

Analysis of factors related to recurrence of paediatric hepatoblastoma -A single centre retrospective study

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Research article

Keywords: relapsed hepatoblastoma, alpha fetoprotein, risk factor

Posted Date: November 11th, 2019

DOI: <https://doi.org/10.21203/rs.2.14548/v2>

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Version of Record: A version of this preprint was published on December 10th, 2019. See the published version at <https://doi.org/10.1186/s12887-019-1870-3>.

Abstract

Purpose: This study was performed to identify risk factors associated with recurrence of hepatoblastoma.

Methods: A retrospective study was conducted on 56 patients with hepatoblastoma from 2012 to 2015 in Beijing Children's Hospital. PRETEXT stage, serum alpha fetoprotein (AFP) value, change trend of tumors after treatment and some other clinical characteristics were collected and analyzed. The comparison of independent variables that were not distributed normally was performed with the log-rank test.

Results: 28 patients with tumor recurrence and 28 non-recurrence patients were included in this study, the median age at presentation was 46.5 (26, 71.5) months. There was a significant difference in the 3-year recurrence free survival (RFS) probability between the patients over 54 months and those younger than 54 months ($p=0.007$). After neoadjuvant chemotherapy, the chance of recurrence in PR patients was shown to be significantly lower than that in SD patients ($p=0.004$). The 3-year RFS of patients with a decrease in AFP of more than 60% after neoadjuvant chemotherapy was significantly higher than that of patients with a decrease rate of less than 60% ($p=0.005$). Postoperative follow-up revealed that patients whose postoperative AFP fell to normal levels within six months of the start of treatment had a three-year RFS of 68.6%, which is higher than that of patients whose AFP fell below the normal range after six months ($p=0.0005$). Finally, multivariate analysis by Cox regression showed that AFP that decreased by less than 60% and tumour size that decreased by less than 50% after neoadjuvant chemotherapy were significant independent prognostic risk factors for 3-year RFS. Other clinical features were not significantly associated with tumor recurrence in this study.

Conclusion: Through this study, we concluded that the prognosis of childhood HB is related to the age at presentation and the response of chemotherapy. The results of the multivariate analysis showed that AFP that decreased by less than 60% and tumour size that decreased by less than 50% after neoadjuvant chemotherapy were significant independent prognostic risk factors. These findings can be helpful to evaluate therapeutic effects and predict prognosis.

Key words: hepatoblastoma; alpha fetoprotein; risk factor

Background

Hepatoblastoma (HB) is a rare type of primary malignant liver tumour that mostly occurs in infants and children under 3 years of age [1]. The pathological features of HB consist of tissues resembling foetal liver cells, mature hepatocytes or biliary cells [2]. The most common symptom is abdominal mass [3]. An important method of examination for HB is measuring the serum alpha-fetoprotein (AFP) value. The patient will be suspected of having HB if he or she has an obviously elevated AFP value. However, the prognosis of patients with HB is poor if AFP is not elevated at diagnosis [4,5]. AFP is also used as a sensitive marker of successful treatment. If the tumour is completely removed, the AFP value will gradually drop to normal [6].

Currently, surgical tumour resection, chemotherapy and orthotopic liver transplantation are used for the treatment of HB [7,8]. The survival of patients with HB relies largely on surgical resection [9,10]. Experience has demonstrated that HBs respond well to chemotherapy and that cisplatin-based regimens result in good outcomes for these tumours. Some clinical research demonstrates that doxorubicin (if not given during initial treatment) and irinotecan are effective for relapsed and refractory tumours [11]. However, the long-term survival of patients with recurrence of refractory HB is relatively low, especially in patients with distant metastases [12,13]. The treatment of relapsed patients still faces some challenge. Thus, it is important to identify relevant factors to predict the possibility and reduce the risk of recurrence.

