Clinical characteristics and prognosis of 132 cases of infantile hepatoblastoma – A 14-year retrospective study from a single center

Tian Zhi

Beijing Tongren Hospital, Capital Medical University

Weiling Zhang

Beijing Tongren Hospital, Capital Medical University

Yi Zhang

Beijing Tongren Hospital, Capital Medical University

Huimin Hu

Beijing Tongren Hospital, Capital Medical University

Dongsheng Huang (✉ dshuang8623@163.com)

Research article

Keywords: hepatoblastoma, infant, AFP, chemotherapy, prognosis

Posted Date: May 21st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-29295/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background The study aimed to summarize the clinical data of hepatoblastoma (HB) in infants under 1 year of age, analyze their treatment effects and factors that affect the prognosis.

Methods Clinical data of 132 pathologically confirmed children under the age of 1 year old with hepatoblastoma who were admitted to the pediatric single center of Beijing Tongren Hospital, Capital Medical University from May 2005 to May 2019 were collected. The clinical efficacy and prognosis of combined treatment were summarized through retrospective analysis.

Results 1. Of the 132 children enrolled, 74 were male and 58 were female; median age was 8.40 months; the onset of disease was the most common (75.0%) of abdominal distension; infant HB had high AFP at the initial diagnosis, with an average level of (127406.5 ± 7232.5) ng/ml, the platelet value was $(405 \pm 166) \times 10^9/L$; the pathological type was mainly epithelial (57.6%), and most of the epithelial types were fetal (67.1%); the PRETEXT stage was mainly stage III (54.5%), followed by stage II (34.1%); 45 cases had distant metastases, most of which were lung metastases (86.7%); 24 patients (18.2%) had portal vein or hepatic vein or vena cava invasion, 5 (3.8%) had tumor rupture, and 26 (19.7%) had multiple intrahepatic lesions. 2. The patients were followed up to May 2020, with a median follow-up time of 58 months. Among them, 84 cases had complete remission and 18 cases had partial remission. According to Kaplan-Meier survival analysis, the 5-year overall survival rates (OS) were 80.1%; the event-free survival rates (EFS) were 77.5%. Log-rank test showed that HB patients with AFP > 1210 ng/ml at first diagnosis had a good prognosis; the EFS of the patients at PRETEXT IV stage was only 28.6%; children with distant tumor metastasis and multiple primary tumor lesions had poor prognosis, which were risk factors affecting the prognosis of infant HB ($P < 0.05$).

Conclusions Infant HB has its own characteristics. Through comprehensive treatment, the prognosis is relatively good, but it is still susceptible to multiple factors such as AFP level, PRETEXT stage, the presence of distant metastasis and multiple intrahepatic lesions.

Background

Hepatoblastoma (HB) is an embryonic malignant tumor with different differentiation methods, which is the most common among liver malignant tumors in infants and young children, and its incidence can reach 50–60%, especially in children under 3 years of age^[1–3]. In recent years, the incidence of HB in young children is rising, more and more infant hepatoblastomas have been diagnosed, and even some cases have found liver occupying in fetal B ultrasound during pregnancy, and then were pathologically confirmed as hepatoblastoma after birth^[4]. Once the diagnosis and treatment are delayed, the mortality rate is very high, which seriously affects the quality of life and prognosis of the children. Therefore, for infant HB, how to detect and intervene early is particularly important, which can effectively prolong the survival period. In this study, we retrospectively analyzed the clinical data of 132 children under the age of 1 year who were diagnosed by pathology in our single center from May 2005 to May 2019, and explored

the efficacy and prognostic factors of multidisciplinary combined therapy in order to provide clinical reference for the diagnosis and treatment of infant HB.

Methods

1 Research object

The clinical data of 132 cases under 1 year old with HB diagnosed by the pathology and/or imaging and serological examination of primary liver tumors admitted to the pediatric single center of Beijing Tongren Hospital, Capital Medical University from May 2005 to May 2019 were collected. In the course of treatment, all relevant examinations and treatments had obtained the consent of their guardians and signed an informed consent form.

