ORIGINAL ARTICLE

Histopathology and Clinicoradiology of Hepatoblastoma-Survival Analysis of an Intriguing Not So Rare Tumor

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ABSTRACT

Background: The incidence of hepatoblastoma is increasing in recent years. Knowledge about various factors associated with improved survival of such patients may aid in early diagnosis and appropriate management of these cases. **Aims and Objectives**: 1) To analyse the clinicoradiological and histopathological features of hepatoblastoma diagnosed in a tertiary care centre 2) To estimate the survival with relation to various prognostic factors recently identified in the latest WHO classification in Indian context. **Materials and Methods**: A total of 41 cases of hepatoblastoma diagnosed over a five year period from 2018-2022 were examined by two pathologists independently. Kaplan meier analyses was done to determine survival. **Results**: The age range was 5 months-12 years. The male: female ratio was 1.6:1. The AFP levels were >65000 ng /ml in 92 % cases. The masses ranged from 5-14 cm in size with 10 cases having multifocal lesions and 5 cases having lung metastases at presentation. The overall survival was 75.26 %. In common with other studies, survival was better in children <2 years, AFP>100 ng/ml, female sex and those without lung metastases. In contrast to studies done worldwide, the survival with PRETEXT stage I was only 5 months (CI 2.861-8.319) despite the most common fetal subtype in this group ($p<0.05$). **Conclusion**: There is no relationship between survival and the histological subtype. Despite having fetal pattern, patients in PRETEXT stage I had a worse survival rate, which shows that the biopsy may not be representative of the entire tumor.

KEY WORDS: Hepatoblastoma, Clinicoradiology, Histopathology, Survival.

Introduction

Approximately 1% of all childhood malignancies are primary malignant tumors of the liver. With an annual incidence of 0.9 per 1 million children, hepatoblastoma is the most prevalent of them.[1] Though still regarded as a rare disease, hepatoblastoma's global incidence increased more than any other pediatric cancer due to an increase in low birth weights, early discovery, and improved imaging modalities.[2–4]

If upfront resection is not an option, the current approach for diagnosing hepatoblastoma is a liver biopsy.[5] The purpose of the biopsy is tissue diagnosis in order to differentiate malignant (embryonal sarcoma and pediatric hepatocellular carcinoma) or benign (mesenchymal hamartoma, adenomas, and localized nodular hyperplasia) liver tumors from hepatoblastomas. This is due to the fact that the traditional PLADO (Sorafenib and cisplatin/doxorubicin) chemotherapy protocol has been shown to effectively treat hepatoblastomas.

In this study, the clinicoradiological and histopathological characteristics of hepatoblastoma diagnosed in a tertiary care center were examined. Additionally, the survival rate was estimated in relation

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to several prognostic factors recently identified in the Indian context of the most recent World Health Organization (WHO) classification.

Materials and Methods

The Institutional Research and Ethics Committee gave its approval for this research. Since no patients were directly involved in this retrospective analytical investigation, no consent was obtained. Included were 41 cases of hepatoblastoma (HB) that were diagnosed in the Department of Oncopathology throughout a five-year period, beginning in January 2018 and ending in December 2022. Alpha-fetoprotein (AFP) serum levels and pertinent clinical information were recorded at the time of the initial diagnosis. The size and location of the tumor, focality, and existence of metastases were among the radiological findings. The radiologic results were reported or used to establish the PRETEXT (pretreatment extent of disease) staging as specified in the 2019 WHO classification.

This investigation contained biopsies as well as slides for review. After being embedded in paraffin, fixed in 10% formalin, and sectioned into 4 micron-thick pieces, they were stained with hematoxylin and eosin. Two pathologists independently inspected the slides again after that. The subtyping of hepatoblastoma was done taking into account the 2019 WHO tumor classification system.

Statistical Analysis

A chi-square or Fisher's exact test was used to compare the association between categorical variables, and a P value of ≤ 0.05 was considered significant. The description of the data was summarized using frequency along with percentages for categorical variables and mean along with standard deviation for continuous variables using SPSS software Version Stata IC/13. OS, or overall survival, was computed. To show survival, Kaplan-Meier curves with log rank (Mantel-Cox) were employed.