Methods

Study subjects

A single-centre retrospective analysis of 56 patients with HB diagnosed in Beijing Children's Hospital between June 2012 and September 2015 was performed to identify risk factors associated with prognosis. This study included 28 patients with relapsed HB (21 with local recurrence and 7 with pulmonary metastases) and 28 patients without recurrence who were selected from 68 patients using a random numbers table method after excluding some patients with missing data in the same period. The patients were diagnosed based on pathological findings and were assessed by serum AFP level and abdominal computed tomography (CT) or magnetic resonance imaging (MRI) with contrast enhancement. Distant metastases, such as lung metastases, were identified by positron emission tomography (PET)/ CT or CT scan. The patients were categorized into four stages based on the pretreatment extension (PRETEXT) staging system adopted by the International Childhood Liver Tumors Strategy Group (SIOPEL) [14]. Furthermore, these cases were stratified into standard-risk and high-risk groups according to additional criteria.

Treatment

For PRETEXT II, III and IV cases, 4 cycles of neoadjuvant chemotherapy were adopted after pathological confirmation via core needle biopsy. Neoadjuvant chemotherapy consisted of C5V (20 mg/m² cisplatin on days 1–5, 300 mg/m² fluorouracil on days 1–2, 1.5 mg/m² vincristine on day 2) for the standard-risk group and C5VD (20 mg/m² cisplatin on days 1–5, 300 mg/m² fluorouracil on days 1–2, 1.5 mg/m² vincristine on day 2, 25 mg/m² pirarubicin on days 1–3) or PLADO (20 mg/m² cisplatin on days 1–5, 25 mg/m² pirarubicin on days 1–3) for the high-risk group. Then, the patients underwent tumourectomy. After surgery, patients underwent 4–8 cycles of chemotherapy. Adjuvant chemotherapy regimens consisted of C5V (20 mg/m² cisplatin on days 1–5, 300 mg/m² fluorouracil on days 1–2, 1.5 mg/m² vincristine on day 2) for the standard-risk group and C5VD (cisplatin on days 1–5, 300 mg/m², fluorouracil on days 1–2, 1.5 mg/m² vincristine on day 2, 25 mg/m² pirarubicin on days 1–3) or cumulative cisplatin dose (CCD) (80 mg/m² cisplatin on day 1, alternating every 2 weeks with 500 mg/m² carboplatin on days 1–2 plus 30 mg/m² doxorubicin on days 1–2).

Clinical evaluation

We evaluated each patient using a post-treatment extension (POSTTEXT) system and analysed the serum AFP value using laboratory tests through the laboratory of Beijing Children's Hospital after neoadjuvant chemotherapy and after surgery. It was recorded as ng/ml (normal range, 0–8 ng/ml). Moreover, the time when the AFP value dropped to normal was recorded. Furthermore, according to the evaluation criteria of the World Health Organization (WHO) solid tumour treatment effect, we measured two major vertical diameters and calculated their product before and after neoadjuvant chemotherapy to evaluate the change trend of tumour size. The evaluation of the response of objective lesions was performed as follows: complete response (CR), disappearance of all target lesions; partial response (PR), at least a 50% decrease in the product of the major vertical diameters of target lesions; stable disease (SD), decrease in the product of major vertical diameters of the target lesions less than 50% or an increase of more than 25%; and progressive disease (PD), a 25% increase in the product of the major vertical diameters of the target lesions or the appearance of new lesions [15]. Other clinical characteristics were collected and analysed retrospectively, including age at presentation, sex, pathological subtype, initial AFP values, surgical strategy, and residual tumour. The purpose was to identify confounding factors.

Followup

Patients were followed up every three months until August 2018 by email and telephone.

We investigated the patient survival, recurrence and progression and the value of serum AFP.

We defined recurrence as both local recurrence and distant metastasis, which were annotated separately in Table 1.

Statistical analysis

Survival was calculated by using the Kaplan-Meier method with a confidence interval (CI) of 95%. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off values and to analyse factors relevant to tumour recurrence. The comparison of independent variables that were not distributed normally was performed with the log-rank test. SPSS software version 20.0 was used for statistical analysis. $P < 0.05$ was considered to represent a significant difference.

