นิพนธ์ต้นฉบับ ▪ Original Article

อัตราการรอดชีวิตในผู้ป่วยมะเร็งตับชนิดเฮปปาโตบลาสโตมา ในเด็ก: ใครที่มีโอกาสรอดชีวิตมากที่สุด

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Survival Outcomes in Patients with Hepatoblastoma: Who has the Greatest Chance of Surviving?

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หลักการและวัตถุประสงค์: โรคมะเร็งตับเฮปปาโตบลาสโตมาจัดเป็นโรคมะเร็งตับที่พบบ่อยในเด็ก การศึกษานี้วัตถุประสงค์เพื่อชี้ถึงข้อมูลและอัตราการรอดชีวิตของโรคมะเร็งตับเฮปปาโตบลาสโตมาในโรงพยาบาลศรีนครินทร์

วิธีการศึกษา: เป็นการศึกษาข้อมูลแบบย้อนหลังของผู้ป่วยเด็กทุกรายที่ได้รับการวินิจฉัยว่าเป็นโรคมะเร็งตับเฮปปาโตบลาสโตมาระหว่าง พ.ศ. 2546 และ 2559 ในโรงพยาบาลศรีนครินทร์

ผลการศึกษา: มีผู้ป่วยที่ได้รับการวินิจฉัยเป็นโรคมะเร็งตับเฮปปาโตบลาสโตมา จำนวน 47 ราย โดยมี 43 รายที่มีข้อมูลสำคัญครบ พบว่ามีค่ามัธยฐานของอายุอยู่ที่ 1.08 ปี (19 วันถึง 13.8 ปี) โดยผู้ป่วยที่เป็น PRETEXT ระดับสามและสี่มีจำนวน 15 และ 10 ราย ตามลำดับ คิดเป็นร้อยละ 34.8 และ 23.3 ตามลำดับ นอกจากนี้ยังพบว่าผู้ป่วย 11 ราย (ร้อยละ 25.6) มีการแพร่กระจายของตัวโรคไปอวัยวะอื่นแล้วเมื่อแรกวินิจฉัย จากการศึกษาพบว่ามีผู้ป่วยเพียง 6 รายที่สามารถเข้ารับการผ่าตัดตับตั้งแต่แรกวินิจฉัย ส่วนที่เหลือจำเป็นต้องได้รับยาเคมีบำบัดก่อน ยิ่งไปกว่านั้น พบว่า ร้อยละ 16.3 ได้รับการประเมินว่าลักษณะก้อนที่ตับไม่สามารถผ่าตัดได้ จากค่ามัธยฐานของระยะเวลาในการติดตามการรักษา คือ 3.18 ปี (1.83 เดือน ถึง 11.03 ปี) พบว่าอัตราการรอดชีวิตโดยรวม 5 ปี คือ ร้อยละ 63.21 สำหรับอัตราการรอดชีวิต 5 ปีโดยรวมในผู้ป่วยที่ได้รับการผ่าตัด คือ ร้อยละ 75.21 และอัตราการรอดชีวิตปลอดโรคในผู้ป่วยที่ได้รับการผ่าตัด คือ ร้อยละ 72.8 และพบว่าผู้ป่วยที่มีอายุรอดมากกว่า 3 ปีหลังได้รับการผ่าตัดจะรอดชีวิตทั้งหมด ในผู้ป่วยที่ได้รับการประเมินว่าสามารถผ่าตัดได้โดยไม่ต้องการเคมีบำบัดก่อนผ่ามีอัตราการรอดชีวิต 5 ปี ร้อยละ 100 ในขณะที่อีกกลุ่มมีอัตรา

Background and Objective: Hepatoblastoma (HB) is the most common malignant liver tumor in children. This study aimed to review the survival outcomes of HB at Srinagarind hospital.

Method: All children diagnosed with HB between 2003 and 2016 were included. The demographic data and outcomes were reviewed, and the survival outcome was analyzed.

