SURVIVAL AND TREATMENT OUTCOMES IN PEDIATRIC HEPATOBLASTOMA: THE FIRST REPORT FROM THAILAND

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Abstract. Hepatoblastoma is the most common malignant liver tumor in children. The treatment approach for hepatoblastoma varies from center to center. At our institute, we have adopted the concept of using initial surgery followed by adjuvant chemotherapy, in accordance with the hepatoblastoma treatment protocol of the Children's Oncology Group (COG). However, the treatment outcomes of our patients have never been evaluated. We therefore retrospectively reviewed the medical records of patients under 15 years of age with newly-diagnosed hepatoblastoma who had been treated at Siriraj Hospital, Thailand, between June 1, 1994 and December 31, 2011, in order to assess the outcomes and event-free survival (EFS) rates. Forty-one patients were diagnosed with hepatoblastoma during the study period, and had the following COG stages: I (22%), II (2.4%), III (56.1%), and IV (19.5%). The five-year EFS and the overall survival rates were 63.4% and 72.2%, respectively. The median follow-up time was 6.3 years (range: 0.2–19.7 years). The EFS rate was significantly better for patients who had achieved complete tumor removal ($p = 0.004$), and significantly worse for those with metastatic disease ($p = 0.002$) or an initial alpha-fetoprotein level < 100 ng/ml) ($p = 0.042$). A complete tumor removal was the most important key to treatment success. Among the patients who initially presented with an unresectable tumor, 82% achieved complete tumor removal after the use of neoadjuvant chemotherapy. However, the treatment outcomes for patients with metastatic diseases were still unsatisfactory; therefore, either more intensive treatment or other novel treatments are warranted in order to improve the survival of such patients.

Keywords: hepatoblastoma, pediatric, event-free survival, overall survival, treatment outcomes

INTRODUCTION

Hepatoblastoma is the most common malignant liver tumor in children and accounts for 1–2% of all childhood cancers (Herzog *et al*, 2000; Olson, 2011). It occurs primarily in young children, with 80% of cases reported before 3 years of age (Perilongo and Shafford, 1999).

The alpha-fetoprotein (AFP) level has been shown to be the most important tumor marker for the diagnosis of hepatoblastoma: about 90% of the patients with hepatoblastoma have an elevated AFP level (Perilongo and Shafford, 1999; Olson, 2011). On most occasions, hepatoblastoma can be diagnosed based on an elevated AFP level plus a radiological finding

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of liver mass. However, a tumor biopsy is still essential in patients who are younger than 6 months or older than 3 years of age since there is a chance of them having other types of liver tumors (Czauderna *et al*, 2005). In addition to that, elevations of the AFP level in young infants should be interpreted carefully since they might be within the normal range for age (Wu *et al*, 1981).

The treatment of hepatoblastoma includes surgery and chemotherapy, which can be given either in a neoadjuvant fashion or as an adjuvant treatment to surgery. In North America, the Children's Oncology Group (COG) prefers upfront surgery followed by adjuvant chemotherapy in most cases. For those with an unresectable tumor, as determined by the surgeon, neoadjuvant chemotherapy is given as the initial treatment, followed by delayed surgery (Ortega *et al*, 2000). In contrast, the International Childhood Liver Tumors Strategy Group (SIOPEL) has recommended giving neoadjuvant chemotherapy to all patients, followed by delayed surgery (Brown *et al*, 2000). The 5-year, event-free survival (EFS) rates reported in COG and SIOPEL studies were 63% and 66%, respectively, with the 5-year, overall survival (OS) rates being 70% and 75%, respectively (Brown *et al*, 2000; Ortega *et al*, 2000).

Our hospital adopted the COG concept and has utilized a standard protocol for treating hepatoblastoma since 1994. The initial chemotherapy protocol that was used in our hospital consisted of carboplatin and doxorubicin. In 2000, however, the protocol was changed by our team to a cisplatin-based regimen after the publication of a report on the ineffectiveness of carboplatin-based chemotherapy for hepatoblastoma (Dall'Igna *et al*, 2001). Nevertheless, the treatment outcomes of hepatoblastoma in our patients have never been formally evaluated. This study will focus on the results of the treatments and the survival rates of the children with hepatoblastoma who had been treated at our hospital. To our knowledge, this is the first report on the treatment outcomes of pediatric hepatoblastoma in Thailand.