The current study was approved by the Committee on Human Study of the Beijing Children's Hospital and the Ethics Review Committee of Beijing Children's Hospital (No. 2019-k-11).

Results

Treatment and response

A total of 56 patients (32 male and 24 female) were included in this study. Twenty-eight patients experienced tumour recurrence after surgery. Among them, 21 (75%) patients had local recurrence, and 7 (25%) had lung metastases. Follow up was performed until August 2018, with a median follow-up time of 44 months. Seven of the patients died due to tumour recurrence or progression, 46 patients survived and 3 were lost to follow-up. The 3-year overall survival (OS) rate was 72% for the recurrence patients and 100% for the non-recurrence patients. Thirty-five patients with standard-risk HB received neoadjuvant chemotherapy of C5V, 17 with high-risk HB received C5VD, and 4 with high-risk HB received PLADO for 4 cycles before surgical tumour resection was performed. After induction chemotherapy, the product of the median of the major vertical diameters decline ratio was 52.5 (40.5, 60.75) %. According to the evaluation criteria of the WHO solid tumour treatment effect, 32 patients defined as achieving a PR, and 24 patients were defined as having SD; there were no CR or PD cases. The 3-year recurrence-free survival (RFS) rates of the PR and SD cases were 65.6% and 29.2%, respectively (Figure 1). Based on the statistical analysis, the chance of recurrence in PR patients after chemotherapy was shown to be significantly lower than that in SD patients ($p = 0.004$) (Table 2).

After receiving 4 cycles of neoadjuvant chemotherapy, serum AFP decreased significantly in most patients before surgery. The AFP values of 10 of the patients fell back into the normal range. The 3-year RFS of patients with a decrease in AFP of more than 60% (68%) after neoadjuvant chemotherapy was significantly higher than that of patients with a decrease rate of less than 60% (28%) ($p = 0.005$) (Table 2) (Figure 1). All patients were reassessed according to the POSTTEXT staging system. There were 9 patients with POSTTEXT I, 30 with POSTTEXT II, and 17 with POSTTEXT III. There were no significant differences in 3-year RFS in terms of different POSTTEXT stages ($p = 0.476$). All patients underwent liver tumour resection, 14 underwent left lobectomy, 33 underwent right lobectomy and 9 underwent extended hepatectomy. The pathological reports showed 45 (80.3%) cases with negative margins and 7 (12.5%) with positive margins, with 3-year RFS rates of 51.1% and 42.9%, respectively ($p = 0.718$). Twenty-nine patients received the C5V chemotherapy regimen, 19 received C5VD and 8 received CCD for 6–8 cycles after operation. Postoperative follow-up revealed that patients whose postoperative AFP fell to normal levels within six months of the start of treatment had a three-year RFS of 68.6%, which is higher than that of patients whose AFP fell below the normal range after six months (50%) ($p = 0.0005$) (Table 2).

Clinical characteristics

In this study, the median age at presentation was 46.5 (26, 71.5) months (range, 7 months to 141 months). There was a significant difference in the 3-year RFS probability between the patients over 54 months (25%) and those younger than 54 months (63.9%) ($p = 0.007$) (Table 1).

The patients were categorized based on 5 pathological subtypes: foetal, embryonal, foetal-embryonal mixed, macro-trabecular and small cell undifferentiated (SCU) based on the international paediatric liver tumour consensus classification of the Children's Oncology Group (COG) [16]. The numbers of patients with each subtype were 2, 9, 35, 3, and 1, respectively. There were six patients for whom the pathological subtype was unable to be defined. Because the number of patients with SCU was small, it was not

possible to conduct a survival analysis for each pathological subtype between children with recurrence and non-recurrence.

