a positive margin.

Immunohistochemistry

Hepatocellular markers, HepPar1 (OCH1E5, PathnSitu) and Arginase1 (SP156, Cell Marque); biliary markers, CK7 (OV-TL12/30, BioGenex), CK19(A53_B/A2.26, Cell Marque), along with β catenin (EP35, PathnSitu) and Glypican-3 (1G12, Cell Marque), were performed for diagnostic and prognostic evaluation. Additional neuroendocrine, mesenchymal, and stem cell markers were performed when required. Area and pattern of staining of each marker were noted carefully.

Primary Outcome

Therapy-induced changes encountered were fibrosis, necrosis, calcification/ossification, and maturation. Higher percentages of therapy-induced changes were associated with

better prognostic factors (reduction in AFP levels and radiological tumor size) and better survival.

Secondary Outcome

Glypican-3 was found to a reliable immunohistochemical marker to differentiate therapy-induced maturation of tumor cells from the non-neoplastic liver at the resection margin.

Inclusion Criteria

Children diagnosed to have HB based on imaging and/or serum AFP levels and who underwent NACT followed by surgical resection were included in the study.

Exclusion Criteria

Pediatric liver tumors other than HB and cases of HB with unavailable slides/blocks were excluded from the study.

Statistical Analysis

SPSS software version 27.0 was used for statistical analysis.

Data were described using frequency with percentage for categorical variables and means along with standard deviation for continuous variables. The date of diagnosis was considered the entry point. The date of recurrence/metastasis was the end point for disease-free survival (DFS) and the date of the last follow-up/date of death was the end point for overall survival (OS). The *t*-test was used for univariate analyses. DFS and OS were evaluated by using the Kaplan–Meier method and compared using log-rank test, and a *p*-value of $\leq$0.05 was considered significant.

For statistical analysis, the histological subtypes were categorized into four types, fetal, mixed fetal and embryonal, and pure embryonal, which were classified as the epithelial type.

Mixed epithelial and mesenchymal and teratoid were grouped into the mesenchymal type, SCUD, and PCR. Therapy-induced mature/maturing areas of the tumor were considered under fetal variant. The cutoff value was considered at 10% for fibrosis and at 30% for necrosis.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Institutional ethical committee clearance was obtained (ECASN-AIMS-2024–335, dated: July 16, 2024).

Results

Clinical Picture and Demography

Twenty children were diagnosed to have HB and underwent NACT and resection over a period of 9 years. Five children were excluded from the study as their block/slides were not traceable. Fifteen children were included, whose age ranged from 1 to 132 months (median age = 10 months). There were 10 male children and 5 male female children (M:F = 2:1). Ten children (66%) were aged $\leq$12 months, three (20%) were between 12 and 48 months, and two (13%) were older 60 months (72 and 132 months, respectively). Mass per abdomen was the most common presenting symptom (86%), followed by incidental detection in two children and congenital liver mass in one child. Two were born preterm; one had maternal family history of malignancy, the details of the cancer could not be traced. One child was born to a mother with gestational diabetes.

PRETEXT III was the most frequent PRETEXT stage (6 cases, 40%), followed by PRETEXT IV and II (4 cases, 26% each). PRETEXT I was the least common (1 case, 6%). The right lobe of the liver was involved in 8 (53%) cases, the left lobe was involved in 4 (27%) cases, the bilateral lobes was involved in 2 (13%) cases, and 1 (6%) case had multifocal involvement. Serum AFP level at diagnosis ranged from 14.93 to 1,538,000 ng/dL (median = 127,870 ng/dL) and the level after NACT ranged from 9.33 to 15,884 ng/dL (median = 405 ng/dL). There was significant reduction in the AFP levels following NACT (>99% fall in 67% of the cases, $p = 0.03$). One child with the SCUD histological variant *presented with normal AFP level* (14 ng/dL) at diagnosis, which remained within normal range throughout the treatment.

There was significant decrease in radiological size of the tumor after NACT (mean PRETEXT size = 10 cm; POSTTEXT size = 5.3 cm; $p = 0.04$). The demography and clinical and radiological features are further detailed in ►**Table 1**.