Results: There were 47 patients diagnosed with HB. After excluded 4 incompletes recorded, 43 cases were calculated. The median age at diagnosis was 1.08-year (19 days to 13.8 years). The number of patients with PRETEXT III and IV were 15 (34.8%) and 10 (23.3%), respectively. Eleven patients (25.6%) came with distant metastasis at the time of diagnosis. Only 6 patients (14%) underwent liver resection without pre-op chemotherapy. The other received pre-op chemotherapy. Still, 16.3% remains unresectable. The median follow-up was 3.18 years (1.83 months to 11.03 years). The overall 5-year survival rate in the hepatoblastoma patients in our study was 63.21%. The overall 5-year survival and disease-free survival rates in operable patients were 75.21% and 72.8%, respectively. Patients who lived longer than 3 years after surgery, survived. The 5-year survival rate for the patients who do not require chemotherapy before

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การรอดชีวิต 5 ปี ร้อยละ 56.24 ยิ่งไปกว่านั้น การศึกษาพบว่ากลุ่มที่ตัวโรคไม่กลับเป็นซ้ำนั้นมีอัตราการรอดชีวิตสูงกว่ากลุ่มที่ตัวโรคกลับเป็นซ้ำอย่างมีนัยสำคัญทางสถิติ (p = 0.0017)

สรุป: อัตราการรอดชีวิตโดยรวม 5 ปีของผู้ป่วยโรคมะเร็งตับเฮปปาโตบลาสโตมามีแนวโน้มเพิ่มขึ้น และพบว่าผู้ป่วยที่มีอายุรอดมากกว่า 3 ปีหลังได้รับการผ่าตัดมีแนวโน้มรอดชีวิต และการกลับเป็นซ้ำของโรคนั้นส่งผลกระทบต่ออัตราการรอดชีวิตอย่างมีนัยสำคัญทางสถิติ

คำสำคัญ: อัตราการรอดชีวิต, มะเร็งตับ, ผู้ป่วย

surgery was 100% whereas the other group had 56.24%. Moreover, we found that the non-recurrent group had a significantly higher survival rate compared to the recurrent group (p = 0.0017).

Conclusions: The overall survival rate in hepatoblastoma patients appeared to be higher including our country, and patients who lived longer than 3 years were likely to survive. The recurrence of hepatoblastoma significantly impacted the survival rate.

Keyword: survival outcome, hepatoblastoma, patient

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Introduction

Hepatoblastoma is the one of the most common types of malignant liver tumor in children, comprising 1% of all pediatric malignancies. It affects mostly i nfants and young children between the ages of 6 months and 3 years.[1] In Western countries, the incidence of hepatoblastoma is about 0.5–1.5 per 1 million children under the age of 15 years[2] and 3.8 per million children aged 4 years or younger.[3] Moreover, the studies have found that the hepatoblastoma incidence has been increasing over time (2.18-5.2%).[3–5] In Thailand, the incidence in children under the age of 15 and in those aged 4 years or younger is about 1.9 and 4.5 per 1 million, respectively.6 Although the incidence of childhood liver tumors in Thailand is higher than those of western countries, the survival rate is lower.[4,6,7] This study aimed to review the survival outcomes of patients with hepatoblastoma at our institution.

Materials and Methods

All children who were diagnosed hepatoblastoma between 2003 and 2016 were included. Patients who had received treatment from another hospital were excluded. The diagnosis of hepatoblastoma was performed based on a pathological report or the findings of typical radiological examination and the presence of elevated alpha-fetoprotein (AFP) levels. The extent of the disease was evaluated using the PRETEXT (pre-treatment extent of disease) staging system.[8]

The treatment protocol in our institution between 2003 and 2012 was based on an IPA (Ifosfamide, Cisplatin/Carboplatin, and Adriamycin) regimen. After 2012, the ThaiPOG9 hepatoblastoma regimen was implemented. In this treatment regimen, tumors are classified into 5 groups (very low risk, low risk, intermediate risk, high risk, and very high risk). Patients with PRETEXT I-III without any high-risk features (tumor invasion of the vena cava or all three major hepatic veins, main portal vein or bifurcation, intra-abdominal extra-hepatic extension, and distant metastasis) proceed to upfront surgery if gross total tumor removal is possible. Patients found to have the high-risk features or in whom the tumor is assessed as being unresectable begin chemotherapy administration within 7-14 days after the diagnosis. After completion of four courses of chemotherapy, the patients are re-evaluated via imaging and, in cases in which the tumor is resectable, undergo surgery plus two additional courses of post-operative chemotherapy. In cases in which the tumor remains unresectable after the initial four courses of chemotherapy, the patient is to undergo two additional courses of chemotherapy followed by surgery.