In this study, 26 (46%) patients were in PRETEXT II, 26 (46%) were in PRETEXT III and 4 (8%) were in PRETEXT IV based on imaging assessment. The 3-year RFS differed between different PRETEXT stages but was not statistically significant ($p = 0.089$). Moreover, the PRETEXT annotation factors were documented as follows: "P"- Macrovascular involvement of portal vein; "V"- involvement of hepatic veins and vena cava; "C"- involvement of the caudate lobe; "F"- multifocal tumour; "E"- extrahepatic tumour; "R"- tumour rupture or haemorrhage; "N"- positive lymph nodes and "M"- distant metastasis. Among these patients, 26 (46%) had annotation factors. The patients were classified into a standard-risk group (27/56, 48%), defined as PRETEXT I, II, or III, and a high-risk group (29/56, 52%), defined as PRETEXT IV or the presence of annotation factors based on risk stratification recommend by SIOPEL (Table 1) [17]. The 3-year RFS differed between different risk groups, but the difference was not statistically significant ($p = 0.239$).

Among the 56 patients, the median initial serum AFP value was 31125 (5434, 74250) ng/ml (range, 1330000 ng/ml to 1778 ng/ml). The product of the two major vertical diameters of tumour lesions was calculated to estimate tumour size at the beginning of treatment, with a median of 100.84 (69.76,142.31) cm^2 (range, 227.52 cm^2 to 36 cm^2). In the assessment of 3-year RFS, these two characteristics had no statistically significant difference in terms of tumour recurrence.

Risk factors

Finally, multivariate analysis by Cox regression was performed. The results showed that AFP that decreased by less than 60% and tumour size that decreased by less than 50% after neoadjuvant chemotherapy were significant independent prognostic risk factors for 3-year RFS.

Discussion

HB is the most common primary hepatic malignant tumour in children, with an annual incidence of 1.2–1.5 cases per million people [18]. The comprehensive treatment strategy of surgery combined with chemotherapy has greatly improved the overall prognosis of HB, but the disease is still life-threatening for some patients due to the recurrence or progression of the disease [19, 20]. This study focused on the factors related to HB recurrence and found the following risk factors in this study: patient age older than 54 months, AFP that decreased by less than 60% after the patient received neoadjuvant chemotherapy, tumour size that failed to achieve partial remission after neoadjuvant chemotherapy, and AFP that failed to return to a normal range within six months after receiving treatment.

HBs occur mostly in young children, especially in patients under three years of age. Age was not considered a separate risk factor in previous risk classifications recommended by the COG and SIOP. In this study, the probability of recurrence in children with an onset age older than 54 months was significantly higher. This finding suggested that older children with HB have a probability of poor

prognosis. As a serum marker of HB, AFP is a sensitive indicator for determining a good response to chemotherapy. After chemotherapy, most patients will have a significant decline in AFP levels. This phenomenon has been studied and reported by many experts [21]. The purpose of this study was to find a specific point value to assess the relationship between prognosis and the trend of AFP decline after neoadjuvant chemotherapy. After analysis, it was shown that if the patient's AFP value dropped by more than 60% after preoperative chemotherapy, they would have a reduced risk of tumour recurrence. A shrinking tumour size after chemotherapy is a characteristic manifestation in most malignant tumours. The reason for the shrinking tumour size is generally thought to be that chemotherapy drugs kill tumour cells, result in massive tumour tissue necrosis, and lead to tumour reduction. In this study, we used the two largest vertical diameters' product to represent the tumour volume and compare the initial tumour size with that after chemotherapy. The results showed that after neoadjuvant chemotherapy, the two largest vertical diameter products of the tumour decreased by more than 50%; that is, patients who achieved PR according to the WHO evaluation criteria had a reduced risk of tumour recurrence. This reduction may be attributed to the shrinkage of tumours, resulting in better resectability and relieving other annotation risk factors, such as major vessel invasion. Monitoring the decrease in AFP after treatment indicated that an AFP value that failed to fall into a normal range within six months was a risk factor associated with recurrence. We hypothesized that tumours' sensitivity to chemotherapy results in a significant decrease in serum AFP before surgery. This decrease results in a reduction in preoperative AFP load, a more effective clearance of tumour cells from the blood and the prevention of tumour cell proliferation, which lead serum AFP levels to return to normal more quickly after surgery. Compared to the patients who had a good respond to chemotherapy, the decrease in serum AFP was slower in patients with a worse response, confirming that active tumour cells remained, which may lead to recurrence after chemotherapy.