Pathological Findings

There were 9 (60%) epithelial tumors (6 pure fetal, 2 pure embryonal and 1 mixed fetal and embryonal variant; ►**Fig. 1A**), 4 (27%) mesenchymal tumors (2 teratoid and 2 mixed epithelial and mesenchymal variants; ►**Fig. 1B**), 1 pure SCUD (6%) variant, and 1 case (6%) of PCR (►**Table 2**). Of the 15 cases, 7 had pretreatment biopsies, of which 6 were epithelial (3 fetal, 2 mixed epithelial and fetal, 1 pure embryonal), and 1 SCUD type (►**Table 2**). Positive margins were seen in five (33%) cases.

Table 1 Patient demography and clinical characteristics

		n = 15	Percentage
Median age (range)	10 (1–132) mo		
Gender	Male	10	66.6
	Female	5	33.3
Symptoms	Mass per abdomen/ abdominal distension	13	86.6
	Incidental detection	2	13.3
PRETEXT stage	I	1	6.7
	II	4	26.7
	III	6	40
	IV	4	26.7
Site	Right lobe	8	53.3
	Left lobe	4	26.6
	Right + left lobe	2	13.3
	Multifocal	1	6.6

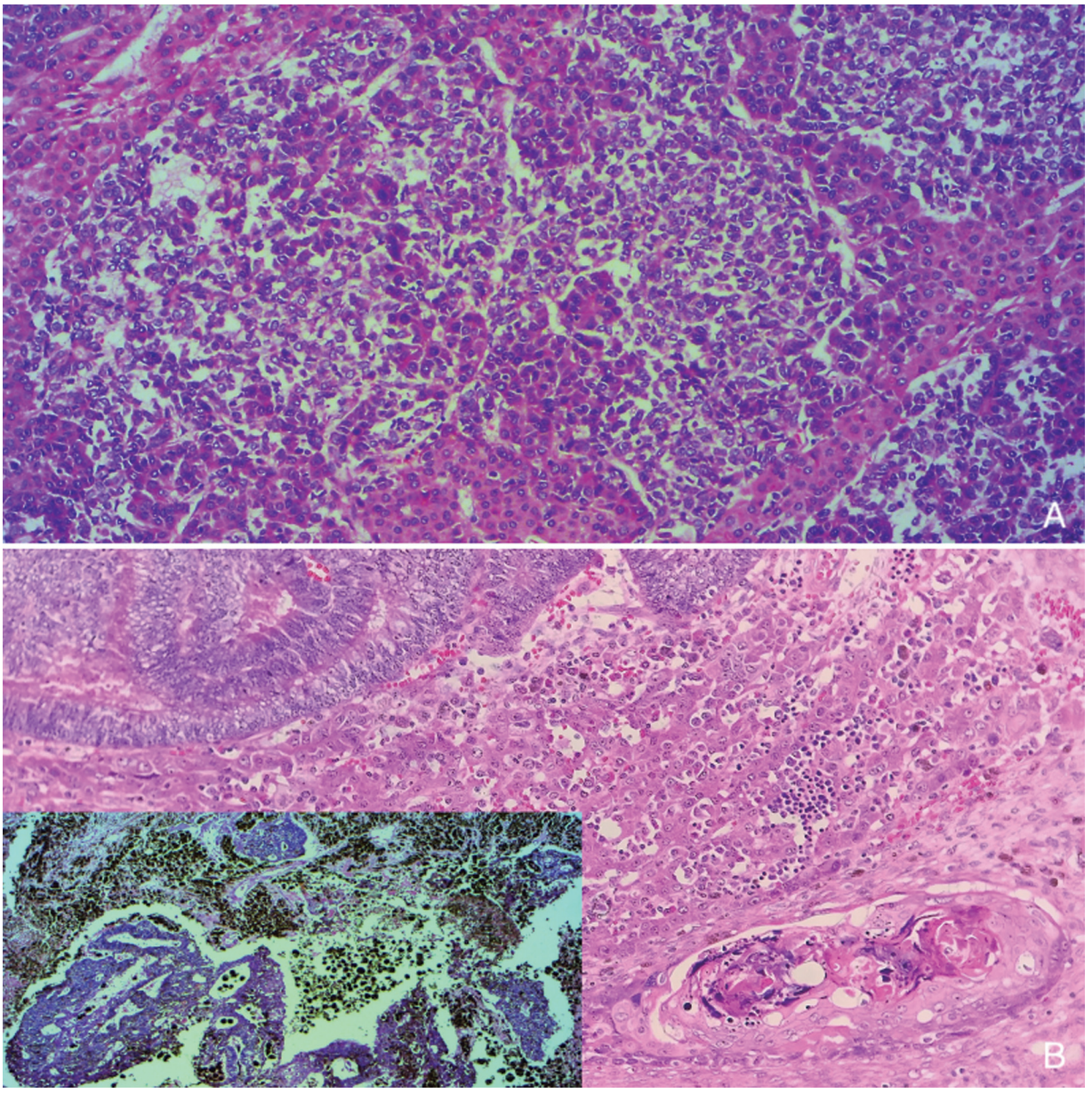

Fig. 1 Photomicrography showing (**A**) embryonal and fetal variant of hepatoblastoma (HB; hematoxylin and eosin [H&E], ×200) and (**B**) teratoid variant with squamous areas; inset showing melanin pigments (H&E, ×200).

Table 2 Distribution of histological subtype

	Prechemotherapy biopsy ($n = 7$)	Post chemotherapy excision ($n = 15$)
Embryonal	1 (14.2%)	2 (13.3%)
Fetal	3 (42.8%)	6 (40%)
Mixed epithelial and fetal	2 (28.5%)	1 (6.6%)
Mixed epithelial and mesenchymal	0	2 (13.3%)
Teratoid	0	2 (6.6%)
Small cell undifferentiated	1 (14.2%)	1 (6.6%)

Therapy-Induced Changes

Grade III tumor regression predominated in our series (53%), while TRG I was the least (20%). Fibrosis was the commonest therapy-induced change (93%), followed by necrosis (83%). Maturation, calcification/ossification (►**Fig. 2A**), and ductular reaction were other therapy-