2 Pathological classification and staging criteria

According to the tumor tissue morphology defined by the International Children's Hepatoblastoma Collaboration Group (CHIC) ^[5], the pathological tissue classification was divided into epithelial and mixed. The epithelial type was divided into fetal type, embryo type, megabeam type, and small cell undifferentiated type. The mixed type was divided into a mixed type of epithelial mesenchymal with teratoid-like tissue and no teratoid-like tissue. The PRETEXT staging system proposed by the International Childhood Liver Tumor Strategy Group (SIOPEL) ^[6] was divided according to the anatomy of the liver and the number of liver segments involved in the mass: in stage I, the tumor was confined to one liver segment, and 3 adjacent liver segments had no tumor invasion; in stage II, the tumor involved 2 liver segments, and the other 2 adjacent liver segments were not affected by tumor; in stage III, the tumor involved 2 liver segments, and the other 2 non-adjacent liver segments were not involved, or the tumor involves 3 liver segments; in stage IV, the tumor involved 4 liver segments.

3 Comprehensive treatment plan

For clinically suspected HB children with PRETEXT stage I or some with stage II tumors, their tumors could be removed by surgery first and then receive chemotherapy. For some children with PRETEXT stage II or children with stage III and IV tumors, neoadjuvant chemotherapy could be given first, and 2–4 chemotherapy cycles should be performed before surgery and 4–6 cycles of postoperative consolidation chemotherapy. The conventional first-line chemotherapy is C5V (cisplatin + fluorouracil + vincristine) and PLADO (cisplatin + doxorubicin). For cases with poor first-line chemotherapy effect or repeated relapses or metastases, individualized chemotherapy regimens could be used, such as irinotecan + cyclophosphamide + cisplatin + vincristine, etoposide + cisplatin + pirarubicin or cyclophosphamide + cisplatin + pirarubicin, the chemotherapy cycle could be extended to 12–18 cycles. All cases were rescued by mesna sodium after cyclophosphamide, and should be evaluated according to the classification

criteria of the toxic and side effects of WHO chemotherapy drugs during the chemotherapy. For patients with huge tumors, difficult surgical resection, or multiple metastases in the liver, arterial interventional embolization could be used [7], and interventional chemotherapy such as cisplatin and adriamycin could be given during the operation (15 patients in this document underwent arterial intervention chemoembolization). For some patients with PRETEXT stage IV tumors, or patients whose tumors could not be removed by portal vein invasion, or traditional surgery, or patients who get postoperative residual / relapse in the liver, liver transplantation could be considered. In addition, new therapeutic methods such as targeted therapy and molecular biological therapy could also be used.

4 Monitoring indicators, follow-up and evaluation criteria

Imaging examination (B-ultrasound, CT) of the primary and / or metastatic lesions was performed every 2 cycles of chemotherapy. Serum alpha-fetoprotein (AFP) was detected before each chemotherapy (the instrument used the Roche Cobas e601 electrochemiluminescence immunoassay analyzer to detect AFP, the normal range was < 20 ng / ml, when the value exceeded 1210 ng / ml, the dilution was used for dilution titration to continue to detect the true value), and human chorionic gonadotropin (hCG) in some cases was also detected (normal value < 2.5mIU / ml). Peripheral blood routine, liver and kidney function, myocardial enzymes and other indicators were monitored during chemotherapy. The follow-up date ended in May 2020, and it was completed by means of returning to the hospital for review and telephone follow-up. According to the follow-up results, the clinical data, overall survival (OS) and event-free survival (EFS) of the children were counted, and the prognostic factors and the safety of chemotherapy were analyzed.

