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Clinical Characteristics and Prognosis of Pediatric Hepatocellular Carcinoma

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Abstract

Introduction: Hepatocellular carcinoma (HCC) is a rare pediatric malignancy that is usually advanced at diagnosis, with a relatively poor prognosis. Extensive treatment, including complete tumor resection, is believed to be necessary for cure. This study was performed to analyze treatment results and to search for prognostic factors of pediatric HCC.

Methods: Between March 1982 and February 2004 a total of 16 children had been diagnosed as having HCC in our institution, and a retrospective analysis was performed.

Results: The median age at diagnosis was 10.5 years, and the male/female ratio was 11:5. As a predisposing condition, hepatitis B virus (HBV) infections were present in 11 (68.8%) and liver cirrhosis in 8 (50.0%). Including 1 patient with a liver transplant, 4 patients (25.0%) underwent a primary operation with complete tumor resection, and 11 (68.8%) received neoadjuvant chemotherapy because of their inoperable state at diagnosis. After neoadjuvant chemotherapy, complete tumor resection was performed in four (36.4%). Thus complete resection was undertaken in a total of eight patients (50.0%). The estimated 5-year survival rate of all patients was 27.3%. The 5-year survival rate for patients who underwent complete tumor resection was 62.5%, and for those who underwent palliative resection or no operation it was 0%. The statistically significant prognostic factors were tumor stage, presence of metastasis, and complete tumor resection.

Conclusions: This study confirmed that complete tumor resection is essential for cure in pediatric patients with HCC, and neoadjuvant chemotherapy improves the tumors' resectability.

Hepatocellular carcinoma (HCC) is a rare disease in children. Primary malignant liver tumors account for 0.8% to 2.5% of all pediatric malignancies and 70% of all pediatric liver tumors. In Western countries, hepatoblastoma is the most common malignant liver tumor in children, and HCC is the second most common but accounts for fewer than 25%. The incidence of pediatric HCC is 0.5 to 1.0 cases per million in Western countries but 2.1 cases per million in Southeast Asia, an area endemic for hepatitis B virus (HBV). In Taiwan, HCC is the most common malignant liver tumor in children and has been reported to represent more than 70% to 80% of pediatric hepatic malignancies. According to Korean reports, the incidence of malignant liver tumors represents 0.7% to 5.0% of all pediatric malignancies, and HCC accounts for 20% to 30% of the malignant liver tumors.[1–9]

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Most pediatric HCCs occur in older children (10–14 years), whereas hepatoblastoma is encountered during the first 3 years of life. Pediatric HCC more commonly affects boys and presents usually as an abdominal mass accompanied by abdominal pain, weight loss, fever, or anorexia. The disease is frequently associated with preexisting liver disease, such as metabolic liver disease (α_1-antitrypsin deficiency, glycogen storage disease, Wilson's disease, hereditary tyrosinemia), viral hepatitis (HBV, HCV), biliary atresia, or total parenteral nutrition (TPN) cholestasis.[1–6] HBV infection is the most common cause of pediatric HCC in endemic areas; and liver cirrhosis, as a predisposing factor, is more frequently present in HBV endemic areas than in the West.[5,8]

Advanced, unresectable disease (*e.g.*, multiple or multifocal disease, portal or hepatic vein invasion, extrahepatic spread, distant metastasis) is frequently present at diagnosis of pediatric HCC. Moreover, HCC has a relatively poor prognosis, with a long-term survival rate of only 10% to 30%. However, it has been shown on a number of occasions that extensive treatment, including complete tumor resection, chemotherapy, with or without additional modalities such as transcatheter arterial chemoembolization (TACE) improve survival.[1–10] Despite recent chemotherapeutic developments for pediatric hepatic malignant tumors, HCC remains more resistant to chemotherapy than hepatoblastoma;[3,11] therefore complete tumor resection is viewed as the most important and essential treatment for cure.[1–5]

In this study, we collected the clinical characteristics of pediatric HCC patients, analyzed treatment results, and searched for prognostic factors.

MATERIALS AND METHODS

During the period between March 1982 and February 2004, a total of 16 children were diagnosed as having HCC at our institution. The diagnosis was based on percutaneous needle biopsy or operative biopsy results. Clinical records, laboratory data, pathologic specimens, and radiologic images were reviewed retrospectively.

Serum α-fetoprotein (AFP) level was used as a tumor marker, and liver function tests (LFTs), including total bilirubin and albumin levels, were checked as a cirrhosis index from the time of diagnosis and through the follow-up period. Abdominal ultrasonography (USG), computed tomography (CT), or magnetic resonance imaging (MRI) was performed at diagnosis and during the treatment period to evaluate tumor volume, extent, resectability, and metastasis. In addition, metastatic spread was assessed by chest simple radiography or chest CT, bone scan, and bone marrow examination. Tumor volume was represented by a V score, which was defined as the volume (cubic centimeters) of a small rectangular hexahedron calculated by multiplying the width, length, and height of the tumor.[12] Tumor extent was defined using the Pretreatment Extent of Disease System (PRETEXT) of the Group for Epithelial Liver Tumors of the International Society of Pediatric Oncology (SIOPEL).[3]