Serum AFP levels are evaluated every 2, 3, 4, and 6 months on years 1, 2, 3, and 4 post treatment, respectively. If serum AFP levels are elevated, high resolution abdominal ultrasound or computed tomography should be performed. In patients with low AFP (< 100 ng/ml) at diagnosis, imaging, such as high resolution abdominal ultrasound or computed tomography, should be performed regularly for at least 4 years.

The demographic data and outcomes were collected and analyzed using STATA version 10. Data are expressed as median (range). The categorical data were analyzed using a Chi-squared test, while the normal distribution of continuous data was analyzed using a T-test. A Mann-Whitney U test was performed for continuous data with non-normal distribution. A

Kaplan-Meier survival analysis was also performed.

Results

There were 47 patients diagnosed with hepatoblastoma. After excluded 4 incompleted records, 43 cases were calculated. The median age at diagnosis was 1.08-years (19 days to 13.8 years). One patient was diagnosed with Kabuki syndrome, but none of the patients had underlying Beckwith Weidemann syndrome, hemihypertrophy, or trisomy [18]. The most common clinical presentation was abdominal mass or abdominal distention (97.8%). Only one patient came with back pain and paralysis of both legs as a result of the metastasis. The median of serum AFP level was 175,761 ng/mL (720-1,678,171 ng/mL). The numbers of patients with PRETEXT I, II, III, and IV were 2 (4.6%), 16 (37.2%), 15 (34.9%), and 10 (23.3%), respectively. Eleven patients (25.6%) had distant metastasis at the time of diagnosis and the lungs were the most common location (Table 1).

Only 6 patients (14%) underwent primary hepatic resection without pre-operative chemotherapy, and the histology confirmed complete resection. There were patients with PRETEXT I, II, and III in this resectable group. All other patients received pre-operative chemotherapy. There was a statistically significant difference between the two groups in terms of disease staging ($p < 0.001$), but there is no statistically significant difference in the number of patients with PRETEXT ($p = 0.10$). After pre-operative chemotherapy, tumors were completely removed in 20 patients, while those in 7 remained unresectable. The median follow-up duration was 3.18 years (1.83 months to 11.03 years). Eight patients experienced tumor recurrence, one of whom had undergone primary liver resection.

The overall 5-year survival rate in the hepatoblastoma patients in our study was 63.21%. The overall 5-year survival and disease-free survival rates in operable patients were 75.21% and 72.8%, respectively. All patients who lived longer than 3 years after surgery survived (Figure 1). Although the treatment protocol for hepatoblastoma patients in our institution has changed since 2012 as part of changes in the national protocol, differences in overall 5-year survival and disease-free survival rates before and after the protocol change were not statistically significant ($p = 0.78$ and 0.99). The 5-year survival rate for the patients who did not require chemotherapy before surgery was 100%, whereas it was 56.25% in the other group. However, there is no statistically significant difference in the survival rate between patients who did and did not undergo pre-operative chemotherapy. The 5-year survival rate in the complete tumor removal group was higher compared to that in the incomplete removal/unresectable group (78.8% vs. 43.8%), but this difference was not statistically significant ($p = 0.0576$; Figure 1). Moreover, we found that the non-recurrent group had a significantly higher survival rate compared to the recurrent group ($p = 0.0017$).

Table 1 This table shows baseline characteristic of resectable and non-resectable groups at the first assessment after diagnosis.

