Analysis of related factors of recurrence in pediatric hepatoblastoma-A single center retrospective study

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Abstract

Introduction This study was performed in order to find out the relevant factors of the recurrence of hepatoblastoma .Materials and Methods 28 patients that presenting with recurrent hepatoblastoma in our hospital from 2012 to 2015 were included in the investigation. The pathological subtype,clinical stage, serum levels of alpha fetoprotein (AFP), the change trend of the tumor volume and AFP value of each case after they received neoadjuvant chemotherapy and after surgical resection were recorded. The $\chi 2$ test was used to analyze the relationship between tumor recurrence and the aforementioned factors.Results The results showed that in the recurrence group, the patients were in higher clinical stage than that in the non-recurrence group. In the patients with recurrent tumors, the rate of tumor volume reduction, the extent of AFP level decrease and the proportion of those in the group whose AFP level fell to normal range in one month after tumor resection were all apparently lower than those in the non-recurrence patients.Conclusion The main risk-altering factors involved in the recurrence of hepatoblastoma were: clinical stage, reduction in tumor size after neoadjuvant chemotherapy, and the rate of descent of AFP levels to within normal range after tumor resection. These indicators can be used as important biomarkers for personalized treatment, assessment of treatment efficacy and prognostic indicators.

Introduction

Hepatoblastoma is a rare type of primary malignant tumors of the liver that occurs in infants and children under 3 years, the pathological features consist of tissues resembling fetal liver cells, mature hepatocytes or biliary cells[1]. Further, the most common symptom is abdominal mass [2]. An important method of examination for hepatoblastoma is measuring the serum alpha-fetoprotein （AFP）value. The normal level for AFP in children is under 8ng/ml. The patient will be suspected of having hepatoblastoma if he or she has an AFP level higher than 500 (ng/ml). however, patient prognosis is still poor if AFP is not elevated at diagnosis. AFP is also used as a marker of successful treatment. If the tumor is completely removed ，the AFP value will drop to the normal level.

Currently, surgical tumor resection, chemotherapy and orthotopic liver transplantation have been used for the treatment of these tumors [3, 4]. However, the 5-year survival rate of patients with recurrence or refractory hepatoblastoma is still in a relatively low level, especially in patients with distant metastasis. [5]. Successful treatment of recurrent hepatoblastoma relies largely on surgical resection[6, 7]. When tumors are responsive, chemotherapy can be used to render patients resectability. Various chemotherapeutic regimens studied in small numbers of hepatoblastoma patients in phase I/II trials have shown limited responses[8–11]. The best available data indicate that doxorubicin (if not given during initial treatment) and irinotecan are the most active agents in recurrent hepatoblastoma. Stem cell transplantation and radiation therapy have been reported in several patients with unclear successes[12]. Advances in therapy for relapsed patients may require further research[13, 14]. Thus，it is significant to find the relevant factors for the recurrence of hepatoblastoma for further research.

A single-center retrospective analysis of 56 patients 28 of them were relapsed cases with hepatoblastoma collected between June 2012 and September 2015 was performed to find out risk factors associated with the prognosis of this disease. These indicators can be used as important biomarkers for personalized treatment, assessment of treatment efficacy and prognostic indicators.

Patients And Methods

Study Subjects

Data from 28 patients (Male 18 cases and Female 10 cases) with relapsed hepatoblastoma were collected by Beijing Children's Hospital from 2012 to 2015 as case group. The age ranged from 0.6 years to 12 years, with an average age of 3.9 years and the average time from postoperative to recurrence was 11.9 months. At the same time, data was collected from a corresponding 28 patients without recurrence (Postoperative follow-up time more than 3 years) in the same period, these were classified as the control group.

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.