5 Criteria for curative effect

[8] Complete remission (CR): the tumor completely disappeared after treatment, there was no evidence of tumor residual on imaging, and serum AFP was normal for more than 4 weeks; Partial remission (PR): tumor shrank by more than 50%, no new lesions, and serum AFP significantly decreased; Progression: the tumor had increased by more than 25% or a new tumor had appeared during treatment, or the AFP had increased or exceeded the normal value for 2 consecutive weeks; Recurrence: after complete remission of the tumor, pathological biopsy confirmed the recurrence of the tumor or there was clear imaging evidence and serum AFP increased three consecutive times within four weeks; or died.

6 Statistical methods

SPSS 19.0 software was used to perform statistical analysis on the data. Comparison between groups was performed using χ^2 test, Kaplan-Meier method was used for survival analysis, and Log-rank test was used to compare survival rates among subgroups. $P < 0.05$ was considered statistically significant.

Result

1 Clinical features

1.1 Clinical symptoms:

The clinical data of 132 patients enrolled are shown in Table 1. Among them, 74 were male and 58 were female, male / female = 1.27, the age ranged from 0.93 months to 11.57 months, the median age was 8.40 months, and the age of onset was more than 6 months (62.1%). In this study, 3 patients' fetal B-ultrasound revealed high echogenicity in the liver area during the pregnancy (32–36 weeks of gestation), that is, hepatic space-occupying lesions were found, and hepatoblastoma was pathologically diagnosed after birth. Among them, one child was born with very low birth weight, and two children were born with low birth weight, with birth weights of 1360 g, 1950 g and 2130 g, respectively. The mothers of 2 cases were advanced aged pregnant with gestational hypertension, and the mother of the other one had a history of smoking. 6 children in this study were test-tube babies, three of which were fraternal twins. The onset of HB in infancy is mostly hidden. At the first diagnosis, 99 cases (75.0%) of abdominal bulging were found most frequently; followed by anorexia, vomiting and diarrhea in 18 cases (13.6%). 6 cases (4.5%) of no weight increase and anemia, 5 cases (3.8%) of yellow skin, and 4 cases (3.0%) of physical examination.

Table 1
Clinical characteristics of 132 infant HB

Characteristics		Number	Proportion (%)
Gender	Male	74	56.1
	Female	58	43.9
Age(months)	≤6	50	37.9
	>6	82	62.1
AFP at initial diagnosis(ng/ml)	≤1210	19	14.4
	>1210	113	85.6
Platelet count at initial diagnosis($\times 10^9/L$)	≤ 400	57	43.2
	>400	75	56.8
Pathological classification	Epithelial type	76	57.6
	Fetal type	51	67.1
	Embryo type	21	27.6
	Megabeam type	2	2.6
	Small cell undifferentiated type	2	2.6
	Mixed type	56	42.4
PRETEXT stage	I	8	6.1
	II	45	34.1
	III	72	54.5
	IV	7	5.3
Vascular invasion	Yes	24	18.2
	No	108	81.8
Tumor rupture	Yes	5	3.8
	No	127	96.2
Distant metastasis	Yes	45	34.1
	No	87	65.9
Multiple liver lesions	Yes	26	19.7
	No	106	80.3

1.2 Laboratory indicators, histopathology and clinical staging:

In this group of data, the platelet value at the time of initial diagnosis was $(405 \pm 166) \times 10^9/L$, the highest value was $1550 \times 10^9/L$, and the lowest value was $102 \times 10^9/L$. 85.6% of HB infants had AFP > 1210 ng/ml at the time of initial diagnosis, with an average level of (127406.5 ± 7232.5) ng/ml, a range maximum value > 484000 ng/ml, and a minimum value of 43.6 ng/ml. We conducted an hCG test on 30 HB infants in this group at the time of initial diagnosis. Among them, 19 patients had elevated hCG, ranging from 7.28-1040mIU/ml. In the 19 cases, there was a 9-month-old male patient with hCG level of 988mIU/ml, who showed precocious puberty signs of penile enlargement and scrotal pigmentation. 76 cases (57.6%) of the pathological tissue types were epithelial and 56 cases (42.4%) mixed. Among the epithelial types, the fetal type was the most (67.1%), and the embryo type was the second (27.6%). The PRETEXT staging system was mostly in stage III, accounting for 54.5%; followed by stage II, accounting for 34.1%.