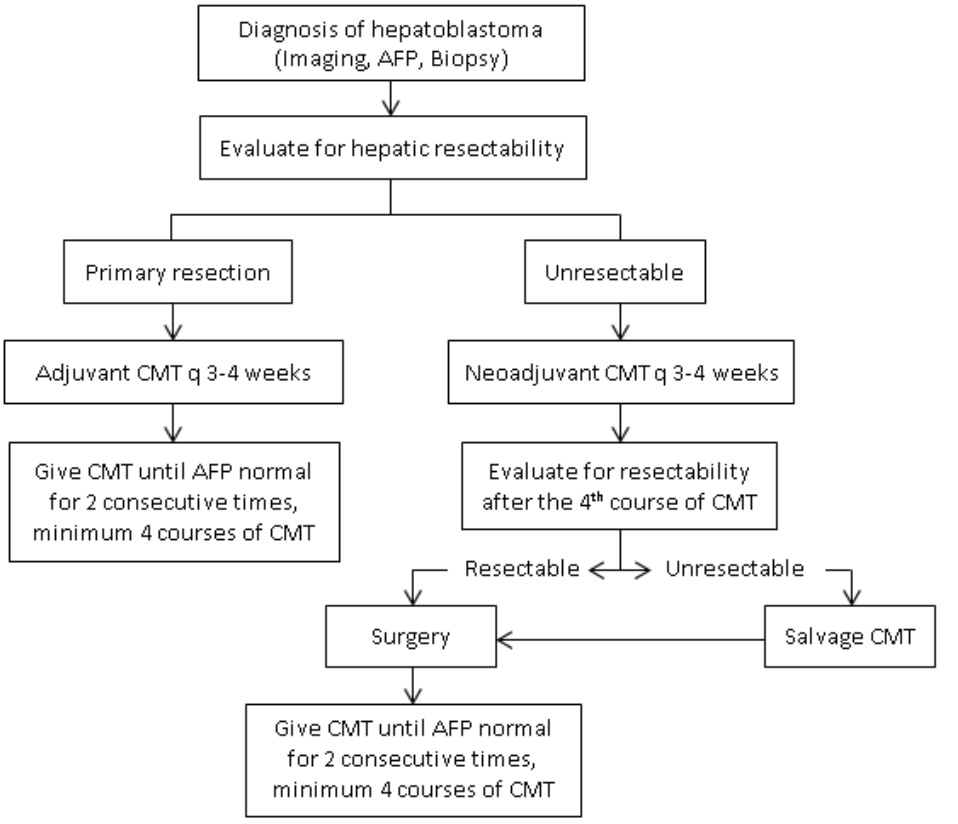
MATERIALS AND METHODS

We retrospectively reviewed the medical records of Thai children with hepatoblastoma who had been treated at the Division of Hematology/Oncology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Thailand, between June 1, 1994 and December 31, 2011. The main objective of this study was to assess the treatment outcomes and the EFS rates of children with hepatoblastoma in our hospital in order to evaluate the efficacy of our current treatments and to identify possible prognostic factors related to the treatment outcomes.

The inclusion criterion was children under 15 years of age with newly-diagnosed hepatoblastoma who had never received treatment prior to the study period. The initial diagnosis of hepatoblastoma could have been made either through a tissue pathology or by clinical diagnosis (*ie*, an elevated AFP level, along with the presence of a liver tumor on radiological imaging). However, all patients must have had a tissue pathology to confirm the diagnosis of hepatoblastoma, either at diagnosis or at the time of definite surgery. This study was approved by the Ethics Committee of the Faculty of Medicine Siriraj Hospital (COA number Si.592/2013).

As per our treatment guidelines, all patients were initially evaluated by a pediatric surgeon and received upfront surgery if the tumor could be removed. For those who had an unresectable tumor in the surgeon's opinion, 4 courses of neoadjuvant chemotherapy were given before a reevaluation. After surgery, adjuvant chemotherapy was given until the AFP level was reported to return to normal on 2 consecutive occasions (Fig 1).