It has been widely accepted that SCU histology is a risk factor for HBs[22]. Due to the low number of SCU patients in this group, statistical analysis was not possible. In this study, there was no significant in 3-year RFS different between cases with negative margins and positive margins. In recent years, some experts reported that the positive margin of surgery will not worsen the prognosis of hepatoblastoma [23]. We do not consider such patients will have a higher risk of recurrence if they accept sufficient intensity and course of chemotherapy. Other clinical factors were analysed retrospectively, including the surgical strategy, initial serum AFP value and tumour size at the beginning of therapy. However, no correlation was found with tumour recurrence. The results of a comparative study using PRETEXT or POSTTEXT stage, annotation factors, and SIOPEL risk stratification showed that there was a difference in 3-year RFS, but the difference was not statistically significant.

The limitation of this study is that it is a retrospective study with a small sample size. We plan to conduct a prospective evaluation and external verification to confirm our findings and supply the research content.

Conclusion

Through this study, we concluded that the prognosis of childhood HB is related to the age at presentation and the response of chemotherapy. The results of the multivariate analysis showed that AFP that decreased by less than 60% and tumour size that decreased by less than 50% after neoadjuvant chemotherapy were significant independent prognostic risk factors. We should perform postoperative intensive chemotherapy for such patients and expand the sample for further validation. These findings can be helpful to evaluate therapeutic effects and predict prognosis.

Declarations

Ethics approval and consent to participate

The current study was approved by the Committee on Human Study of the Beijing Children's Hospital and the Ethics Review Committee of Beijing Children's Hospital (No. 2019-k-11).

Consent to publish

All the Authors agree to publication in BMC pediatric.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

All of the authors including Wei Yang, Yiwei Chen, Yijin Huang and Huanmin Wang declare that they had no conflict of interests.

Fund

All the authors do not receive any fund, salary, royalty, intellectual property rights, consulting fee, honoraria, ownership interest, or other financial benefit.

Authors' Contributions

Wei Yang: Study conception and design, Data acquisition, Analysis and data interpretation, Drafting of the manuscript and Critical revision.

Yiwei Chen: Data acquisition, Analysis and data interpretation,

Yijin Huang: Data acquisition, Drafting of the manuscript

Huanmin Wang: Study conception and design, Critical revision

Acknowledgement: All authors revised the paper critically for important intellectual content and gave final approval of the version to be published.

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Tables

Table 1 clinical characteristics of HBs associated to 3-year RFS

		Number of patients (n)	Medians and interquartile range	%	3-year RFS	P
Total		56				
Gender	Male	32				
	Female	24				
Age	Younger than 54 months		46.5-26,71.5		63.9%	0.007
	At least 54 months				25%	
PRETEXT	I	0				0.089
	II	26		46%	65.4%	
	III	26		46%	38.5%	
	IV	4		8%	25%	
SIOPEL risk stratification	SR	27		48%	59.9%	0.239
	HR	29		52%	40.1%	
SIOPEL annotation factors	P	5				
	V	8				
	C	2				
	F					
	E					
	R	3				
	N					
	M	8				
Tumor size-two major vertical diametersprodut,cm ²			100.84(69.76,142.31)			
Initial serum AFP [ng/ml]			31125-5434,74250			
Recurrent		28				
Non-recurrent		28				
Site of tumour	Local	21			75%	
Recurrence	Lung metastasis	7			25%	
Prognosis	Survive	46				
	Death	7				
	Lost to follow up	3				
Median follow-up time [months]			44			