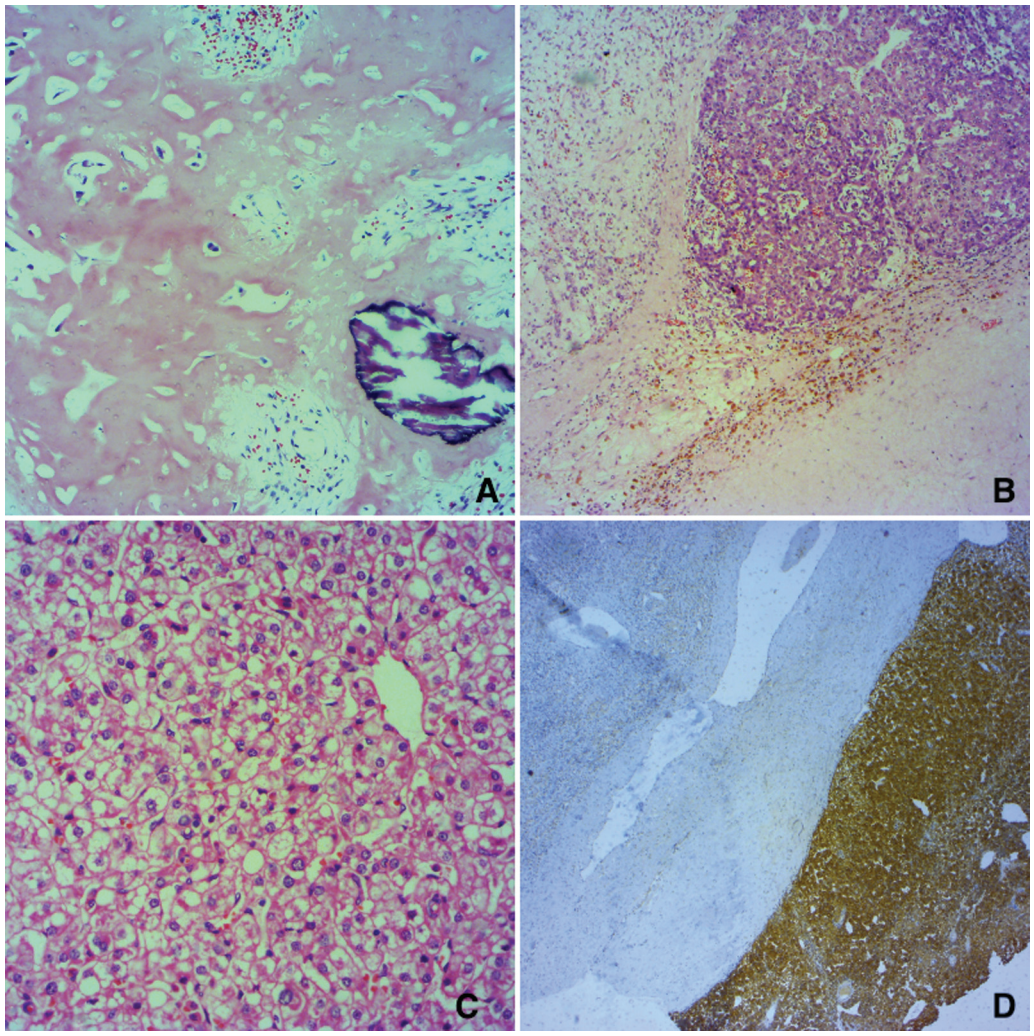

Fig. 2 Photomicrography showing neoadjuvant chemotherapy (NACT) induced changes in hepatoblastoma (HB). (**A**) Osteoid and calcification (hematoxylin and eosin [H&E], ×200). (**B**) Fibrosis with hyalinization and hemosiderin-laden macrophages (H&E, ×100). (**C**) Therapy-induced maturation (H&E, ×400). (**D**) Glypican-3 positivity in maturing areas as opposed to a normal liver (immunohistochemistry [IHC, ×25).

induced changes (60, 53, and 33% cases, respectively; ►**Table 3**).

Fibrosis ranged from zero in SCUD variant to 92% in the case of PCR (mean fibrosis = 26%; ►**Fig. 2B**). The average posttreatment AFP was higher in tumors showing less than 10% fibrosis as compared with tumors showing greater than 10% fibrosis (►**Table 4**).

Histologically, the embryonal variant showed the least amount of fibrosis. However, there was no significant difference in OS and DFS between the two groups (►**Table 5**). Therapy-induced necrosis ranged from 0 to 48% (mean necrosis = 21%). The mean posttherapy AFP level was higher in tumors showing no necrosis as compared with those showing greater than 30% necrosis (►**Table 4**). Likewise, tumors showing no necrosis had lower DFS as compared with tumors showing necrosis; the difference was not statistically significant (►**Table 5**). Therapy-induced maturation was noted in all cases with pure fetal morphology, 50% of mesenchymal type, and 40% of mixed epithelial type. SCUD showed no maturation. Mature areas were often seen at the interface of the tumor with the normal liver and closely resembled a normal liver (►**Fig. 2C**). Interestingly, therapy-induced maturation was directly related to the amount of fibrosis and inversely related to necrosis. Maturation was associated with better survival (►**Table 5**). The most common histological type showing calcification and ductular reaction was the mixed epithelial type. There was significant association of ductular reaction with fibrosis ($p = 0.017$).

