Epidemiological Aspects, Clinical Features and Treatment Outcome in Children Suffering Hepatoblastoma

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Abstract

Introduction: Hepatoblastoma (HBL) is the most common primary liver tumor within childhood. Entire tumor resection is basis for ultimate cure for HBL and supports the only pleasant chance of long-standing disease-free survival.

Objectives: In the current survey, we attempted to evaluate the long-term survival of children with HBL with surgical resection in a referral children hospital in Iran within the last decade.

Materials and Methods: This retrospective descriptive study was conducted on all children who suffered HBL and undergone surgery between 2006 and 2016. Reviewing the recorded hospital files led to a sample of 30 eligible patients. The baseline characteristics of the patients were all collected by reviewing the files.

Results: In total, 30 consecutive children (21 male and 9 female) suffering HBL were described. Of those, 40.0% aged less than 12 months and only 6.7% aged higher than 36 months. The most common clinical manifestations were asymptomatic abdominal mass (in 66.7%) followed by fever (in 10.0%) and pain (in 10.0%). In more than half of the patients (53.3%), right lobe involved, while left lobe involved in 16.7%. based on histological report,marginal involvement was found in 75.0% of children,

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margin intact in 15.0% and margin free feature in 5.0%. Forty percent of children suffered from epithelial subtype of tumor, 20.0% from mixed epithelial and mesenchymal subtypes, and 13.3% from embryonal pattern. In total, 63.3% were scheduled for complete surgical resection followed by chemotherapy. Postoperatively, 40.0% of children remained free of complications, whereas postoperative bleeding occurred in 20.0% and biloma in 40.0%. Overall, 76.9% of patients were completely cured, 7.7% suffered from pulmonary metastasis and 3.9% required liver transplantation. Postoperative death occurred in 11.5%.

Conclusions: Considering surgical resection followed by chemotherapy leads to high cure rate, however a notable number of affected children suffer postoperative complication, requiring liver transplantation, pulmonary metastasis, or even non-survived emphasizing a serious review of the treatment protocols.

Keywords

- Hepatoblastoma
- Children
- Liver tumor

Introduction

Hepatoblastoma (HBL) is the mainly primary liver tumor within infancy that regularly

identifies within the initial three years of life.[1] This tumor frequently appears sporadically, however, accompanying disease with some genetic abnormalities such as familial adenomatous polyposis or Beckwith-Wiedemann syndrome has been also described.[2] Within the last decades, we have witnessed an increase in the incidence of the disease especially in very low birth weight children.[3] HBL is commonly manifested by abdominal distension and mass as well as abdominal discomfort, loss of appetite and fatigue. In cases with tumor rupture, peritoneal irritation and severe anemia are prominent signs.[4] Diagnostic approach to HBL is based on clinical, laboratory and imaging studies. Elevated serum alpha-fetoprotein (AFP) is a good marker for suspecting HBL; however, it was not specific and might be increased in other tumors such as rhabdoid tumor.[5] In ultrasonography assessment, it revealed as a huge mass in liver alongside with satellite tumors and regions of hemorrhage.[6] The most sensitive modalities for detection of HBL are multiphase computed tomography (MPCT) or magnetic resonance imaging (MRI) reveal hyper-vascular lesions in the liver with delayed contrast excretion.[7,8] Histological studies lead us to a definitive diagnosis especially in those children with low or moderate level of AFP.[9] Some risk scoring systems are recommended to stratify the risk for HBL among children. The Children's Hepatic Tumors International Collaboration (CHIC) risk stratification system classify the risk for HBL based on child's age, the presence of distant metastases, portal vein conflict, hepatic vein/cava involvement, neighboring extra-hepatic cancer,

rupture identification, multifocality,elevated level of AFP, and pretreatment extent of disease.[10] In the PRETEXT system, two components have been made as the PRETEXT group describing the extent of tumor within the liver and the annotation factors including the evidences of vascular involvement, multifocality, extra-hepatic involvement, tumor rupture and metastasis.[11] Overall, the risk stratification for HBL is essential before treatment.