Diagnosis

These cases were diagnosed with hepatoblastoma according to pathological and clinical findings such as radiological examination and serum AFP level. They were categorized into four clinical stages on the basis of the pretreatment extension (PRETEXT) staging system [15] which adopted by the International Childhood Liver Tumors Strategy Group (SIOPEL).In addition, these cases were grouped based on pathology as fetal, embryonal, macro trabecular, small cell undifferentiated or embryonal-fetal mixed type [16][17]. The detailed categorization and clinical stages of the patients are listed in Table 1.

Treatment

Surgical operation was performed on patients in PRETEXT I patients of both groups following clinical diagnosis. After operation, patients underwent chemotherapy for 4–6 cycles. For PRETEXT II, III and IV cases Neoadjuvant chemotherapy was adopted after pathological examination by core needle biopsy for 2–4 cycles. Radiographic and serum AFP examinations were checked every 2 cycles. Then the patients underwent tumor resection. After surgery, patients need to undergo 6–9 cycles for chemotherapy. All patients had negative margins of pathological findings.Neoadjuvant chemotherapy consisted of 20 mg /m^2 cisplatin on day 1–5, 300mg/m^2 fluorouracil on day 1–2 vincristine for 1.5 mg/m^2 on day 2 and. This was continued for 2–4 cycles. Adjuvant chemotherapy consisted of the AEP regimen (90 mg/m^2 cisplatin on day 1, 25 mg/m^2 pirarubicin on days 1–3 and 100 mg/m^2 etoposide on days 1–4) and the ACP regimen (90 mg/m^2 cisplatin on day 1, 25 mg/m^2 pirarubicin on days 1–3 and 800–1,000 mg/m^2 cyclophosphamide on day 1), alternately.

Followup

Follow-up was performed every three months until August 2018. Subjects were regarded as eliminated if they gave up treatment or were lost to follow-up. Patients with postoperative follow-up time of more than 3 years with no sign of recurrence were classified into the control group.

Clinical indicators

The clinical stage, pathological type, AFP level, tumor volume after preoperative chemotherapy, AFP level change trend and AFP level decline after surgical resection were recorded.

Statistical analysis

Data were expressed as the mean ± standard deviation. Data that distributed normally were compared by a standard t test. The $\chi 2$ test for comparing the number of patients. Comparison of data that did not distributed normally was made according to the Mantel-Cox log-rank test. SPSS software version 20.0was used for statistical analysis. $P < 0.05$ is considered to represent a significant difference in statistics.

Results

The average age of patients in the relapse group was 3.9 years (ranging from 0.6 years to 12 years) and the average time from postoperation to recurrence was 11.9 months. Correspondingly, the non-relapsed hepatoblastoma patients were aged 2.6 years (ranging from 0.6 years to 4.4 years). Based on the results from pathological findings, patients were diagnosed as having fetal, embryonal, fetal-embryonal mixed, macro trabecular or small cell undifferentiated type hepatoblastoma, or, they were classified as ‘unable to determine pathology’ maybe due to the effects of chemotherapy. The number of patients in the relapsed group with embryonal, fetal, mixed-type, macro trabecular and small cell undifferentiated type were 5, 1, 16, 2, and 1, respectively. Meanwhile, the number of patients of each subtype in the non-recurring group were 4, 1, 19, 1, and 0, respectively. There were 3 cases for which we could not determine pathology after surgery. There was not any obvious difference in the numbers of patients with each of the pathology subtypes between the recurrence and non-recurrence groups (Figure 1).

In recurrent cases, the mean time from surgery to recurrence was 11.9 months. Recurrence of hepatoblastoma was detected in 3 stage I, 6 stage II, 18 stage III patients and 1 stage IV patients. Comparatively, the results from non-relapsed patients were as follows; 7 Stage I, 16 Stage II, 5 Stage III, and 0 Stage IV patients (Table 1). A comparison of the two groups shows that 19 patients with recurrent hepatoblastoma were stage III or IV, accounting for 68% of the recurrant cases, a proportion that is significantly higher than 18% patients being stage III or IV in the non-recurrent group.