Table 3 Histological assessment of therapy-induced changes

$n = 15$	Seen	Not seen
Fibrosis	14 (93.3%)	1 (6.6%)
Necrosis	12 (80%)	3 (20%)
Maturing areas	9 (60%)	6 (40%)
Calcification	8 (53.3%)	7 (46.6%)
Ductular reaction	5 (33.3%)	10 (66.6%)

Table 4 Correlation of therapy-induced changes with known prognostic factors of hepatoblastoma

Therapy-induced change	Fibrosis		Necrosis		Maturation	
Prognostic factors	≤10%	>10%	≤30%	>30%	Yes	No
Predominant histological type	Embryonal	Mesenchymal	Embryonal, mesenchymal	Fetal embryonal	Fetal	Embryonal
AFP at diagnosis (ng/mL)	100,000	370,000	280,000	380,000	270,000	240,000
Postchemotherapy AFP levels (ng/mL)	11,328	1,465	2366	370	2015	2197
Pretext	III, IV	II	III, IV	I, II	III, IV	III, IV
Age (mo)	22	28	17	71	26	23

Abbreviations: AFP, alpha-fetoprotein.

Immunohistochemistry

IHC was performed in 10 cases. β-catenin staining was seen in seven cases (membranous/nuclear). Nuclear β-catenin was seen in embryonal areas only. Membranous β-catenin was observed in the mature areas, fetal area, and non-neoplastic liver. Glypican-3 was positive in all 10 cases, with a variable staining pattern (►**Fig. 2D**). It was strongly cytoplasmic in embryonal, canalicular to moderate cytoplasmic in mature and fetal areas, focal patchy positive in SCUD areas, and negative in non-neoplastic livers.

Patient Follow-Up and Survival

OS and DFS by the Kaplan–Meier analysis was 62.54 ± 13.414 and 53.44 ± 12.603 months, respectively. Nine patients were disease free. Six patients had progression of disease in the form of recurrence in the residual liver (3 cases) and distant metastases (3 cases).

Four patients (2 embryonal, 1 mesenchymal, and 1SCUD histology) succumbed to the disease. Children younger than 3 years and female patients had better OS and DFS when compared with the children older than 3 years and males. Among *children younger than 3 years, 50% showed good response to therapy* with the tumor showing greater than 50% nonviable areas, while among *children older than 3 years, 33% showed a good response*. The difference was not statistically significant ($p = 0.60$).

Histological subtypes, PRETEXT/POSTTEXT staging, therapy-induced changes, or margin positivity showed no significant difference in survival (►**Table 5**).

Table 5 Correlation of clinical and therapy-induced pathological parameters with patient survival

Clinical and pathological parameters		Disease free survival	*p* value	Overall survival	*p* value
Age	≤36 mo	57.22 ± 14.18	0.117	60.75 ± 15.74	0.003
	>36 mo	31.00 ± 7.42		38.00 ± 12.24	
Gender	Male	30.41 ± 7.32	0.95	67.33 ± 24.22	0.95
	Female	67.00 ± 24.49		39.25 ± 6.86	
Calcification	Yes	52.94 ± 17.52	–	68.33 ± 16.56	0.83
	No	30.667 ± 9.60		38.40 ± 8.65	
Fibrosis	≤10%	51.5 ± 16.09	0.2	59.14 ± 16.55	0.2
	>10%	30.00 ± 4.97		40.00 ± 0.00	
Necrosis	0%	17.50 ± 3.18	0.13		
	0–30%	51.5 ± 16.09		–	–
	>30%	43.50 ± 7.42		–	
Maturing areas	No	34.05 ± 8.00	0.09	46.50 ± 4.59	0.18
	Yes	51.5 ± 18.58		52.68 ± 18.07	
Viable areas	>50%	45 ± 17.02	1.02	52.83 ± 18.07	1.026
	≤50%	41.6 ± 7.35		47.00 ± 4.95	
Regression grading	I	35 ± 1.41	1.11	–	–
	II	36 ± 9.67		–	
	III	42 ± 20.02		–	

Discussion

HB is a well-recognized, unique pediatric malignant liver tumor, which recapitulates the normal hepatic ontogenesis.[2] The comprehensive treatment strategy of surgery combined with chemotherapy has greatly improved the overall prognosis of HB over the years. Yet the disease is life-threatening to some with disease recurrence and progression.[9]

Two-thirds of HBs are diagnosed by 24 months.[2] The mean age at diagnosis ranges from 11 to 46 months and was 10 months in our study.[2,10] A male predominance was seen in our study similar to few other studies.[4,10] Our study showed significant better OS in children younger than 36 months and worse OS in children older than 36 months. Similarly, a study by Yang et al[9] showed significant lower DFS in patients older than 54 months. Age is not a risk factor in the COG or SIOPEL guidelines, while the CHIC study states that older children with HB do worse.[6,9]

HB in adults is extremely rare, with less than 75 reported cases so far, and has dismal prognosis.[11,12] The highest age at diagnosis in our study was 11 years.