Three chemotherapy regimens were used during the study period. The Siriraj-HP-94



Siriraj-HP-94 protocol (from 1994-2000)	
Carboplatin	300 mg/m^2/day IV drip in 15 minutes on Day 1
Doxorubicin	20 mg/m^2/day IV continuous drip in 24 hours on Days 1-4

Siriraj-HP-00-A protocol (since the year 2000)	
Cisplatin	90 mg/m^2/day IV drip in 6 hours on Day 1
Doxorubicin	20 mg/m^2/day IV continuous drip in 24 hours on Days 1-4

Siriraj-HP-00-B (since the year 2000)	
Cisplatin	90 mg/m^2/day IV drip in 6 hours on Day 1
Vincristine	1.5 mg/ m^2/day (maximum 2 mg) IV push on Day 2
5-Fluorouracil	600 mg/ m^2/day IV push on Day 2

Fig 1– Flow chart of the management of hepatoblastoma and details of chemotherapy regimens at Department of Pediatrics, Siriraj Hospital. AFP, alpha-fetoprotein; CMT, chemotherapy; IV, intravenous.

protocol – the main treatment regimen from 1994 to 2000 – consisted of carboplatin and doxorubicin. After 2000, that protocol was changed to a cisplatin-based regimen: Siriraj-HP-00-A (cisplatin/doxorubicin) and Siriraj HP-00-B (cisplatin/5-fluorouracil/vincristine) protocols. The new regimen was adopted from the INT-0098 study by the North American Intergroup

(Ortega *et al*, 2000). This meant that all Siriraj Hospital patients diagnosed after the year 2000 were initially treated with the Siriraj-HP-00-A protocol, and switched to the Siriraj-HP-00-B protocol later if either the cumulative dose of doxorubicin had exceeded 480 mg/m^2 or there had been no response to Siriraj-HP-00-A (*ie*, the tumor was still unresectable).

The patients' demographic data, clinical presentation, treatment details and treatment outcomes were collected and analyzed using SPSS version 16.0 (SPSS, Chicago, IL). All statistical analyses were assessed on an intention-to-treat basis.

Tumor staging, determined by surgical extent before the initiation of chemotherapy, was designated as follows: stage I: complete tumor removal; stage II: gross tumor removal with microscopic residual disease; stage III: inoperable tumor or gross residual disease, including an intra-abdominal lymph node or intraoperative tumor spilling; and stage IV: distant metastasis (Ortega *et al*, 2000). The response to neoadjuvant chemotherapy was evaluated by the tumor resectability at the time of definite surgery. Complete remission was defined as no evidence of the tumor, with a normal level of serum AFP for more than 4 weeks. Treatment toxicities were graded as 1 to 4, based on the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) (Trotti *et al*, 2003).

RESULTS

During the study period, 53 patients with a liver mass and an elevated AFP level were identified from our pediatric cancer database. Fourteen patients had an initial tumor biopsy, 10 of whom were found to have hepatocellular carcinoma (HCC) and were excluded from the study. Two other patients were found to have a hepatic hemangioma and a hepatic germ cell tumor at the time of definite surgery, so they were also excluded from the study. Thus, 41 hepatoblastoma patients were eligible for the study.

Patient characteristics, including demographic data, the initial AFP level, staging, and pathology results, are presented in Table 1. The most common presenting symptoms were abdominal mass (70.7%), abdominal distension (22%), and abdominal pain (7.3%).

The initial laboratory results showed that 73.2% of patients were anemic, based on World Health Organization criteria (McLean *et al*, 2009), and 68.8% had thrombocytosis with platelet counts > 500,000/mm^3. One patient had significant transaminase elevation without a history of liver disease.

In terms of the treatment approach, 13 patients (32%) underwent upfront surgery followed by adjuvant chemotherapy, while 28 patients (68%) received neoadjuvant chemotherapy as their first treatment.

All patients received chemotherapy as a part of their treatment. Chemotherapy was given for a total of 258 courses, with the median number of courses of chemotherapy, neoadjuvant chemotherapy and adjuvant chemotherapy per patient being 6 (range: 2-12 courses), 4 (range: 1-12 courses), and 4 (range: 2-6 courses), respectively. Twenty patients (48.8%) were treated with the Siriraj-HP-94 protocol as their main chemotherapy regimen, and another 20 patients (48.8%) with the Siriraj-HP-00-A protocol. One patient received the Siriraj-HP-00-B protocol as a first line adjuvant chemotherapy without any documented reason, while 4 patients received the Siriraj-HP-00-B as part of the adjuvant chemotherapy because the accumulated dose of doxorubicin exceeded 480 mg/m^2.

Complete tumor removal was achieved in 12 of the 13 patients who had initial surgery. In addition, the patient who had partial tumor removal subsequently had a complete resolution

Table 1
Demographic data and tumor characteristic of 41 Thai hepatoblastoma patients.