If the tumor had involved all four liver sectors or if there was massive invasion of the great vessels or distant metastasis, it was considered unresectable.[12,13] Patients with a resectable tumor underwent a primary operation, and those with unresectable disease at diagnosis received neoadjuvant chemotherapy. Usually, chemotherapy was performed based on the protocols of the Children's Cancer Group (CCG), which consist of cisplatin, doxorubicin, vincristine, and fluorouracil, among others. In most patients, the CCG-823F protocol was used, which is a combination of cisplatin and doxorubicin; the CCG-8881A, 8881B, and 881c regimens were also used in some patients.[8,10,14] After neoadjuvant chemotherapy, if the disease was evaluated as having a partial response or was stable, the delayed operation followed. Adjuvant chemotherapy was applied after a primary or a delayed operation.

Complete remission was defined as no evidence of disease and a normal serum AFP level after chemotherapy. Partial response was defined as a decrease of more than 50% of the tumor volume associated with a decreasing AFP level. Stable disease was defined as any response less than a partial response. Progressive disease was defined as an increase of more than 25% in the tumor volume, an increasing AFP level, or the appearance of new lesions.[8,10]

Statistical analysis was conducted with SPSS for Windows, version 11.0. Univariate analysis was performed by Fisher's exact test and Spearman's rho. Survival curves were generated using the Kaplan-Meier method, and prognostic factors were evaluated using the log-rank test.

RESULTS

Age at diagnosis ranged from 1 to 15 years (median 10.5 years); only two children were less than 5 years old. Males were affected more than females (male/female ratio 11:5). Altogether, 13 patients (81.3%) had one or more symptoms. Abdominal pain was present in seven children, an abdominal mass in five, abdominal distension

in two, weight loss in two, vomiting in two, hematemesis in one, headache and dizziness in one, general weakness in one, and cough in one. HBV infection was present in 11 patients (68.8%), and liver cirrhosis was present in 8 patients (50%) at diagnosis as demonstrated by abnormal LFTs, the clinical presentation, or radiologic images. Two children had underlying liver disease related to cirrhosis; one had Wilson's disease, and the other had Byler's disease, which is also called progressive familiar intrahepatic cholestasis.[15] Serum AFP levels at diagnosis were elevated to more than 400 ng/ml in all patients.[16] All 16 patients were diagnosed as having typical HCC by histopathology, and there were none with the fibrolamellar variant. One patient had been diagnosed as having fetal-type hepatoblastoma by percutaneous needle biopsy, but after surgical resection he was eventually confirmed as having HCC by immunohistochemical staining. Tumor nodules were multiple in 12 patients (75.0%). Maximal tumor diameters varied from 2 to 18 cm (median 7.0 cm), and V scores ranged from 8 to 1864 cm^3 (median 288.0 cm^3). Six children (37.5%) had distant metastases at diagnosis, all of them lung metastasis. Concomitantly, there was brain metastasis in one child, bone marrow metastasis in one, and metastasis to both kidneys in one. Of the six patients with distant metastases, four had stage III disease and two had stage IV disease ($P = 0.000$) (Table 1).

Table 1.
Clinical characteristics of pediatric hepatocellular carcinoma at diagnosis

Characteristic	No. of patients	%
Age		
<5 Years	2	12.5
≥5 Years	5	31.3
≥10 Years	9	56.3
Sex		
Male	11	68.8
Female	5	31.3
HBV infection	11	68.8
Liver cirrhosis	8	50.0
Symptomatic	13	81.3
AFP > 400 ng/ml	16	100
Total bilirubin > 1.2 mg/dl	4	25.0
Albumin < 3.5 mg/dl	3	18.8
Tumor location		
Right lobe	8	50
Left lobe	2	12.5
Both lobes	6	37.5
Multiplicity (≥2 tumors)	12	75
Stage		
I	1	6.3
II	7	43.8
III	5	31.3
IV	3	18.8
Major vascular invasion	8	50
Intraabdominal tumor extension	2	12.5
Distant metastasis	6	37.5

HBV: hepatitis B virus; AFP: α-fetoprotein.

Four patients (25.0%) underwent primary operation with complete tumor resection, but 12 patients (75.0%) had inoperable tumors at diagnosis due to its advanced state; 11 of the 12 patients (68.8%) received neoadjuvant chemotherapy. One child refused any further treatment after diagnosis. After neoadjuvant chemotherapy, a partial response was observed in six patients (54.5%), stable disease in one (9.1%), and disease progression in three (27.3%). One patient died during the first cycle of chemotherapy owing to aggravated liver cirrhosis, so the effectiveness of chemotherapy could not be evaluated. One of the patients with disease progression had been initially evaluated as having a partial response after neoadjuvant chemotherapy, and he underwent a delayed operation. However, during the intraoperative evaluation his disease was found to have progressed. When the tumor sizes in the partial response and stable disease groups before and after neoadjuvant chemotherapy were compared using V scores, the median reduction rate was found to be 80.7% (Fig. 1). Of the six patients with distant metastasis at diagnosis, a partial response with no evidence of metastasis was observed in one after neoadjuvant chemotherapy. Another four also showed a partial response but still had metastatic lesions, and one experienced disease progression.