Elevated AFP[2] is the diagnostic hallmark of HB. The serum AFP level and radiological PRETEXT staging are important for risk stratification and staging of HB.[5,7] As per SIOPEL,[7] PRETEXT I, II, and III with elevated AFP (>100 ng/dL) are considered standard risk, while PRETEXT IV, low AFP, and very high AFP (>1.2 million ng/mL) are high-risk HBs. In our study, the percentage of recurrence and death was higher with PRETEXT IV (75 and 50%, respectively) compared with the combined PRETEXT I, II, and III (27 and 18%, respectively). In another study,[10] PRETEXT I and II had a significantly better DFS and lower mortality when compared with PRETEXT III and IV. The average reduction of the AFP level post-NACT in our cases was 42%, which was comparable to the study by Wang et al.[8] Yang et al[9] showed that reduction of AFP levels by greater than 60% and radiological tumor size by greater than 50% following NACT is an independent prognostic factor for the 3-year DFS.

HB is thought to arise from an embryonal precursor and displays diverse histologies.[13,14] Wnt pathway[15] is believed to be involved in embryonal and mixed histology and the Notch pathway in the pure fetal type. Tumor heterogeneity[16] is claimed to be one of the causes for the varied behaviors of HB. In our study, the pure fetal variant showed the highest survival and lowest mortality and good response to treatment (TRG I), which was similar to the findings in the literature.[5,17] Akin to this, one of our patients with pure fetal variant and lung metastasis at diagnosis responded well to resection and chemotherapy and was disease free. The embryonal, mixed epithelial and mesenchymal, and SCUD variants showed poorer response to chemotherapy (TRG 2 and 3). Likewise, the mesenchymal subtype and the embryonal variant with high mitosis were found to have aggressive behaviors in few studies.[10,18,19] On the contrary, the study by Wang et al[8] showed the mesenchymal component to be associated with better outcome. Although fetal histology had better survival as compared with other histology, statistical significance could not be reached in our studies and many other studies.[8,15,20] The SCUD subtype warrants accurate histological diagnosis as it presents with a normal/low AFP level and has aggressive behavior with worst survival. SCUD in pure or combined with other histological types puts the patient in the high-risk category.[5,6] The SCUD tumor must be differentiated from the malignant rhabdoid tumor by IHC for Integrase interactor 1 (INI1) as it requires distinct management.[9,17] In our study, the child with the SCUD variant with retained INI1 responded poorly to both standard and second-line therapies, and succumbed to the disease within 5 months of diagnosis.

Our study, like the study by Wang et al,[8] did not show a significant survival difference between positive and negative margins. According to the current SIOPEL guideline,[21] the microscopic positive resection margin is no longer a poor prognostic indicator if the tumor has shown good pathological and radiological response to NACT.