Currently, total tumor resection forHBL suggests the only reasonable possibility of long-standing disease-free survival.[12] Within the last two decades, introducing chemotherapeutic protocol led to considerably decreasing postoperative recurrence rate.[13] Besides, applying advanced surgical techniques have resulted in improving the prognosis of patients suffering HBL. In this regard, the arrangement of surgery and chemotherapy remains best selection for therapeutic strategy in HBLwith respect to achieving appropriate long-term prognosis as well as increasing patients' survival.[14] In the current survey, we attempted to evaluate the long-term survival of children with HBL, with surgical resection at Mofid Children Hospital, a large referral children hospital in Iranwithin the last decade.

Materials and Methods

This retrospective descriptive study was conducted on all children suffering from HBL and undergoing surgery between 2006 and 2016. Reviewing the recorded hospital files led to a number of 30 eligible patients. The baseline characteristics of the patients including gender, age, clinical manifestations, early postoperative outcome, procedure-related mortality, rate of requiring liver transplantation, rate of lung metastasis, pathological report related to definitive diagnosis of the disease, and disease stage, were all collected by reviewing the files. The disease staging was based on the 2005 PRETEXT staging system that previously described.[15] The study endpoint was to describe preoperative characteristics, histological findings and subtypes of tumor, tumor staging, considering concomitant neoadjuvant chemotherapy, as well as postoperative consequences regarding recovery rate, mortality, and surgical complications. In terms of ethical considerations, observance is trusted to review resources and articles. Personal information obtained from the patients was kept confidential and all information useful for the research was sought to be made available for use. All study protocols were approved by the ethical committee at Tehran University of Medical Sciences.

Descriptive analysis employed to explain the data, counting mean ± standard deviation (SD) for quantitative variables and frequency (percentage) for categorical variables. Statistical analysis was employed with statistical software IBM SPSS Statistics version 22.0 (IBM Corp. Released 2013, Armonk, New York).

Results

In total, 30 consecutive children (21 male and 9 female) suffering HBL were described. Of those, 40.0% aged less than 12 months and only 6.7% aged higher than 36 months **Table 1.** Regarding stage of disease, 66.7% were classified at the stage II, 23.3% at the stage III and 3.3% at the stage IV and therefore, metastasis was revealed only in

3.3% of the participants. The most common clinical manifestations included asymptomatic abdominal mass (in 66.7%) followed by fever (in 10.0%) and pain (in 10.0%), while fatigue simultaneous with anorexia, weight loss and jaundice were found in 3.3% of affected children **Table 1**.

Table 1: Baseline characteristics of study population

Gender	
Male	21 (70.0)
Female	9 (30.0)
Age groups, month	
0 to 12	12 (40.0)
13 to 24	9 (30.0)
25 to 36	6 (20.0)
> 36	2 (6.7)
Disease stage	
I	0 (0.0)
II	20 (66.7)
III	7 (23.3)
IV	1 (3.3)
Clinical manifestation	
Asymptomatic abdominal mass	20 (66.7)
Fever	3 (10.0)
Pain	3 (10.0)
Fatigue, anorexia, weight loss, jaundice	1 (3.3)
Asymptomatic abdominal mass, fatigue, anemia	1 (3.3)
Asymptomatic abdominal mass, anorexia, weight loss	1 (3.3)
Fatigue, fever	1 (3.3)

Regarding degree of liver involvement, in more than half of the patients (53.3%), right lobe involved, while left lobe involved in 16.7% and bilateral involvement was found in 3.3%. Also, midportion and central lobe involvement was revealed in 3.3% and 3.3% respectively. With respect to the degree of histological involvement, marginal involvement was found in 75.0% of children, margin intact in 15.0% and margin free feature in 5.0%. The different subtypes of HBL according to pathological assessment are shown in **Figure 1**. In total, 40.0% of children suffered from epithelial subtype of tumor, 20.0% from mixed epithelial and mesenchymal subtypes,

and 13.3% from embryonal pattern. Regarding therapeutic management, 63.3% were scheduled for complete surgical resection followed by chemotherapy. Also, surgical biopsy, neoadjuvant chemotherapy followed by complete surgical resection was planned for 13.3% of patients and percutaneous biopsy, neoadjuvant chemotherapy followed by complete surgical resection for 10.0%.