Parameters	Number of patients (%)
Age at diagnosis	
< 1 month	4 (9.8)
1-6 months	4 (9.8)
6 months-3 years	27 (65.8)
> 3 years	6 (14.6)
Median age at diagnosis	14 months (range: 1 day-11.1 years)
Gender	
Male	21 (51.2)
Female	20 (48.8)
Median follow-up time	6.3 years (range: 0.2-19.7 years)
AFP level (ng/ml)	
< 100	2 (4.9)
100-9,999	3 (7.3)
10,000-99,999	9 (22)
>100,000	26 (63.4)
No data	1 (2.4)
Median AFP level	100,000 ng/ml (range: 0.49-726,700 ng/ml)
COG staging[a]	
Stage I	9 (22)
Stage II	1 (2.4)
Stage III	23 (56.1)
Stage IV	8 (19.5)
Initial metastasis	
Lung	7 (17.1)
Bone	1 (2.4)
No metastasis	33 (80.5)
Pathological results	
Mixed epithelial and mesenchymal type	18 (43.9)
Mixed epithelial type	11 (26.8)
Pure fetal type	5 (12.2)
Embryonal type	2 (4.9)
Unclassified type due to tumor necrosis	5 (12.2)
Radiological findings of tumor	
Location	
Right lobe	20 (48.8)
Left lobe	8 (19.5)
Both lobes	13 (31.7)
Number of tumor	
1 mass	39 (95.2)
2 masses	1 (2.4)
3 masses	1 (2.4)

[a]Tumor staging according to the children's Oncology Group classification system (Ortega *et al*, 2000).
AFP, alpha-fetoprotein; COG, children's Oncology Group.

of the residual tumor after receiving adjuvant chemotherapy.

Among the 28 patients who received neoadjuvant chemotherapy, gross tumor removal was eventually achieved in 23 cases, and the tumor resectability rate between each chemotherapy protocol did not differ significantly (p = 0.68) (Table 2). Five patients who had not responded to the first neoadjuvant chemotherapy (2 of the Siriraj-HP-94, and 3 of the Siriraj-HP-00-A protocols) underwent various salvage chemotherapy regimens. However, only 2 patients responded and were able to proceed to surgery, while the remaining 3 patients died from disease progression.

Chemotherapy toxicity was reported in 27 patients (Table 3). Of note, only 14 patients had hearing tests to assess ototoxicity, and 7 patients had echocardiography to evaluate therapy-related cardiotoxicity. Surgical complications were reported in 2 patients, including intraoperative bleeding in 1 patient and injury to the inferior vena cava in the other patient.

Four patients had a tumor relapse at a median time of 1.2 years (range: 0.8-1.7 years). All relapses occurred in the liver. Two patients achieved a second remission after having surgery and salvage chemotherapy.

At the end of the study, 28 patients (68.3%) were in complete remission, 2 patients (4.9%) were lost to follow-up, and 11 patients (26.8%) died from disease progression. The median follow-up time was 6.3 years (range: 0.2-19.7 years).

Table 2
Treatment summary of our Thai hepatoblastoma patients, and the results of treatment.

Treatment (n = number)	Number of patients (%)
Treatment approach (n = 41)	
Upfront surgery with adjuvant CMT	13 (31.7)
Neoadjuvant CMT with delayed surgery	28 (68.3)
Surgery result	
Upfront surgery group (n = 13)	
Complete tumor removal	12 (92.3)
Partial tumor removal	1 (7.7)
Neoadjuvant CMT group (n = 28)	
Complete tumor removal	16 (57.1)
Microscopic residual disease	7 (25)
Gross residual disease	2 (7.1)
Surgery not performed	3 (10.8)
Main chemotherapy protocol (n = 41)	
Siriraj-HP-94 protocol	20 (48.8)
Siriraj-HP-00-A protocol	20 (48.8)
Siriraj-HP-00-B protocol	1 (2.4)
Tumor resectability after neoadjuvant CMT (n = 28)	
Siriraj-HP-94 protocol (resectable/total)	7/9 (77.8)
Siriraj-HP-00-A protocol (resectable/total)	16/19 (84.2)

CMT, chemotherapy; Siriraj-HP-94 protocol, carboplatin/doxorubicin; Siriraj-HP-00-A, cisplatin/doxorubicin; Siriraj-HP-00-B, cisplatin/5-fluorouracil/vincristine (see Fig 1).