The AFP levels are shown in Table 1. Serum AFP levels at onset ranged from 1,080,000 ng / ml to 1,778 ng / ml. After preoperative neoadjuvant chemotherapy, AFP levels fell to the normal range in 1 patient, whilst 1 patient’s AFP levels dropped normally within one month after surgery, and four fell normally

within three months. AFP levels continued to beyond normal for the most patients after surgery. The AFP levels of non-recurrent cases in the same period was compared with the cases in the relapse group. Two data groups were compared using the chi-square test. There were no significant differences in onset AFP levels between the two groups ($p>0.05$). However, regarding the difference in the reduction trends in AFP level, there was a statistically significant difference after neoadjuvant chemotherapy between the relapsed group and the non-relapsed group ($p<0.05$). Similarly, the AFP level reduction rate after operation in the relapse group was lower than that in the non-relapse group. This is displayed by the fact that the proportion of patients in the relapsed group whose AFP level fell to the normal range was significantly lower than in the non-relapsed group ($p<0.05$).

According to the evaluation criteria of WHO solid tumor chemotherapy effect, they were divided into CR （tumor disappear）、PR（50% decrease）、SD（Neither PR nor PD ）、PD（25% increase）[18]. In these two groups ，there were no CR cases in either of the two groups. The ratio of relapse vs non-relapse patients who had PR was 12(relapse):21(non-relapse), and for SD this ratio was 16:7. Finally, the rate of tumor volume reduction after preoperative chemotherapy in the relapse group was significantly lower than that in the non-recurrence group ($p<0.05$).

Discussion

The main pathological hepatoblastoma types include fetal, embryonal, fetal- embryonal mixed, macro trabecular and small cell undifferentiated hepatoblastoma. People with familial Adenomatous polyposis (FAP), a syndrome of early-onset colonic polyps and adenocarcinoma, are prone to hepatoblastomas[19]. Further, Abnormal regulation of WNT B-catenin signaling pathway is common in patients with hepatoblastoma, occurring in as many as 67% of patients[20].

The study by SIOPEL suggested that, overall, hepatoblastoma patients have relatively good prognosis. Further, the prognosis of children with hepatoblastoma has been improved substantially over the past few years through the efforts of many cooperative study groups. However, there are still some recurrent cases[21][22].

The result of current study suggests that there is no significant difference between the two (relapse vs non-relapse) groups when comparing pathological types. Some experts have reported that pure fetal subtype had the best prognosis, while patients with the small cell undifferentiated form had the worst prognosis[23]. However, these are the least common forms of the disease amongst all groups. Thus, a comparative study is needed to further accumulate the number of cases. In our study, patients in stage II and above were given chemotherapy before surgery, and the in the mixed pathology group we included embryonal and fetal type hepatoblastoma, which accounted for the majority in both recurrence and non-recurrence groups. Furthermore, there were 3 patients for which we could not give a definite pathological classification. Further study is required to distinguish whether the results of our study are the effects of chemotherapy drugs on tumor cells or a change in the pathological type.

In the risk classification of the International Society of Pediatric Oncology (SIOP), patients with PRETEXT I, II and III were assigned to the standard risk group. While patients with stage IV were assigned to the high-risk group, suggesting the clinical prognosis is related to tumor stage. [24]. In our study, the number of patients in stage IV was low, and the proportion of stage III in the relapse group was obviously higher than that in the non-recurrent group. These results indicated that the recurrence of hepatoblastoma was associated with tumor stage, and the patients in the advanced stage were more likely to relapse due to more serious illness. Additionally, the invasion of liver was more extensive, and the surgical resection was more difficult, and subsequently, the relative recurrence probability was higher.