Characteristic	Non-Resectable at 1st (N=37)	Resectable at 1st (N=6)	p-value
Sex			0.184
Male	23 (62.16)	2(33.33)	
Female	14 (37.14)	4 (66.67)	
Birth weight (gm.); mean (SD)	2,981.46 (502.76)	3,245 (395.82)	0.27
Alpha fetoprotein (ng/mL); mean (SD)	326,977 (415,642.6)	138,900 (160,037.9)	0.28
PRETEXT			0.10
1	1 (2.70)	1 (16.67)	
2	12 (34.21)	4 (66.67)	
3	14 (37.84)	1(16.67)	
4	10 (27.03)	0 (0)	
Stage			<0.001
1	0 (0)	4 (66.67)	
2	1 (2.78)	2 (33.33)	
3	25 (69.44)	0 (0)	
4	10 (27.78)	0 (0)	
Location of metastasis (N=11)			0.224
Lung	7	0	
Bone	3	0	
Lymph node	1	0	
Thrombosis of IVC/HV/PV	10 (27.78)	1 (16.7)	1
Recurrent	7 (18.92)	1 (16.7)	1

Discussion

The overall survival outcome appeared to be increased from time to time (63-100%).[4,10–13] Previous population-based studies[6,7] have found the overall 5-year survival rate for Thai children with hepatic tumors to be 34-44.5%, which is lower than those in many other countries. However, our results found that the overall 5-year survival rate in hepatoblastoma patients was 63.21%, and that it increased to 75.21% in operable patients.

Complete surgical resection remains the cornerstone of treatment in pediatric patients with hepatoblastoma, and in cases with favorable tumor histology the condition can be cured with surgery alone.[14] A previous study found that the ten-year survival rate was significantly higher in patients with resectable tumors who underwent operative treatment in comparison with those with unresectable hepatoblastoma.[4] Consistent with that study, we found that the 5-year survival rate for patients who did not