Results

A total of 41 biopsies, including slides for review, received during a 5-year period from 2018 to 2022 were examined. The age range in this study was 5 months to 12 years (mean 2.6 years). The male-female ratio was 1.6:1 (25 and 16). The most common clinical presentation was abdominal mass (38.2%), followed by fever (31%) and abdominal pain (14.6%). None of the patients showed any association with genetic syndromes like familial adenomatous polyposis or Beckwith-Weidmann syndrome.

The AFP levels were >65000 ng/ml (the upper limit of AFP in our biochemistry lab is 65000 ng/ml) in 38/41 (92%). Three out of forty-one cases had low AFP levels at diagnosis. Liver function tests and beta HCG levels were within normal limits in all the cases. None of the cases were positive for HBsAg or HCV.

On radiology, the masses ranged from 5 to 14 cm in size, with 10/41 (24%) cases having multifocal lesions and 4 cases having lung metastases at presentation. None of the cases showed radiologic evidence of macrovascular invasion. Details about the PRETEXT stage were available to all patients. Ten patients (24%) belonged to PRETEXT-I, 24/41 (59%) to PRETEXT-II, 7/41 (17%) to PRETEXT-III, and none to PRETEXT-IV.

The most common epithelial subtype was fetal in 35/41 (85%). Other subtypes included embryonal, mixed epithelial, and mesenchymal types.

A recurrence was not found in any patient. Metastasis was documented in 10/41 (%) patients, with the most common site of distant metastases being the lung in 5/10 (50%) cases. Survival data was available for 31/41 patients, and 10 (42.9%) died due to disease. Overall median (range) survival was 70.7 (1.7 to 109.9) months. It was found that a higher number of patients in PRETEXT I succumbed to the disease despite being of the fetal subtype. The survival of those patients receiving Cispaltin+Doxorubicin according to the conventional PLADO protocol was improved ($P \leq 0.05$) compared to those who received Irinotecan+Vincristine+Fluorouracil in addition to the PLADO protocol.

Table 1: Correlation of survival with various prognostic factors (Chi-square analysis)

Profnostic factor	Chi-Square	Sig. (P-Value)
PRETEXT	3.375	0.185
SITE	4.001	0.135
TREATMENT	6.002	0.014
GENDER (male /female)	1.488	0.223
AGE	.419	0.517
AFP level (low and high)	0.238	0.625
FETAL TYPE (and other subtypes)	1.33	0.249

Table 2: Overall survival in relation to various prognostic factors

Variables		No.	Survived	Survival
Overall		41	31	75.6%
PRETEXT	PRETEXT - 1	10	6	60.0%
	PRETEXT - 2	24	21	87.5%
	PRETEXT - 3	7	4	57.1%
Metastases	Lung	5	3	60.0%
	No metastases	36	28	77.78%
Treatment	C+D	25	20	80.0%
	Others	16	11	68.8%
Gender	Female	16	14	87.5%
	Male	25	17	68.0%
Age	<2 Years	29	23	79.3%
	>2 Years	12	8	66.7%
AFP	<100	5	4	80%
	>100	36	27	75%
Type	Fetal	35	25	71.4%
	Others	6	6	100