1.3 Transfer situation:

In this study, 45 patients were found to have distant metastases at the time of diagnosis. The most common metastatic sites were lungs, accounting for 86.7% (39/45). There were 27 cases of single lung metastasis (10 cases of left lung metastasis and 17 cases of right lung metastasis), and 12 cases of double lung metastasis; 29 cases of marginal zone metastasis (74.4%) and 10 cases of marginal zone combined with central lung metastasis (25.6%). There were 6 cases of intracranial metastasis, 4 cases of bone metastasis, 2 cases of right atrial tumor thrombus, 1 case of intestinal and mesenteric metastases, and 1 case of intraspinal metastases. At the time of diagnosis, 24 patients (18.2%) had portal vein or hepatic vein or vena cava invasion, 5 (3.8%) had tumor rupture and hemorrhage, and 26 (19.7%) had multiple intrahepatic lesions.

2 Survival And Prognosis Analysis

The patients were followed up to May 2020 (follow-up time 2-162 months), with a median follow-up time of 58 months. Among them, 84 cases had complete remission and 18 cases had partial remission and the treatment effective rate was 77.3% (102/132); 9 cases progressed and 21 died. According to Kaplan-Meier survival analysis, the 1-year, 3-year, and 5-year survival rates (OS) were 94.3%, 88.8%, and 80.1%; the event-free survival rates (EFS) were 91.8%, 86.9% and 77.5%, respectively (Fig. 1). A total of 78 cases achieved complete tumor resection (32 of them could not be resected due to their huge tumors, but the tumors were significantly smaller than before after regular chemotherapy in our center before surgery, thus obtaining the operative opportunity for complete tumor resection), with a complete resection rate of 59.1%.

We conducted a log-rank test to analyze the factors that may affect the prognosis of HB, and compared the 5-year EFS between different subgroups (Table 2). The results showed that HB patients with AFP > 1210 ng/ml at the initial diagnosis had a better prognosis, and the 5-year EFS could reach 84.5% (Fig. 2).

The PRETEXT stage is also a statistically significant risk factor. All children in PRETEXT I survived, while the survival rate of children in PRETEXT IV decreased significantly, only 28.6% (Fig. 3). In addition, children with distant tumor metastases and multiple primary tumors had a poor prognosis (Fig. 4–5). Survival rate was not significantly related to gender, age of onset, platelet level, pathological classification, presence or absence of vascular invasion, and tumor rupture ($P > 0.05$, no statistical difference) in this study.

Table 2
Single factor comparison of 132 cases of infantile HB with 5-year EFS

Factor		5 years EFS (%)	χ^2	P
AFP at initial diagnosis(ng/ml)	≤1210	50.3	4.074	0.044
	>1210	84.5		
PRETEXT stage	I	100	18.682	0.000
	II	97.8		
	III	69.4		
	IV	28.6		
Distant metastasis	Yes	63.5	15.032	0.007
	No	89.2		
Multiple liver lesions	Yes	31.5	32.087	0.000
	No	85.7		