Unlike other pediatric malignancies (acute lymphoblastic leukemia, Wilms' tumor), the role of histological assessment and grading of response to NACT in predicting survival and further therapeutic interventions is not established in HB. [20,22,23] Histological assessment of response to NACT could potentially be used to modify adjuvant therapy[9] by intensifying/reducing dose or adding newer drugs for improved outcome in HB. A study by Kiruthiga et al[10] demonstrated that patients with less than 50% of viable tumors following chemotherapy had higher DFS when compared with patients with greater than 50% viable tumors. On the contrary, our study did not show a significant difference in survival between the three TRG groups or with cutoff of 50% for viable tumors (►**Table 5**). However, when each of the therapy-induced changes were considered separately (presence of calcification, fibrosis, necrosis, and maturation), it was seen that patients showing treatment-induced changes had better survival compared with patients without therapy-induced changes (►**Table 5**). In our study, patients with tumor showing greater than 10% fibrosis and greater than 30% necrosis were associated with lower posttreatment AFP levels, better histological type, and higher survival (►**Table 4**). The presence of tumor-induced maturation, necrosis, and calcification showed better survival (►**Table 5**). Similarly, Venkatramani et al[20] showed that the risk of disease progression and death in HB decreases significantly with increasing percentage of tumor necrosis. Necrosis greater than 30% was shown as an independent prognostic factor in their study. The presence of osteoid or calcification post-NACT was considered a sign of maturity[24] and hence considered a good prognostic indicator in HB, similar to Wilms' tumor and germ cell tumor.

Assessing tumor-induced maturation at the resection margin is challenging. In our study, 60% of cases showed a maturation pattern indistinguishable from a normal liver. Glypican-3 positivity in the maturing areas and negativity in the non-neoplastic liver were valuable in delineating two areas (►**Fig. 2D**). While two-thirds of cases in the series by Wang et al[8] showed mature areas mimicking a non-

neoplastic liver, they found β-catenin with CK7 to be useful in differentiating two areas.

Nuclear β-catenin expression was seen in 30% of our cases and only in the embryonal areas. Significant β-catenin staining in the embryonal component was also observed by Bera et al.[16]

Treatment strategies for HB differ across countries. NACT followed by resection[3,5] is followed in most centers. All our patients underwent NACT with four to five cycles of PLADO (doxorubicin and cisplatin) followed by resection and three more cycles of the PLADO regimen postsurgery. The ongoing Pediatric Hepatic International Tumor Trial (PHITT) trial[6,25] is expected to reduce the controversies regarding the treatment of HB.

While treating pediatric cancers, risk stratification of patients is essential for adjusting the doses of adjuvant chemotherapy, adding/deleting radiation therapy and the decision on the extent of surgery. Histology and assessment of response to therapy plays a major role in risk stratification in most of the pediatric solid tumors.[26] Risk stratification ensures fine-tuning of the offered treatment to establish long-term cure while minimizing the side effects of the therapy.[26] HB has rare incidence worldwide. Hence, multi-institutional studies involving larger sample size are desired to conclusively establish a definite relationship of therapy-related changes in HB with the prognosis and pave the way to individualized therapy in these patients. High-throughput studies have revealed many genomic, epigenetic, and transcriptomic alteration in HB[27] in the recent years. Further insights into molecular biomarkers and targets for HB will facilitate newer and less aggressive therapeutic modalities that would heighten HB survivors with improved quality of life after therapy.

Limitations of the Study

HB is a rare neoplasm with a low incidence worldwide. Similarly, due to the study being conducted at a single institute, the sample size of the present study was small and hence no statistical correlation between the treatment-induced changes and the prognosis could be reached. Multi-institutional studies with a larger sample size may throw more light on the prognostic significance of therapy-induced changes in HB and pave the way for a more personalized therapy in these children.

Conclusion

This is a descriptive study of HB encountered at a tertiary care center with emphasis on the role of the histological assessment of therapy-induced changes. Higher percentages of therapy-induced changes in the form of fibrosis, necrosis, calcification, and tumor maturation are associated with better outcome and may have a role in postsurgery therapeutic interventions, leading to personalized medicine and improved therapy for HB. Further inter-institutional studies with larger sample sizes are needed to definitely demonstrate the significance of assessing therapy-induced changes as a prognostic factor in HB.

Authors' Contributions

D.A. contributed to data curation, writing of the original draft, preparation, and editing of the manuscript. M.E. contributed to the conceptualization, methodology, and supervision of the study, and editing of the manuscript. P.K. contributed to the visualization, investigation, supervision, and reviewing of the study. S.S. contributed to the visualization, investigation, supervision, and reviewing of the study. N.V. contributed to the visualization, investigation, supervision, and reviewing of the study.

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None.

Conflict of Interest

None declared.

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