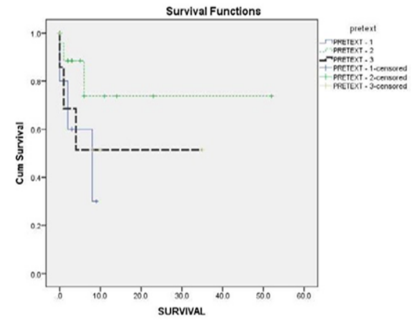

Fig 1a : Survival curves in correlation with the PRETEXT stage

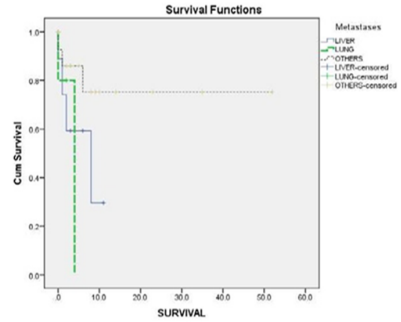

Fig 1b : Survival curves in correlation with metastases

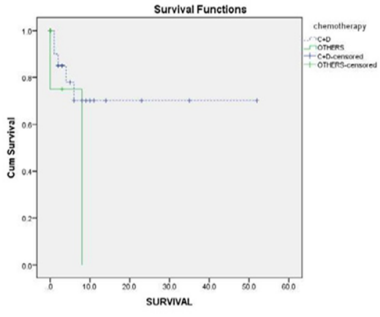

Fig 1c : Survival curves in correlation with chemotherapy

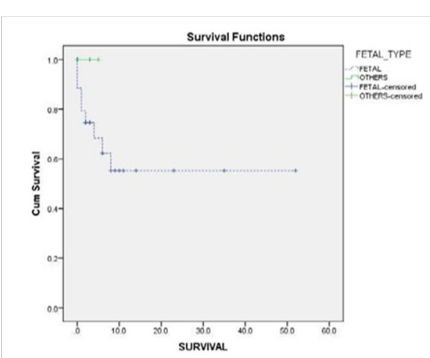

Fig 1d : Survival curves in correlation with histological subtype

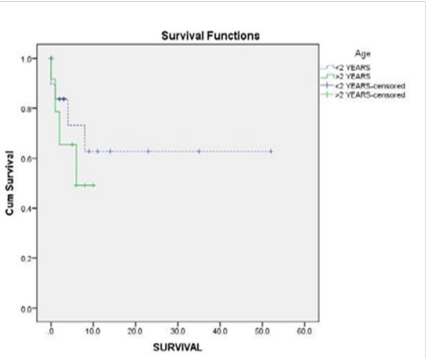

Fig 1e : Survival curves in correlation with age

Figure 1: Kaplan Meier log rank curves using mantel cox test in relation to various parameters

Discussion

The most frequent primary malignant tumor of the liver in children is hepatoblastoma. In children ages five or younger, it makes up 90% of tumors.[6] It is an embryonal tumor that develops from hepatocellular precursors, which frequently mimic various phases of the development of the liver. Therefore, it is rare for these tumors to include only one kind of cell; instead, a mixture of epithelial, mesenchymal, undifferentiated, and other histological components are typically present.[1,6,7]

According to previous studies, 70% of the participants in this study presented within the first two years of their lives, with a mean age of 2.6 years.[8,9] A modest male preponderance of 1.7:1[10] is seen in this tumor, which is consistent with what our study found.

Due to the early advancement and adverse outcome in these cases, a link has been identified with extreme preterm and very low birth weight (< 1000 g).[10] Likewise, correlations have been demonstrated with Beckwith-Weidman syndrome[11], familial adenomatous polyposis[12], Gardner's syndrome, hemihypertrophy, and adrenal agenesis. In this study, only 4 out of 41 instances (10%) had premature births, and none of the cases had any syndromic associations.

According to a study by Buckley et al.[5], this occurrence was more common in children of mothers who were significantly overexposed to metals used in welding and soldering, as well as lubricants and protective greases both before and during pregnancy.[13] There was also more metal exposure among the fathers. The parents of patients in our study had no history of any kind of exposure.

In 90% of HB patients, serum AFP, a highly sensitive test, is increased. In our analysis, 92% of patients had a high AFP at the time of presentation. Reduced AFP levels in 8% of instances were not linked to the small cell undifferentiated subtype that has been seen in other research.[12]

Compared to PRETEXT III and IV phases, patients in PRETEXT I and II had better overall survival (OS), and as reported in other studies, more patients in PRETEXT III and IV died from the disease than in PRETEXT I and II ($P \leq 0.001$).[14,15] However, a contradicting fact that came out in our study was that greater proportion of patients with PRETEXT I died of the tumor.