3 Treatment Safety Evaluation

Systemic chemotherapy may show toxic effects in children with HB. According to the WHO classification criteria for toxic and side effects of chemotherapy, 15 cases (11.4%) were of grade 0 toxic reactions after chemotherapy, 28 cases of grade I (21.2%), 48 cases of grade II (36.3%), 31 cases of grade III (23.5%) and 10 cases of grade IV (7.6%) in this study. The main manifestations are bone marrow suppression, liver and kidney function damage and myocardial injury after chemotherapy. Among them, 8 cases of grade IV showed hemoglobin < 65 g/L and/or platelet $< 25 \times 10^9$ /L, and improved after giving the component blood transfusion. There were 32 children (24.2%) with transient liver and kidney function damage, which improved with symptomatic treatment. One patient had severe myocardial damage, whose BNP was 1068 pg/ml and electrocardiogram showed a prolonged QT interval and non-specific ST-T segment change. There were no obvious abnormalities in echocardiography, creatine kinase and creatine kinase isoenzyme. After stopping using the drugs that may affect myocardial function immediately, and receive active nutritional myocardial treatment, BNP gradually returned to the normal range, and the

electrocardiogram was better than before. No obvious abnormalities in hearing were found in all patients during chemotherapy. No second tumor occurred after chemotherapy in this study.

Discussion

In recent years, with the continuous improvement of diagnosis and treatment, the prognosis of HB has been greatly improved. The research led by Einar Hafberg^[9] showed that the current 5-year overall survival rate of HB children had reached 75%, and the 5-year EFS had also reached about 65–70%. In this paper, HB was investigated for infants under 1 year old (median age 8.40 months). The median follow-up time was 58 months. The results showed that the 5-year overall survival rate was 80.1% and the event-free survival rate was 77.5%, both of which were higher than those reported in the literature, suggesting that infants with HB had a relatively good prognosis.

Some scholars had studied children with HB found in pregnancy and diagnosed after birth, and found that children with low birth weight, especially those with a weight less than 1000 g, were more likely to develop HB in the future^[10]. Other studies had shown that factors such as advanced maternal age, hypertension during pregnancy, excessive weight, excessive amniotic fluid, and a history of smoking all increased the incidence of HB^[11–12]. The three HB patients found during pregnancy in this study were all low birth weight infants, and there were risk factors such as advanced maternal age, maternal hypertension and smoking history, which were consistent with the views of foreign scholars. In this data, 6 IVF (in-vitro fertilization) infants were also diagnosed with HB in infancy, and 3 of them were fraternal twins. Although there are no studies to prove that IVF, twin or multiple pregnancy may increase the prevalence of HB, it is important to note that the pregnant state is easy to cause fetal hydramnios and increase the risk of pregnancy complications, these factors could increase the test-tube baby and multiple birth's probability of developing HB.

Studies had shown that^[13], peripheral platelet count may increase when patients getting infected or having malignant tumors and some chronic diseases. More than half (56.8%) of the cases in this data have elevated platelets. However, through risk factor analysis, whether the platelets will increase is not significantly related to the prognosis of infant HB, it is not consistent with the report above, and this may because the cases are very few. AFP is a special protein in the blood produced by the liver. At present, domestic and foreign experts had reached a consensus that AFP was an important tumor marker of HB. Not only the level of its initial diagnosis was important for prognosis judgment, but also it was always an important indicator for observation of therapeutic effects in the treatment process. Scholars such as Meyers RL had suggested that low levels of AFP at the initial diagnosis were indicators of poor prognosis^[14]. The results of this study showed that the AFP of infant HB was mostly high at the initial diagnosis, and the prognosis was relatively good; while the prognosis of cases with AFP < 1210 ng/ml was poor, consistent with relevant foreign reports. Such children are often insensitive to chemotherapy and easy to relapse, resulting in shortened survival period. It should be noted that some normal full-term newborns may also have increased AFP, which needs to be distinguished from HB in the neonatal period, but the

former falls to the normal range more than 2–3 months after birth. HCG is secreted and synthesized by the trophoblast cells of the placenta, and can stimulate the testes of the fetus to secrete testosterone to promote male differentiation ^[15]. In rare cases, HB tumor cells can secrete hCG, which leads to precocious puberty and is more common in boys. Malati T ^[16] believes that increased secretion of hCG is not a common phenomenon of HB, and its level has no clear relationship with the prognosis of HB, and the occurrence of precocious puberty is rare. At present, domestic and international reports of precocious puberty caused by hCG are mainly based on case reports. The case of HB in our center with premature puberty caused by elevated hCG was a boy. After comprehensive treatment, the hCG progressively decreased, suggesting that the level of hCG might become another important biological marker of HB after AFP. However, a large sample of clinical data is needed for subsequent research and verification.