Table 3
Summary of chemotherapy toxicities in Thai hepatoblastoma patients, according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0) (Trotti *et al*, 2003).

Toxicities	Number of patients (%)	Number of cycles (%)
Infections	27 (65.9)	65 (25.2)
Fever with neutropenia	19 (46.3)	32 (12.4)
Hematotoxicity	18 (43.9)	44 (17.1)
Grade 3 to 4 neutropenia	18 (43.9)	35 (13.6)
Ototoxicity (*n* = 14)	5 (35.7)	-
Nephrotoxicity	6 (14.6)	-
Cardiotoxicity (*n* = 7)	0 (0)	-

Table 4
Survival rates of Thai hepatoblastoma patients, according to various clinical parameters.

Parameters	5-year EFS (%)	*p*-value	5-year OS (%)	*p*-value
Tumor staging[a]				
Stage I (*n* = 9)	77.8	0.035	87.5	0.253
Stage II (*n* = 1)	100		100	
Stage III (*n* = 23)	69.6		73.9	
Stage IV (*n* = 8)	25		46.9	
Initial CMT (intention-to-treat)				
Siriraj-HP-94 protocol (*n* = 20)	60	0.561	64.3	0.302
Siriraj-HP-00-A protocol (*n* = 20)	71.4		80.7	
Pathology subtypes				
Completely resected PFH (*n* = 4)	60	0.887	80	0.943
Other[b] (*n* = 36)	67.7		76.2	
Treatment approach				
Upfront surgery (*n* = 13)	69.2	0.494	83.3	0.272
Neoadjuvant CMT (*n* = 28)	60.7		67.3	

[a]Tumor staging according to the Children's Oncology Group classification system (Ortega *et al*, 2000).
[b]Pure fetal histology with residual tumor after surgery, or other pathology subtypes.EFS, event-free survival; OS, overall survival; CMT, chemotherapy; PFH, pure fetal histology; Siriraj-HP-94 protocol, carboplatin/doxorubicin; Siriraj-HP-00-A: cisplatin/doxorubicin (see Fig 1).

The 5-year EFS and OS rates for all patients were 63.4% and 72.2%, respectively; the survival rates for each COG stage are at Table 4. The 5-year EFS rate was significantly better for patients who had achieved complete tumor removal without microscopic disease ($p = 0.004$), and significantly worse for those who had a metastatic disease ($p = 0.002$) or those who had an initial AFP level < 100 ng/ml ($p = 0.042$) (Fig 2). Other factors (namely, the chemotherapy protocol, the tissue pathology subtype, and the type of treatment approach) did not show a statistically significant difference in the 5-year EFS and OS rates (Table 4).