When comparing histological subtypes with adverse effects, it has been noted that the fetal subtype had a decreased frequency of metastasis, mortality, recurrence, and MVI.[16,17] Nevertheless, there was no discernible correlation between survival and histological subtype in our investigation. These results were in line with those of Gupta et al.[18] and Conran et al.[19]

Five instances (12%) had distant metastases, with the lung being the most often observed location.[20] Who, in contrast to those without, had a shorter overall survival (3.2 months).[21,22] Ten of the 41 cases (or 24%) had a disease-related death. This is comparable to findings from studies conducted in North India[18] and Germany[23], which showed just 21% and 23% of deaths, respectively.

Our patients' overall median survival was 70.7 months, and their 5-year OS was 60%, which is comparable to the 6-year OS of 63% and 58.7% reported in other studies.[24,25] For PRETEXT I, II, III, and IV, they reported 5-year OS values of 100%, 87.1%, 89.7%, and 78.3%, respectively. In this study, the 5-year OS for metastatic disease was 49%.

How to differentiate from Hepatocellular carcinoma?

Hepatocellular carcinoma exhibits a bimodal peak at 1 and 14 years of age.[24] However, if the cancer develops before 1 year of age or appears histologically as low grade, it can be closely associated with hepatoblastoma, particularly the fetal form.[25] AFP and imaging characteristics might not be able to distinguish the two. But the hereditary disorders and etiology linked to each tumor are distinct. Differentiating fetal hepatoblastoma from pediatric well-differentiated hepatocellular carcinoma involves identifying features such as thickened trabeculae, high nucleus-cytoplasm ratios, absence of light and dark regions, and, in the case of the latter, typically negative nuclear β-catenin. A nearly perfect diagnostic clue for hepatoblastoma is the presence of embryonal-type epithelial or mesenchymal components on the histology.

Although most pediatric hepatocellular carcinomas do not have the same strong nuclear beta-catenin staining as hepatoblastomas, there is currently no immunostain to confidently distinguish hepatocellular carcinoma from hepatoblastoma. Glypican-3, beta-catenin, and glutamine synthetase (GS) immunohistochemistry helps differentiate hepato-

blastoma from a healthy liver.

Based on histological examination, eight cases in this investigation presented diagnostic challenges. To address these issues, immunohistochemistry was used, employing markers such as beta-catenin, Hep-par1, glutamine synthetase, and alpha-fetoprotein. Every single case (100%) had a consistent nuclear stain of beta-catenin. This result is in contrast to research by Kruthiga et al.[26], Gupta et al.[18], and others, which found that nuclear expression of beta-catenin was present in 48.7% and 57.1% of tumors in the groups that had chemotherapy before and after it.

A biopsy sample is rarely representative of the complete tumor, comprising less than 0.003% of the total. Histological examination of the tumor that remains after neoadjuvant treatment is therefore essential.

However, it should be noted that radiologic features—particularly the presence of bone—need to be taken into account for subtyping because not all components may necessarily be obtained in a biopsy. The latest CAP standards indicate that radiologic evidence of bone or calcification may reflect a mixed epithelial-mesenchymal hepatoblastoma and aid in the differentiation from other cancers, even in cases where mesenchymal components are not detected histologically in a biopsy.

Limitations of the study

Hepatoblastomas are not only uncommon, but their diversity severely restricts the expertise of any one hospital or pathologist. In this investigation, karyotype information was unavailable for any of the reported genetic abnormalities, including loss of heterozygosity (LOH) at the 11p15.5 locus, high incidence of trisomy 20, 2, and rarely, 18.

Conclusion

Survival is not correlated with the histological subtyping on the biopsy. In order to identify the hepatoblastoma subtype, radiological characteristics must also be considered, as evidenced by the decreased survival of patients in PRETEXT stage I while having a fetal pattern on histology.

Abbreviations

WHO: World Health Organization; HB: hepatoblastoma; AFP: Alpha Feto Protein; PRETEXT: Pretreatment extent of Disease.

Disclosure

Ethics approval and consent to participate

The study has been approved by institute research committee of GCRI assuring legal and ethical criteria fulfilment in the study.

Consent for publication

Written informed consent was taken from Parents of all the patients.

Identity of any patient is not revealed in the pictures or in manuscript.

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Conflict of interest

The authors declare that they have no competing interests.