Postoperatively, 40.0% of children remained free of complications, whereas postoperative bleeding occurred in 20.0% and biloma in 40.0%. Overall, 76.9% of patients were completely cured, 7.7% suffered from pulmonary metastasis and 3.9% required liver transplantation. Postoperative death occurred in 11.5%. The characteristics of non-cured patients are summarized in **Table 2.**

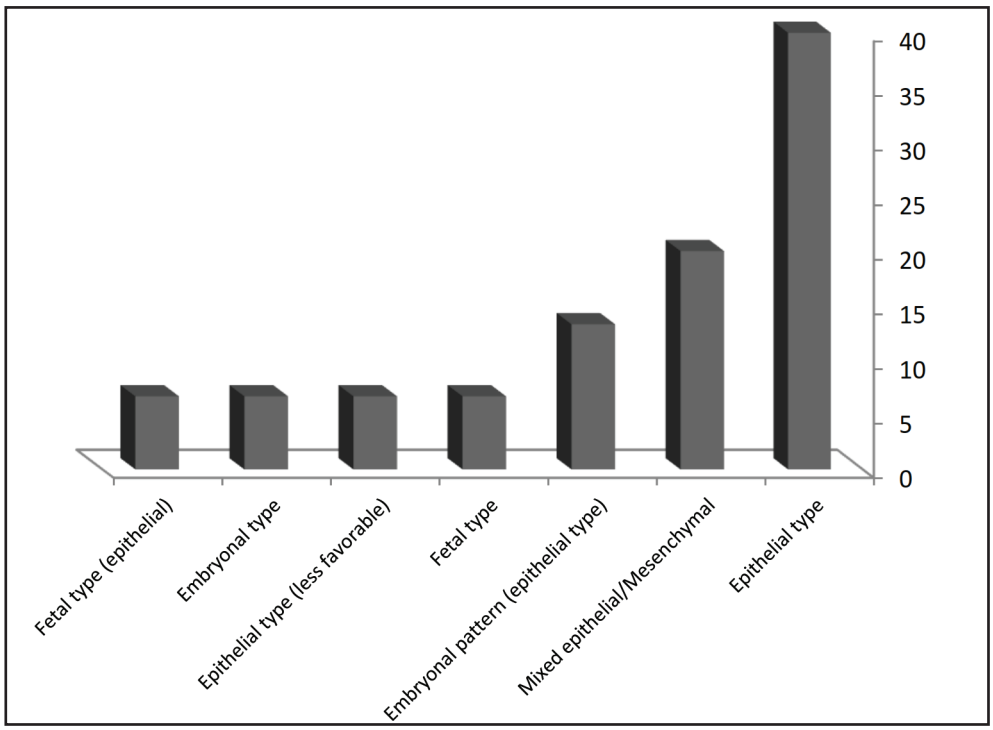

Figure 1: Histological subtypes of hepatoblastoma

Table 2: Characteristics of non-cured group with hepatoblatoma

Event	Sex/age	Stage	Liver involvement
Lung metastasis			
Case 1	F/24m	IV	Both lobes
Case 2	M/16m	II	Right lobe
Liver transplant			
Case 1	F/8y	IV	Both lobes
Expired			
Case 1	F/12m	II	Left lobe
Case 2	M/18m	III	Right lobe
Case 3	M/5y	II	Left lobe