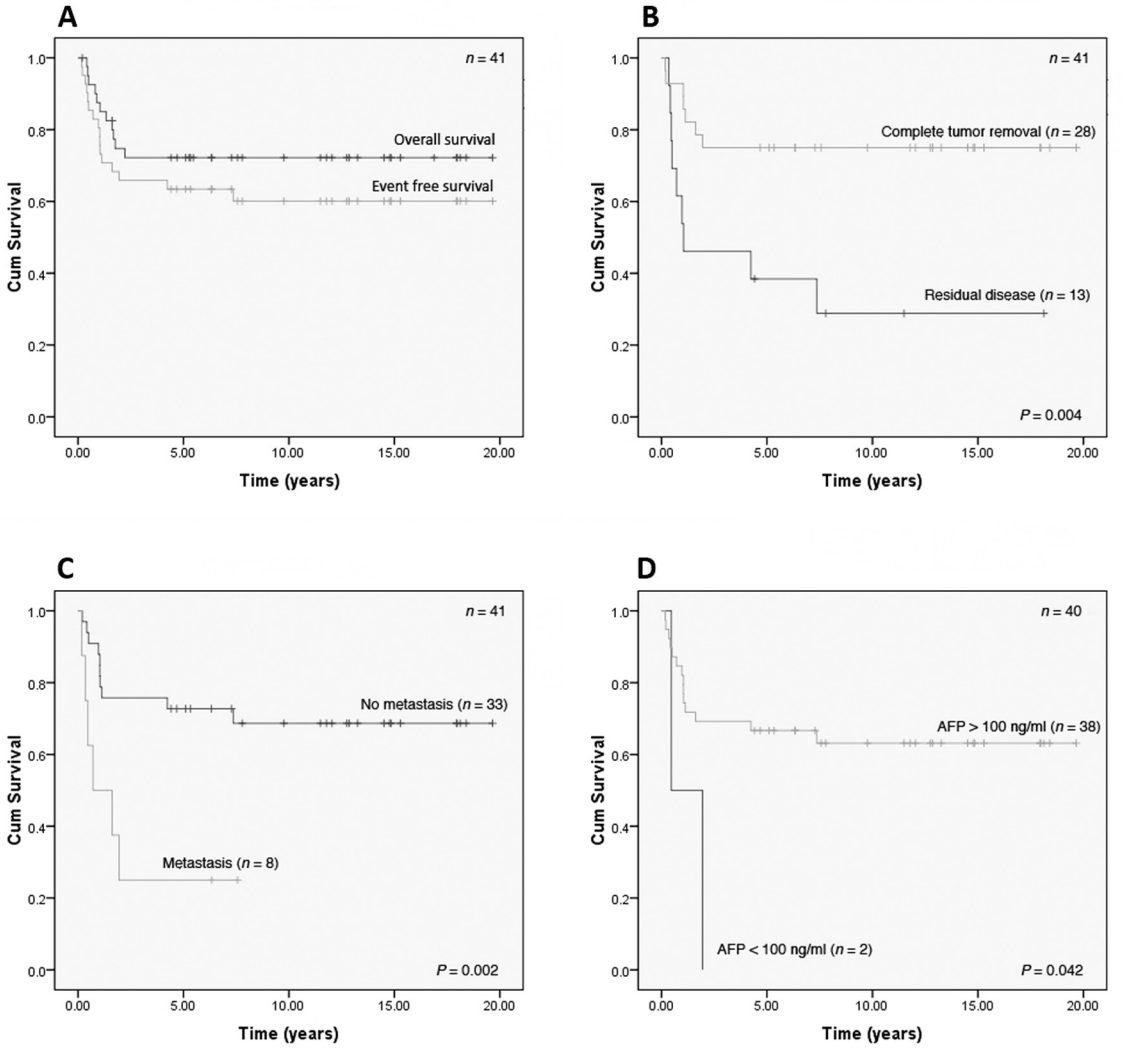


Fig 2– Kaplan-Meier curve showing survival rate of Thai hepatoblastoma patients in this study. A) 5-year event-free survival (EFS) and 5-year overall survival (OS) rates of all patients. B) 5-year EFS rate for patients who had complete tumor removal and had residual disease. C) 5-year EFS rate for patients with and without initial metastasis. D) 5-year EFS rate for patients with initial AFP level of < 100 ng/ml or > 100 ng/ml.

DISCUSSION

Hepatoblastoma, although rare, is responsible for the majority of malignant liver tumors in young children. It is known that most hepatoblastoma can be diagnosed without a need for tumor biopsy, except for those who are younger than 6 months or older than 3 years (Czauderna *et al*, 2005). The results of our study supported the need for a tumor biopsy in those age groups. Twelve out of the 53 patients with a primary liver tumor and an elevated AFP level in our study turned out to have a diagnosis other than hepatoblastoma. Ten of those 12 patients had HCC, and all ten were older than 3 years; the other 2 patients had either a hemangioma or a germ cell tumor, and both were younger than 6 months.

Initial lung metastasis was found in almost 20% of the patients in this study, which was similar to other reports (Douglass *et al*, 1993; Brown *et al*, 2000; Ortega *et al*, 2000). This raises the importance of having an initial chest computed tomography scan for the primary surveillance of lung metastasis.

Data from our study showed that, in general, tumors of a lower stage had better 5-year EFS and OS rates than tumors of a higher stage; this was similar to the results of previous reports (Brown *et al*, 2000; Ortega *et al*, 2000; Fuchs *et al*, 2002; Perilongo *et al*, 2009; Zsiros *et al*, 2010). Interestingly, we found that our stage II patient had better EFS and OS rates than those of the stage I patients. This finding was also observed in studies by the German Society for Pediatric Oncology and Hematology (HB-94), and by the North American Intergroup (INT-0098) (Ortega *et al*, 2000; Fuchs *et al*, 2002). However, there was no explanation of this finding in those studies, and our limited number of only 1 patient in stage II made it difficult to draw any conclusions.