As an important serological tumor marker, AFP has clinical significance in the diagnosis and treatment of patients with hepatoblastoma [25]. It has been reported in the literature that AFP>1200000ng/ml is a high-risk factor in hepatoblastoma[26], but for the present study, there was no statistical difference in AFP level between the two groups at first onset. Furthermore, there was no significant association between tumor recurrence in patients and the absolute value of AFP at the time of first onset. However, by comparing the rate of AFP decline in preoperative chemotherapy between the two groups, a significant difference was observed. There is no significantly decrease in the relapse group, but comparatively, the AFP decrease was significantly more rapid in the non-recurrent group. In analyzing the reasons for this, we suppose that tumor cells in the non-recurrent group were more sensitive to chemotherapy, and that chemotherapy drugs have stronger inactivation effects on these patients. Further, since AFP is a glycoprotein secreted by hepatoblastoma cells, the tumor cell necrosis rate was faster after chemotherapy, which in turn led to a more significant decrease in AFP levels. The sensitivity of tumors to chemotherapy drugs aids postoperative chemotherapy, helping to achieve better results by inhibiting tumor cell proliferation[27–28].

Currently, hepatoblastoma is treated with chemotherapy, using cisplatin-based combination including cisplatin, fluorouracil, epirubicin, and vincristine[29–32]. The purpose of preoperative chemotherapy is to reduce the tumor volume, clear the tumor cells from the blood and remove micro-metastases in the body. This results in improving the success rate of surgical resection and reduces the chance of recurrence. The preoperative chemotherapy effect of patients in this study was evaluated according to the WHO standard. Subsequently, we found that the preoperative chemotherapy effect of the patients in the relapse group is not as good as that in the non-relapse group.

AFP studies in hepatoblastoma patients suggest that AFP should be significantly reduced after tumor resection[33, 34]. Additionally, most patients will fall to normal or near normal levels within one month after surgery[35]. However, only one of the relapsed patients in our study fell to the normal range within one month, and most of the cases did not fall to normal from postoperative to the time of tumor recurrence. When comparing the AFP level data from the patients with and without recurrence, it can be seen that there is a significant difference between the two groups. Our data indicated that the patients in the recurrent group are more likely to present with minor residual, and the tumor cells in the body are still continuing to secrete AFP, which may be causing the higher values that we identify. From these results, we

can draw a conclusion that the monitoring of serum AFP levels in patients with hepatoblastoma can help clinicians to detect tumor recurrence in time and then take corresponding measures to deal with it.

Conclusion

In summary, the main factors involved in the recurrence of hepatoblastoma were preoperative staging, tumor volume reduction, and the rate of AFP level decrease to normal. These indicators can be used as an important biomarker for the personalized treatment, the evaluation of therapeutic effect and the predictive indicator of prognosis.

Declarations

Compliance with Ethical Standards: All of the authors including Wei Yang Yiwei Chen Yijin Huang and Huanmin Wang declare that they had no conflict of interests.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

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

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Table 1

Table 1: Comparison of clinical features and AFP related conditons for the patients with hepatoblastoma between the two groups

Clincial feature			
Stage	Relapsed hepatoblastoma (N=28)	Non- relapsed hepatoblastoma (N=28)	P-valve*
	3	7	0.21
	6	16	0.06
	18	5	0.055
	1	0	/
AFP（ng/ml）			
Maximum	1080000	1380000	0.32
Minimum value	1778	1976	0.56
average value	128205	120762	0.87
AFP changes			
Down to normal	1	9	0.015
Decrease >50%	11	13	
Decrease <50%	16	6	
AFP falls to normal range time			
Within 30 days after surgery	1	25	0.011
More than 30 days after surgery	4	3	
Not falling to normal	23	0	
Tumor volume change			
Decrease >50%	12	21	0.002
Decrease <50%	16	7	

P-valve* Normally distributed data were compared using the t test. The $\chi 2$ test was used to compare the number of patients. Comparison of data that did not follow a normal distribution was performed according to the Mantel-Cox log-rank test.