Discussion

As the first result, the incidence of HBL was considerably higher in male than in female children with the male to female ratio of 2.3 indicating higher tendency of disease to male individuals. Although some reports indicated a male: female ratio of 1.2 for HBL, in a large survey in the United States and the Europe showed a range of 1.3 to 3.3 for male to female ratio indicating our sex distribution in global range.[16-19] Regarding clinical manifestations, an asymptomatic abdominal mass was the prominent sign discovering in about two-third of the patients, while other manifestations included fever, upper zone abdominal pain and rarely fatigue, anorexia, weight loss, and jaundice. The literature shows that the majority of cases may identify with an enlarged abdominal tumor that the right lobe is concerned three times compared with the left. In this regard, anorexia, weight loss, and pain were less common that was comparable with our observations.[20, 21] In our study and regarding histological feature, 40.0% of children suffered from epithelial subtype of tumor, and 20.0% from mixed epithelial and mesenchymal subtypes. It has been shown that HBL is classified as epithelial in about 56% or mixed epithelial/ mesenchymal in 44%. Also, epithelial type was also sub-classified to pure fetal in 31%, embryonal in 19%, macrotrabecular in 3%, and small cell un-differentiated in less than 3%.[22] It should be also noted that association of mesenchymal elements has been suggested with better prognosis in cases with extensive HBL.[23]

With respect to the therapeutic management, all patients were planned for complete surgical resection followed by neoadjuvant chemotherapy led to a complete cure rate of 76.9% that was considered as acceptable treatment successfulness. However, the rate of postoperative complications as well as poor prognosis due to pulmonary metastasis or even death remains high. In our study, despite proper management of patients by a combination therapy plus chemotherapy, 11.5% of patients died, 7.7% suffered from pulmonary metastasis and 3.9% required liver transplantation. Entire resection of the tumor permits the most excellent expect for long-standing survival; on the other hand, the beginning of successful chemotherapy may allow healing despite metastatic disorder.

Chemotherapy showed to be efficient both in an adjuvant as well as neoadjuvant situation. The employ of neoadjuvant chemotherapy had been led to mainly no metastatic hepatoblastomas become resectable. This indicates that in spite of employing advanced surgical techniques and updated surgical approach, the prognosis of the treated patients remains partially poor yet. Also, in our study, about half of the patients suffered from postoperative complications such as bleeding or biloma. Due to such surgery-related complications, selecting surgical approach for the treatment may not be first choice among majority of clinicians especially in advanced stages of disease. As shown by Seo et al.[23], less complications were reported following preoperative chemotherapy, but complications were advanced, with second-look surgeries after an open incisional biopsy or cannulation of hepatic artery. One of the main complications of disease included lung metastasis revealing in 7.7%. The majority site of distant metastasis for

HBL reported in the lungs. The violent approach to excision of pulmonary metastasis may lead in long-standing survival particularly in the presence of AFP <25ng/ml, early resection of metastasis, favorable response of metastasis to chemotherapy, and complete surgical resection of the tumor.[24]

Conclusion

In total, although we achieved high cure rate of 76.9%, the rate of complications or unpredictable adverse outcome including pulmonary metastasis, requiring liver transplantation or even death showed that our treatment approach has not been completely successful needing modification of the current protocols.

Ethical Consideration

This study was approved by School of Medicine - Shahid Beheshti University of Medical Sciences with code number IR.SBMU.MSP.REC.1395.478.

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Conflict of interests

There is no conflict of interest.