Authors' contributions

PM, SK, DN: acquisition of data, analysis and research of literature and preparation of manuscript. PM, MS: conception and design of manuscript and critical revision of manuscript for intellectual content. PM, NM, SK: critical revision of manuscript for intellectual content. MS: administrative support and supervision. All authors read and approved the final manuscript.

References

1. Weinberg AG, Finegold MJ. Primary hepatic tumors of childhood. Human Pathology. 1983;14(6):512–537. Available from: https://doi.org/10.1016/s0046-8177(83)80005-7.
2. Czauderna P, Lopez-Terrada D, Hiyama E, Häberle B, Malogolowkin MH, Meyers RL. Hepatoblastoma state of the art: pathology, genetics, risk stratification, and chemotherapy. Current Opinion in Pediatrics. 2014;26(1):19–28. Available from: https://doi.org/10.1097/mop.0000000000000046.
3. Kehm RD, Osypuk TL, Poynter JN, Vock DM, Spector LG. Do pregnancy characteristics contribute to rising childhood cancer incidence rates in the United States? Pediatric Blood & Cancer. 2018;65(3):5766387. Available from: https://doi.org/10.1002/pbc.26888.
4. Feng J, Polychronidis G, Heger U, Frongia G, Mehrabi A, Hoffmann K. Incidence trends and survival prediction of hepatoblastoma in children: a population-based study. Cancer Communications. 2019;39(1):1–9. Available from: https://doi.org/10.1186/s40880-019-