Compared with older children, HB in infancy is dominated by pure fetal type with relatively good differentiation ^[17]. Through statistical analysis of big data, Piotr Czauderna ^[18] concluded that complete fetal HB had a better event-free survival time than other pathological types, and small cell undifferentiated type was considered to be an important negative factor to affect prognosis. According to the distribution of pathological tissues in this study, epithelial type was dominant in infant HB, and the fetal type with good prognosis was the most in the epithelial type, which was consistent with the literature reports. Although the final statistical results of this study did not support the correlation between pathological classifications and prognosis ($P > 0.05$), 2 children with small cell undifferentiated type all died finally in this group of data. According to a retrospective study, SIOPEL believes that the PRETEXT stage can predict the resectability of the tumor to a certain extent ^[19], which is important for the prognosis either. Because the complete resection of liver tumors is the key to treatment for HB children. The data in this group showed that the EFS of patients with PRETEXT stage IV was significantly lower than that of children with other stages. It also confirmed that PRETEXT stage was significantly related to prognosis.

Infant HB can have systemic metastasis early in the course of the disease. Like older HB children, the lung is the most common metastatic site, mostly from blood transfer, and it is likely to occur in the lung margin or terminal vascular supply area ^[20], and nodular shadow of extrapulmonary zone can be seen in imaging. In the 45 cases of distant metastasis in this study, 86.7% had lung metastasis, which is consistent with literature reports. Other metastatic sites can also be found in brain, bone, etc. It is worth mentioning that there was one case of HB with right atrial tumor thrombus in this data. It is very difficult for the tumor cells to form a tumor thrombus in heart blood vessels where blood flows very fast, so this was a rare case in China. Unfortunately, despite receiving active treatment, the patient eventually died of ventricular fibrillation due to the shedding of atrial tumor thrombus. Because much more blood flows in the liver, HB is prone to intrahepatic metastasis, forming multiple liver lesions and venous tumor thrombus. If it is not clear, it is prone to tumor recurrence and distant dissemination. The results of this study showed that the prognoses of HB with distant metastases and multiple liver lesions were relatively poor, which were consistent with literature reports ^[21].

Infant HB is sensitive to chemotherapy [22]. Although multidisciplinary treatments such as surgery, interventional therapy, targeted therapy and immunotherapy are gradually developed, surgical resection combined with chemotherapy is still the main treatment option. Preoperative chemotherapy can effectively shrink the tumor to create an opportunity for complete surgery to remove the tumor. Postoperative consolidation chemotherapy can effectively prevent the recurrence of residual tumor and improve the cure rate. The patients in this group mainly used chemotherapy combined with surgical treatment. Individualized chemotherapy was adopted for high-risk cases of recurrence, distant metastasis, tumor thrombus invasion and refractory, and achieved good clinical efficacy. According to the WHO classification criteria for toxicity of chemotherapy, the systemic toxic and side effects of chemotherapy for infants with HB in this data are mainly concentrated in grade II, and the proportion of grade IV is not high. This may be related to the body's strong metabolism regeneration ability, and good tolerance to chemotherapy drugs in infant. It can also be seen that the chemotherapy regimen in this study is safe. However, because infants are young, the organs are imperfectly developed, and chemotherapy drugs can cause organ damage (especially platinum drugs can cause liver and kidney function and hearing damage, anthracycline drugs can cause heart damage) and even the risk of secondary tumors, it is necessary to regularly evaluate organ functions to ensure the safety of medication. For children with refractory HB, high-dose chemotherapy combined with autologous peripheral blood stem cell transplantation (APBSCT) can also be used. Our center had treated APBSCT for a 3-year-old HB patient, which had significantly prolonged the survival time of the child, but it had not yet been carried out in infant HB. I look forward to the next treatment in infant HB. In recent years, liver transplantation had been successful in treating unresectable or PRETEXT IV HB children, and there were reports in the literature that its 5-year survival rate was close to 85% [23]. In this study, 1 infantile child with HB who had multiple intrahepatic tumor foci was still not effective after conventional surgery, chemotherapy and arterial embolization. Living liver transplantation was performed at the age of 8 months and was successful. After transplantation, the patient underwent consolidation chemotherapy for 2 cycles. Regular reexamination of AFP and imaging showed CR after that.