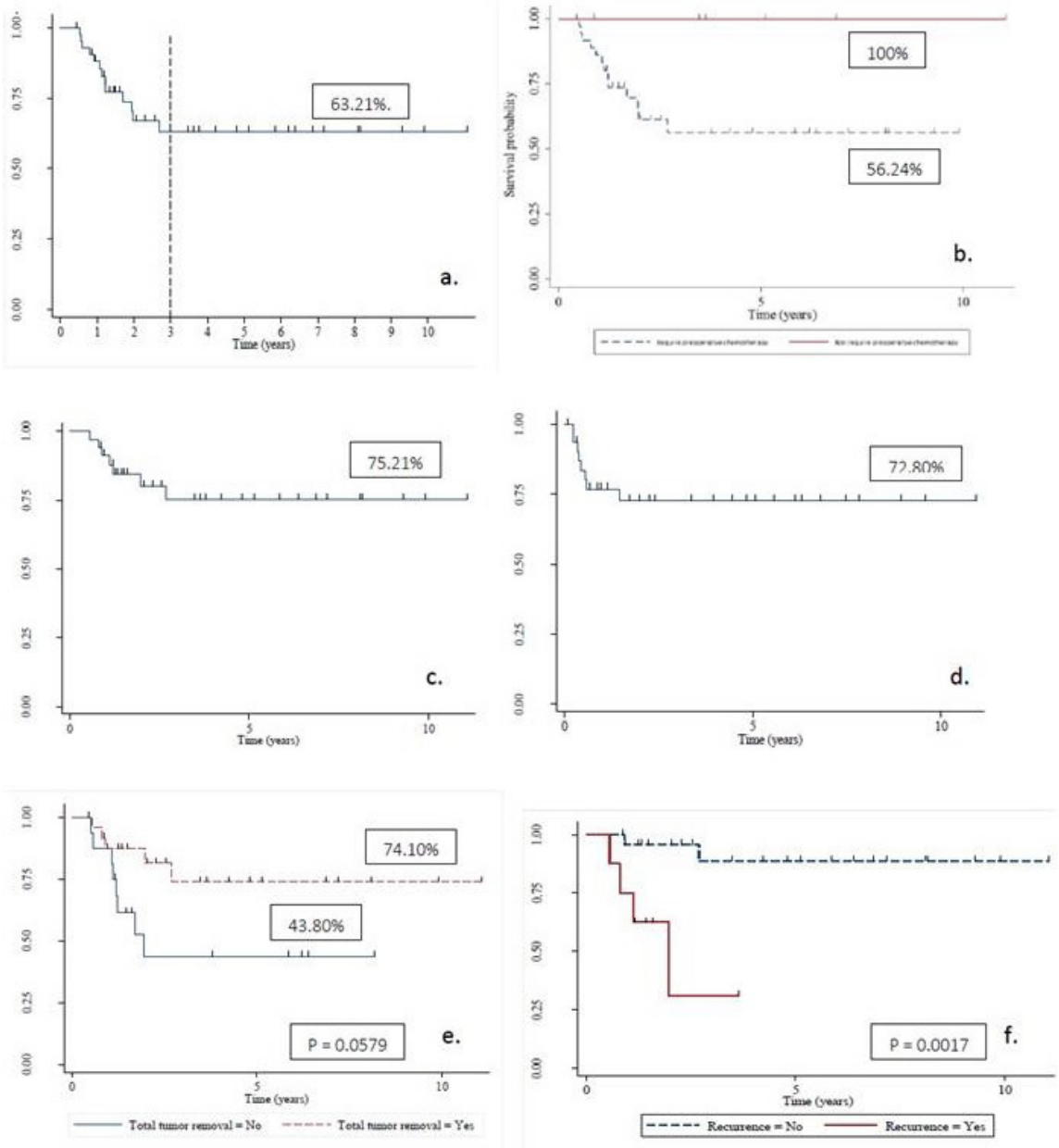

Figure 1 The overall 5-years survival and disease-free survival rate in hepatoblastoma patients

a: The overall 5-years survieal rate in hepatoblastoma patients.

b: The 5-years survival rate for the patients who require vs. do not chemotherapy before surgery

c: The overall 5-years survieal rate in operable patients.

d: The overall 5-years disease free survival rate in operable patients.

e; The overall 5-years survieal rate for complete tumor removal group was higher comparing to incomplete and unresectable groups.

require chemotherapy before surgery was 100%, whereas that of other patients was 56.24%. The 5-year survival rate for the complete tumor removal group was 74.1%, whereas that of the incomplete/unresectable group was 43.8%. In addition, patients with recurrent hepatoblastoma had a significantly lower survival rate (p = 0.0017).

Although the pathogenesis responsible for the development of hepatoblastoma remain unclear, several studies 15–22 have found an increased risk of hepatoblastoma in infants born prematurely or with low birth weight. "Very low" and "extremely low" birth weight has been found to carry an especially elevated risk of hepatoblastoma. In this study, all cases of prematurity and low birth weight required pre-operative chemotherapy. In addition, patients with low birth weight had a lower overall survival rate compared to those with normal birth weight. In addition, there is evidence that certain congenital anomalies, including Beckwith–Wiedemann syndrome, hemihypertrophy, and trisomy[18], are associated with increased hepatoblastoma risk.[23–25] Although none of the hepatoblastoma patients in our study had these anomalies, one patient was diagnosed with Kabuki syndrome. Tumino et al,[26] reported on a 6-year-old boy with Kabuki syndrome in whom a mass was found at the right lobe of the liver, which a liver biopsy confirmed to be hepatoblastoma. Based on these findings, we agree that increased attention should be paid to potential malignancy in children with Kabuki syndrome.

The limitations in this study included the retrospective design and the small number of cases that were included, which may affect the statistical significance of the findings. However, the differences found among groups of patients in this study did seem to have clinical significance. In addition, liver transplantation, which has been shown to have favorable outcomes, should be considered in cases in which the resectability of tumors is questionable or in which the tumors are unresponsive to chemotherapy in order to improve outcomes.[27–29]

Conclusion

The overall survival rate in hepatoblastoma patients appeared to be higher including our country, and patients who lived longer than 3 years were likely to survive. The recurrence of hepatoblastoma significantly impacted the survival rate.

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