0411-7.
5. Buckley JD, Sather H, Ruccione K, Rogers PC, Haas JE, Henderson BE, et al. A case-control study of risk factors for hepatoblastoma. A report from the Childrens Cancer Study Group. Cancer. 1989;64(5):1169–1176. Available from: https://doi.org/10.1002/1097-0142(19890901)64:5%3C1169::aid-cncr2820640534%3E3.0.co;2-i.
6. López-Terrada D, Alaggio R, De Dávila MT, Czauderna P, Hiyama E, Katzenstein H, et al. Towards an international pediatric liver tumor consensus classification: proceedings of the Los Angeles COG liver tumors symposium. Modern Pathology. 2014;27(3):472–491. Available from: https://doi.org/10.1038/modpathol.2013.80.
7. Stocker JT. Hepatic tumors in children. Clinics in Liver Disease. 2001;5(1):259–281. Available from: https://doi.org/10.1016/S1089-3261(05)70163-X.
8. Ross JA. Hepatoblastoma and birth weight: too little, too big, or just right? Journal of Pediatrics. 1997;130(4):516–517. Available from: https://pubmed.ncbi.nlm.nih.gov/9108845/.
9. Balabaud C, Bioulac-Sage P, Goodman ZD, Makhlouf HR. Inflammatory pseudotumor of the liver: a rare but distinct tumor-like lesion. Gastroenterology & Hepatology. 2012;8(9):633–634. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3594961/.
10. McLaughlin CC, Baptiste MS, Schymura MJ, Nasca PC, Zdeb MS. Maternal and infant birth characteristics and hepatoblastoma. American Journal of Epidemiology. 2006;163(9):818–828. Available from: https://doi.org/10.1093/aje/kwj104.
11. Tan TY, Amor DJ. Tumour surveillance in Beckwith-Wiedemann syndrome and hemihyperplasia: a critical review of the evidence and suggested guidelines for local practice. Journal of Paediatrics and Child Health. 2006;42(9):486–490. Available from: https://doi.org/10.1111/j.1440-1754.2006.00908.x.
12. Aretz S, Koch A, Uhlhaas S, Friedl W, Propping P, Schweinitz DV, et al. Should children at risk for familial adenomatous polyposis be screened for hepatoblastoma and children with apparently sporadic hepatoblastoma be screened for APC germline mutations? Pediatric Blood & Cancer. 2006;47(6):811–818. Available from: https://doi.org/10.1002/pbc.20698.
13. Cho SJ. Pediatric Liver Tumors: Updates in Classification. Surgical Pathology Clinics. 2020;13(4):601–623. Available from: https://doi.org/10.1016/j.path.2020.09.002.
14. Meyers RL, Rowland JR, Krailo M, Chen Z, Katzenstein HM, Malogolowkin MH. Predictive power of pretreatment prognostic factors in children with hepatoblastoma: A report from the Children's Oncology Group. Pediatric Blood & Cancer. 2009;53(6):1016–1022. Available from: https://doi.org/10.1002/pbc.22088.
15. Ismail H, Broniszczak D, Kalici□ski P, Dembowska-Bagi□ska B, Perek D, Teisseyre J, et al. Changing treatment and outcome of children with hepatoblastoma: analysis of a single center experience over the last 20 years. Journal of Pediatric Surgery. 2012;47(7):1331–1339. Available from: https://doi.org/10.1016/j.jpedsurg.2011.11.073.
16. Kasai M, Watanabe I. Histologic classification of liver-cell carcinoma in infancy and childhood and its clinical evaluation. A study of 70 cases collected in Japan. Cancer. 1970;25(3):551–563. Available from: https://doi.org/10.1002/1097-0142(197003)25:3%3C551::aid-cncr2820250309%3E3.0.co;2-5.
17. Malogolowkin MH, Katzenstein HM, Meyers RL, Krailo MD, Rowland JM, Haas J, et al. Complete surgical resection is curative for children with hepatoblastoma with pure fetal histology: a report from the Children's Oncology Group. Journal of Clinical Oncology. 2011;29(24):3301–3306. Available from: https://doi.org/10.1200/jco.2010.29.3837.
18. Gupta K, Rane S, Das A, Marwaha RK, Menon P, Rao KLN. Relationship of β-catenin and postchemotherapy histopathologic changes with overall survival in patients with hepatoblastoma. Journal of Pediatric Hematology/Oncology. 2012;34(8):320–328. Available from: https://doi.org/10.1097/mph.0b013e3182580471.
19. Conran RM, Hitchcock CL, Waclawiw MA, Stocker JT, Ishak KG. Hepatoblastoma: the prognostic significance of histologic type. Paediatric Pathology. 1992;12(2):167–183. Available from: https://doi.org/10.3109/15513819209023293.
20. Emre S, Umman V, Rodriguez-Davalos M. Current concepts in pediatric liver tumors. Pediatric Transplantation. 2012;16(6):549–563. Available from: https://dx.doi.org/10.1111/j.1399-3046.2012.01704.x.
21. Wanaguru D, Shun A, Price N, Karpelowsky J. Outcomes of pulmonary metastases in hepatoblastoma — is the prognosis always poor? Journal of Pediatric Surgery. 2013;48(12):2474–2478. Available from: https://dx.doi.org/10.1016/j.jpedsurg.2013.08.023.
22. Perilongo G, Brown J, Shafford E, Brock P, De Camargo B, Keeling JW, et al. Hepatoblastoma presenting with lung metastases: treatment results of the first cooperative, prospective study of the International Society of Paediatric Oncology on childhood liver tumors. Cancer. 2000;89(8):1845–1853. Available from: https://doi.org/10.1002/1097-0142(20001015)89:8%3C1845::aid-cncr27%3E3.0.co;2-d.
23. Fuchs J, Rydzynski J, Schweinitz DV, Bode U, Hecker H, Weinel P, et al. 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(1):172–182. Available from: https://doi.org/10.1002/cncr.10632.
24. Allan BJ, Parikh PP, Diaz S, Perez EA, Neville HL, Sola JE. Predictors of survival and incidence of hepatoblastoma in the paediatric population. HPB. 2013;15(10):741–746. Available from: https://dx.doi.

org/10.1111/hpb.12112.
25. Liu G, Liu B, Li K, Dong K, Xiao X. Outcome of hepatoblastoma: experience with 63 patients received chemotherapy with the regimen C5V. Zhonghua Er Ke Za Zhi. 2015;53(2):119–123. Available from: https://pubmed.ncbi.nlm.nih.gov/25876687/.
26. Maruyama K, Ikeda H, Koizumi T, Tsuchida Y, Tanimura M, Nishida H, et al. Case-control study of perinatal factors and hepatoblastoma in children with an extremely low birthweight. Pediatrics International. 2000;42(5):492–498. Available from: https://dx.doi.org/10.1046/j.1442-200x.2000.01287.x.

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