Conclusions

Infant HB has its corresponding characteristics. Through comprehensive treatment methods such as chemotherapy and surgery, infant HB has a relatively good prognosis, but it is still susceptible to multiple factors such as AFP level, PRETEXT stage, whether there are distant metastasis and multiple intrahepatic lesions. At the same time, this study is only for the diagnosis and treatment data collected by the single center of Beijing Tongren Hospital, Capital Medical University, and the number of cases is still small. More clinical data and multi-center joint research will be collected in the future, so as to provide clinical reference for the multidisciplinary treatment of HB.

Abbreviations

AFP

alpha-fetoprotein

APBSCT

autologous peripheral blood stem cell transplantation

CHIC

Children 's Hepatoblastoma Collaboration Group

CR

complete remission

EFS

event-free survival

HB

hepatoblastoma

hCG

human chorionic gonadotropin

OS

overall survival

PR

partial remission

PRETEXT

Pre-treatment extent of tumour

SIOPEL

International Childhood Liver Tumor Strategy Group

Declarations

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

In the course of treatment, all relevant examinations and treatments had obtained the consent of their guardians and signed an informed consent form, ,and had been approved by the ethics committee of Beijing Tongren Hospital, Capital Medical University(Ethical batch No: TRECKY2019-033).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding.

Authors' contributions

DSH conceptualized and designed the study, TZ drafted the initial manuscript, DSH and WLZ reviewed and revised the manuscript. TZ, YZ and HMM collected data, and carried out the initial analyses. DSH coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Acknowledgements

None.

References

1. Tan ZH, Lai A, Chen CK,et al. Association of trisomy 18 with hepatoblastoma and its implications [J]. Eur J Pediatr. 2014;173,(12):1595–8.
2. Alicia M, Waters ,Michelle S, Mathis, Elizabeth A, Beierle. A Synopsis of Pediatric Patients With Hepatoblastoma and Wilms Tumor: NSQIP-P 2012–2016[J]. The Journal of surgical research,2019,244: 338–342.
3. Ayllon Teran D, Gmez Behran O, Ciria Bru R. et a1.Efficacy of neoadjuvant therapy and surgical rescue for locally advancedhep,atoblastomas: 10 year sinde.center experience and literature review[J]. World J Gastroenterol. 2014;20(29):10137–10143.
4. Hadžić Nedim; Cho Soo-Jin; Finegold Milton J. Hepatoblastoma surveillance in infants born with very low birth weight: Has the time come? [J] The Journal of pediatrics,2020,216:248–249.
5. Rebecka L. Meyers R,Tiao G,et a1.Hepatoblastoma state of the art: pretreatmentextent of disease.surgical resection guidelines and the role of liver transplantationI [J]. Curt Opin Pediatr. 2014;26(1):29–36.
6. Roebuck DJ, Aronson D, Clapuyt P, Czauderna P, de Ville de Goyet J, Gauthier F, et al. International Childhood Liver Tumor Strategy Group 2005 PRETEXT: A revised staging system for primary