Figures

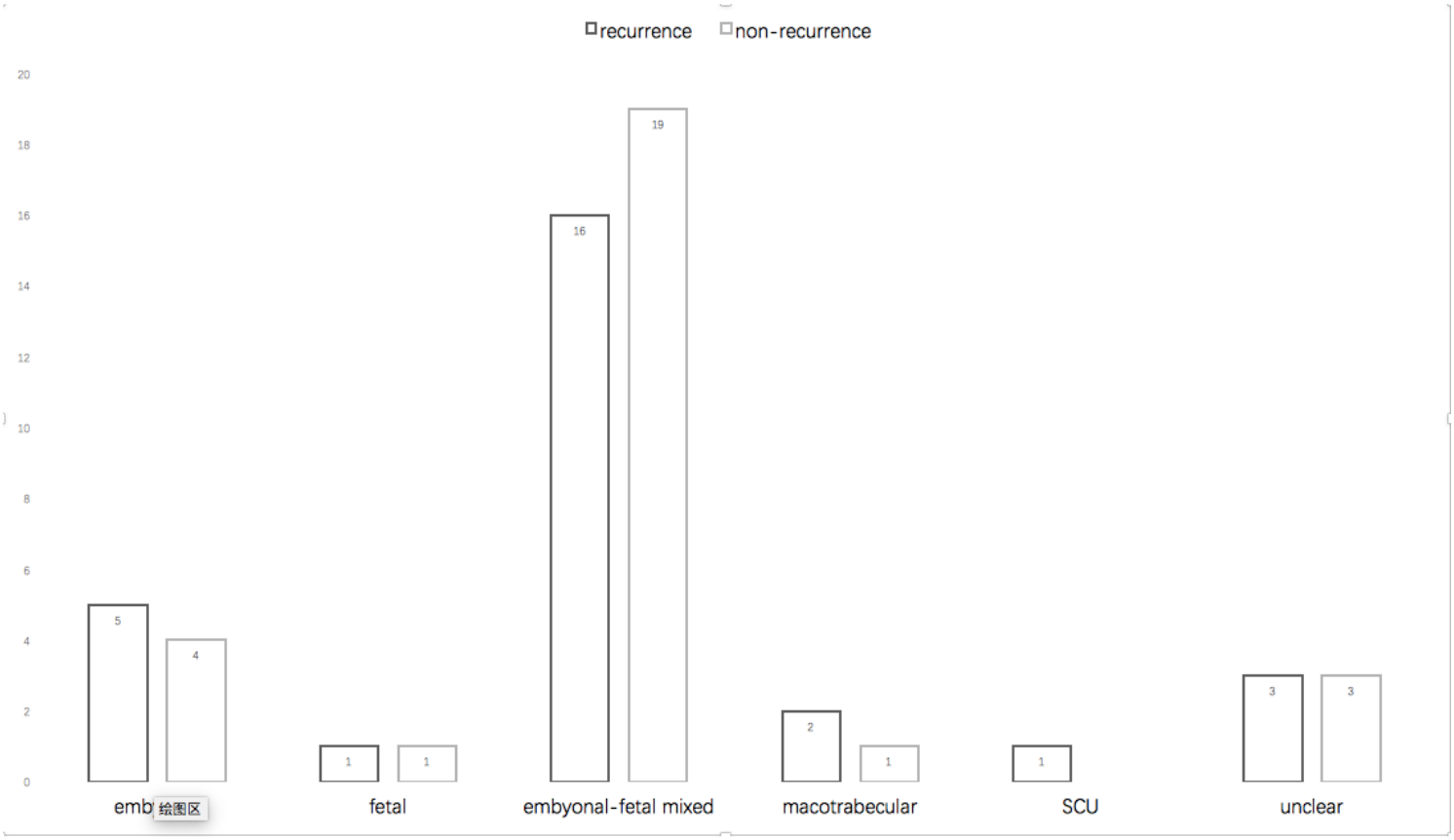

Figure 1

Comparison of pathological types between the two groups. Based on the result from pathological analyses, subjects were diagnosed as embryonal type, fetal type, mixed type, macotrabecular type, small cell undifferentiated type and unable to determine pathology type