References

1. Hiyama E: Pediatric hepatoblastoma: diagnosis and treatment. Transl Pediatr 2014;3(4):293-9.
2. Czauderna P, Garnier H: Hepatoblastoma: current understanding, recent advances, and controversies. F1000Res 2018;7:53.
3. Spector LG, Birch J: The epidemiology of hepatoblastoma. Pediatr Blood Cancer 2012;59(5):776-9.
4. Schnater JM, Köhler SE, Lamers WH, et al: Where do we stand with hepatoblastoma? A review. Cancer 2003; 98(4):668-78.
5. Meyers RL, Maibach R, Hiyama E, et al: Risk-stratified staging in paediatric hepatoblastoma: a unified analysis from the Children's Hepatic tumors International Collaboration. Lancet Oncol 2017;18(1):122-131.
6. Sharma D, Subbarao G, Saxena R: Hepatoblastoma. Semin Diagn Pathol 2017;34(2):192-200.
7. O'Neill AF, Towbin AJ, Krailo MD, et al: Characterization of Pulmonary Metastases in Children With Hepatoblastoma Treated on Children's Oncology Group Protocol AHEP0731 (The Treatment of Children With All Stages of Hepatoblastoma): A Report From the Children's Oncology Group. J Clin Oncol 2017;35(30):3465-3473.
8. Chavhan GB, Mann E, Kamath BM, et al: Gadobenate-dimeglumine-enhanced magnetic resonance imaging for hepatic lesions in children. Pediatr Radiol 2014;44(10):1266-74.

9. Kremer N, Walther AE, Tiao GM: Management of hepatoblastoma: an update. Curr Opin Pediatr 2014;26(3):362-9.

10. Czauderna P, Haeberle B, Hiyama E, et al: The Children's Hepatic tumors International Collaboration (CHIC): Novel global rare tumor database yields new prognostic factors in hepatoblastoma and becomes a research model. Eur J Cancer 2016;52:92-101.

11. Meyers RL, Maibach R, Hiyama E, et al: Risk-stratified staging in paediatric hepatoblastoma: a unified analysis from the Children's Hepatic tumors International Collaboration. Lancet Oncol 2017; 18(1):122-131.

12. Busweiler LA, Wijnen MH, Wilde JC, et al: Surgical treatment of childhood hepatoblastoma in the Netherlands (1990-2013). Pediatr Surg Int 2017;33(1):23-31.

13. Czauderna P1, Lopez-Terrada D, Hiyama E, et al: Hepatoblastoma state of the art: pathology, genetics, risk stratification, and chemotherapy. Curr Opin Pediatr 2014;26(1):19-28.

14. Musick SR, Smith M, Rouster AS, et al: Hepatoblastoma. StatPearls [Internet] 2020 Nov 19.

15. Roebuck DJ, Aronson D, Clapuyt P, et al: International Childhood LiverTumor Strategy Group.2005 PRETEXT:a revised staging system for primary malignant liver tumours of childhood developed by the SIOPEL group. Pediatr Radiol 2007;37(2):123-32; quiz 249-50.

16. Ortega JA, Krailo MD, Haas JE, et al: Effective treatment of unresectable or metastatic hepatoblastoma with cisplatin and continuous infusion doxorubicin chemotherapy: a report from the Children's Cancer Study Group. J Clin Oncol 1991;9:2167-2176.

17. Douglass EC, Reynolds M, Finegold M, et al: Cisplatin, vincristine, and fluorouracil therapy for hepatoblastoma: a Pediatric Oncology Group Study. J Clin Oncol 1993;11:96-99.

18. 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;18:2665-2675.

19. Ammann RA, Plaschkes J, Leibundgut K: Congenital hepatoblastoma: a distinct entity? Med Pediatr Oncol 1999;32:466-468.

20. Stocker JT: Hepatoblastoma. Semin Diagn Pathol. 1994;11:136-143.

21. Haas JE, Muczynski KA, Krailo M, et al: Histopathology and prognosis in childhood hepatoblastoma and hepatocarcinoma. Cancer 1989;64:1082-1095.

22. Stringer MD, Hennayake S, Howard ER, et al: Improved outcome for children with hepatoblastoma. Br J Surg 1995;82:386-391.

23. Seo T, Ando H, Watanabe Y, et al: Treatment of hepatoblastoma: less extensive hepatectomy after effective preoperative chemotherapy with cisplatin and Adriamycin. Surgery 1998;123:407-414.

24. Black CT, Luck SR, Musemeche CA, et al: Aggressive excision of pulmonary metastases is warranted in the management of childhood hepatic tumors. J Pediatr Surg 1991;26:1082-1086.