Previous studies have shown that the use of a cisplatin-based regimen leads to better survival rates than a carboplatin-based regimen (Ortega *et al*, 2000; Dall'Igna *et al*, 2001). The result of our study was in line with this finding, but it was not statistically significant. However, this finding supports our decision to change the main chemotherapy regimen from the carboplatin-based one (Siriraj-HP-94) to the cisplatin-based protocol (Siriraj-HP-00-A).

It is known that tumor metastasis, the outcomes of surgery, the initial AFP level and the pathological subtype are the important prognostic factors for hepatoblastoma (Haas *et al*, 1989; von Schweinitz *et al*, 1995; van Tornout *et al*, 1997; Haas *et al*, 2001; Katzenstein *et al*, 2002; Tomlinson and Finegold, 2006). In our study, we also observed that patients who had complete tumor removal without microscopic residual disease had better survival, indicating the important role of radical surgery in treating hepatoblastoma. Furthermore, our data showed that patients with a metastatic disease or those who had an initial AFP level of < 100 ng/ml had a worse outcome; a more intensive treatment might be needed for those patients to achieve better outcomes.

Several reports have shown that a tumor with a pure fetal histology (PFH) had a better outcome, especially for those patients whose tumor could be completely resected (Haas *et al*, 1989). Four patients (9.7%) in our study had a completely resected PFH subtype tumor, but the outcomes of those patients were not better than those of other patients. Moreover, 1 of those 4 patients had disease relapse and eventually died. Interestingly, the result of the tissue pathology showed that the patient had a very close surgical margin to the normal liver tissue, whereas the other 3 patients had an adequate surgical margin; this finding might be responsible for the local relapse in that patient. A previous report had shown that a close surgical margin of < 1 centimeter did not affect the treatment outcome (Dicken *et al*, 2004). However, due to the small number of patients in that study, we suggest that

the correlation between the surgical margin and the survival rate should be further studied in a larger sample.

The most common chemotherapy toxicities in our study were infections and hematotoxicity, especially grade III and IV neutropenia (Table 3). The use of granulocyte colony stimulating factor might have played a role in preventing prolonged neutropenia in those patients. Moreover, in our opinion, a reduction of treatment intensity might have prevented those complications, especially in the case of patients with a low-stage tumor, who generally have a good survival rate and might not need intensive treatment. However, the risks and benefits of such a procedure should be examined carefully.

The COG study revealed that the efficacies of cisplatin/doxorubicin and cisplatin/5-fluorouracil/vincristine regimen are comparable (Ortega *et al*, 2000). However, the COG prefers the latter regimen in order to avoid cardiotoxicity from doxorubicin (Rodriguez-Galindo *et al*, 2013). Nevertheless, we have been using the cisplatin/doxorubicin regimen (Siriraj-HP-00-A) as our main chemotherapy since the year 2000 and have not seen cardiotoxicity in our patients. However, the main limitation of our study was the lack of a long-term evaluation of this particular regimen's impact on the cardiovascular system; further evaluation of the cardiotoxicity of the cisplatin/doxorubicin regimen is therefore needed.

Despite having different treatment approaches or using different chemotherapy regimens, the patients in our study had 5-year EFS and OS rates comparable to those reported in studies from North America and Europe (Brown *et al*, 2000; Ortega *et al*, 2000; Fuchs *et al*, 2002; Perilongo *et al*, 2009; Zsiros *et al*, 2010). However, one of our stage I patients who had a very close surgical margin to the normal liver tissue had a subsequent tumor relapse and did not respond to the relapse treatment. This led to an inferior 5-year-EFS rate for our stage I patients (77.8%) relative to those reported by the North American Intergroup (91% in the INT-0098 study) and SIOPEL (100% in the SIOPEL-1 study).

In conclusion, hepatoblastoma, although rare, is still an important solid tumor in young children. The treatment outcomes for hepatoblastoma at our institute are comparable to those in developed countries. Complete tumor removal is the most important prognostic factor. Neoadjuvant chemotherapy, followed by delayed surgery, is suggested if complete resection is not feasible at the beginning. Tumor resectability did not differ among the two main chemotherapy protocols that were used in our hospital during the study period. Infections and significant neutropenia are the most common treatment-related toxicities. As a low-stage tumor has a better prognosis, reduction of the treatment intensity should be considered to prevent treatment-related toxicities; however, more intensive treatment is needed in cases with metastatic disease or having an initial AFP level of < 100 ng/ml.

CONFLICTS OF INTEREST

The authors hereby declare that there are no conflicts of interest.

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