- malignant liver tumors of childhood developed by the SIOPEL group. [J] *Pediatr Radiol*. 2007;37:123–32.
7. Jiang Y, Zhou S, Shen G, et al. Microwave ablation combined with transcatheter arterial chemoembolization is effective for treating unresectable hepatoblastoma in infants and children. [J] *Medicine*,2018,97(42):e12607.
 8. Matsunaga T, Sasaki F, Ohira M, et al. Analysis of treatment outcome for children with recurrent or metastatic hepatoblastoma [J]. *Pediatr Surg Int*,2003,19(3): 142–146.
 9. Einar Hafberg S, Borinstein, Sophoclis P, et al. Contemporary management of hepatoblastoma[J]. *Current opinion in organ transplantation*, 2019,24(3):113–117.
 10. Kenichi Maruyama H, Ikeda. Takenobu Koizumi, et al. Prenatal and postnatal histories of very low birthweight infants who developed hepatoblastoma [J]. *Pediatrics International*,1999,41(1): 82–89.
 11. Heck JE, Meyers TJ, Lombardi C, et al. Case-control study of birth characteristics and the risk of hepatoblastoma[J]. *Cancer Epidemiol*. 2013;37(4):390–5.
 12. Johnson KJ, Carozza SE, Chow EJ. et al. Parental age and risk of childhood cancer: a pooled analysis. *Epidemiology*,2009,20: 475–483.
 13. Zhang Y, Zhang W, Tang S, et al. A single-center retrospective study of pediatric hepatoblastoma[J]. *Oncology Letters*, 2016,12(5):3919–3925.
 14. Meyers RL, Tiao G, Goyet JV, et al. Hepatoblastoma state of the art: pre-treatment extent of disease, surgical resection guidelines and the role of liver transplantation[J]. *Curr Opin Pediatr*. 2014;26(1):29–36.
 15. Yoshida E, Lone YA, Mahajan JK. et al. Hepatoblastoma with Precocious Puberty. [J] *Indian Assoc Pediatr Surg*. 2019;24(1):68–71.
 16. Malati T. Clinical relevance of AFP, its molecular variants and hCG in hepatoblastoma and childhood germ cell tumors. *Clin Biochem*. 2014;47:734.
 17. Angela D, Rebecka L, Allison F, et al. Unresectable hepatoblastoma : current perspectives. [J] *Hepatic Medicine*. 2017;9:2–6.
 18. Piotr Czauderna B, Haeberle E, Hiyama, 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.[J]. *Eur J Cancer*. 2016;52:92–101.
 19. Maibach R, Roebuck D, Brugieres L, et al. Prognostic stratification for children with hepatoblastoma: The SIOPEL experience. [J]. *Eur J Cancer*. 2012;48:1543–9.
 20. Roberta Angelico C, Grimaldi. Carlo Gazia, et al. How Do Synchronous Lung Metastases Influence the Surgical Management of Children with Hepatoblastoma? An Update and Systematic Review of the Literature[J]. *Cancers*, 2019,11(11).
 21. Lake CM, Tiao GM, Bondoc AJ, et al. Surgical management of locally-advanced and metastatic hepatoblastoma[J]. *Semin Pediatr Surg*. 2019;28(6):150856.

22. Naresh Shanmugam,Julius Xavier Scott,Vimal Kumar. et al. Multidisciplinary management of hepatoblastoma in children: Experience from a developing country[J]. Pediatric Blood and Cancer. 2017 (3).

23. Leandro Lauferman E, Halac D, Aredes, et al. Prognostic factors for event-free survival in liver transplantation for hepatoblastoma: A single-center experience. [J]Pediatric Transplantation. 2019;23(8):e13581.

Figures

Figure 1

Overall survival curve and event-free survival curve of 132 infant HB

Figure 2

The effect on prognosis of different AFP level at the initial diagnosis

Figure 3

Comparison of survival in different PRETEXT stages

Figure 4

Comparison of survival for distant metastasis

Figure 5

Comparison of survival of primary tumors with multiple lesions or not