“P”- Macrovascular involvement of portal vein; “V”- involvement of hepatic veins and vena cava; “C”- involvement of the caudate lobe; “F”- multifocal tumour; “E”- extrahepatic tumour; “R”- tumour rupture; “N”- positive lymph nodes and

“M”- distant metastasis; “SR”- standard risk; “HR”- high risk

Table 2 treatment and response of HBs associated to 3-year RFS

		Number of cases (n)	Medians and interquartile range	%	3-year RFS	P
neoadjuvant chemotherapy	C5V	35				
	C5VD	17				
	PLADO	4				
AFP decreased after neoadjuvant chemotherapy	Less than 60%			28%		0.005
	At least 60%			68%		
Tumour size decreased %			52.5[40.5,60.75]			
evaluation criteria of WHO	CR	0				
	PR	32		65.6%		0.004
	SD	24		29.2%		
	PD	0				
POSTTEXT	1	9		66.7%		0.476
	2	30		50.0%		
	3	17		41.1%		
	4	0				
Surgical margin	Negative	45		51.1%		0.718
	Positive	7		42.9%		
	Unknown	4				
surgical strategy	Left lobectomy	14				
	Right lobectomy	33				
	Extended hepatectomy	9				
adjuvant chemotherapy	C5V	29				

	C5VD	19		
	CCD	8		
AFP fell to normal	Less than or equal to 6 months		68.6%	0.0005
	More than 6 months		50.0%	

Figures

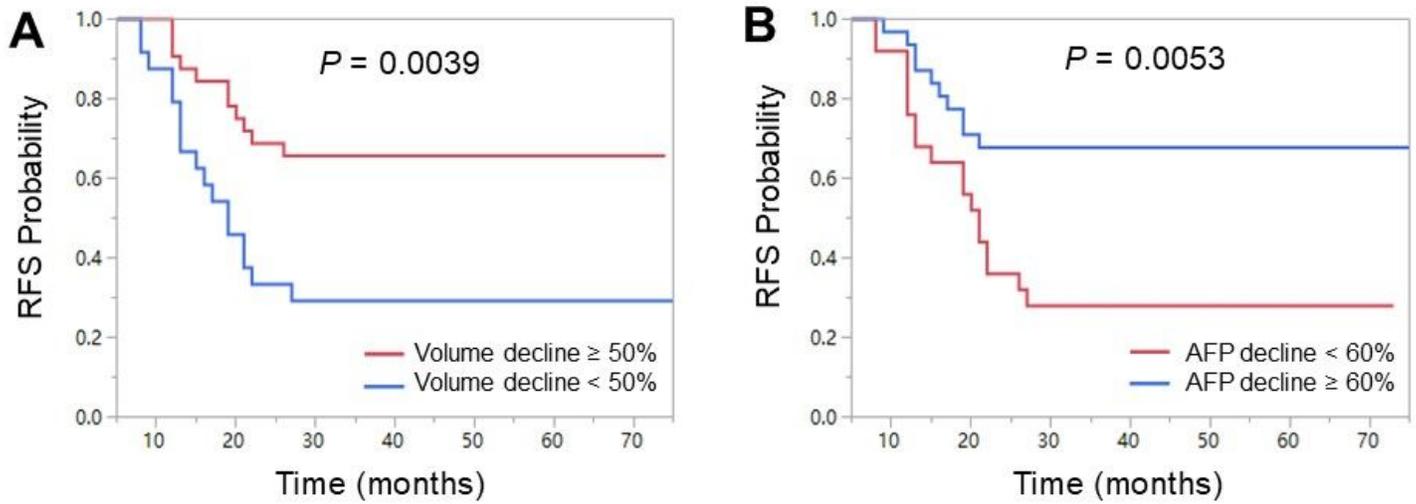


Figure 1

Decline of tumor volume and AFP values associated and prognoses of patients in this study