After neoadjuvant chemotherapy, eight patients who had been considered as having had a partial response or stable disease, including the one who was eventually proven to have disease progression, underwent operative treatment. In four of these patients (36.4%), an unresectable tumor had been converted to resectable after neoadjuvant chemotherapy, and complete tumor resection was performed; in the other four patients (36.4%), a palliative operation was done. Altogether, operative treatment was undertaken in 12 patients (75.0%): 8 curative and 4 palliative operations (Fig. 2). The eight curative operations (complete tumor resection) were comprised of four primary operations and four delayed operations. Of the four primary resections, three were partial hepatectomies and one was a living donor liver transplantation, which was required because of the presence of Byler's disease, an intractable underlying liver disease. The overall curative operation rate was 50.0%. Four palliative operations after neoadjuvant chemotherapy were performed in patients with partial

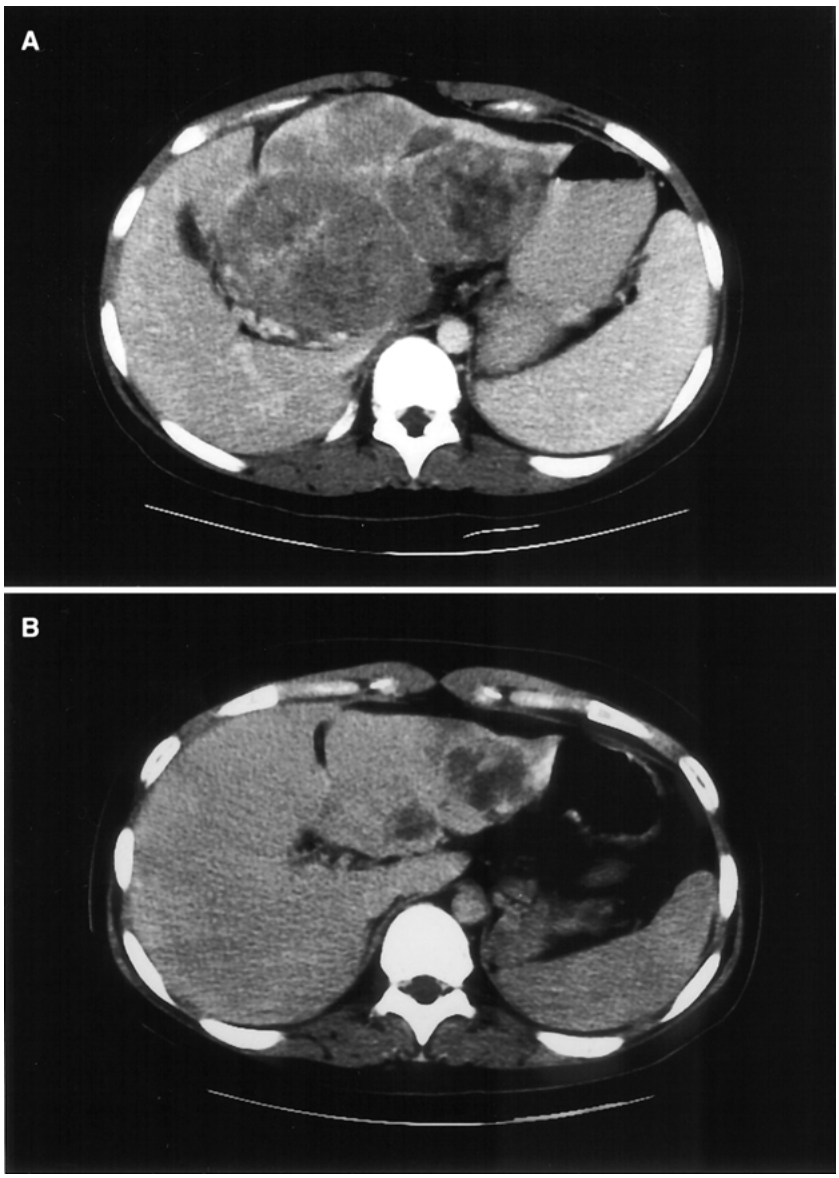

Figure 1. Computed tomography (CT) image of a pediatric patient with hepatocellular carcinoma (HCC). **A.** Inoperable state at diagnosis. **B.** Conversion to operable state after neoadjuvant chemotherapy.

responses despite the unresolved distant metastasis, as the metastatic lesions were expected to show a further response to adjuvant chemotherapy after the operation. Adjuvant chemotherapy was performed in 11 patients following tumor resection. In the patient who underwent transplantation, adjuvant chemotherapy was not planned, and only close observation was performed. Three patients underwent transarterial embolization (TAE) during the preoperative or mainly postoperative periods as an additional, complementary treatment.

Recurrence developed in three (37.5%) of the eight patients who had undergone a curative operation. The site of recurrence was the liver in all three cases. In one child, tumor recurrence was detected 14 months after a delayed operation following neoadjuvant chemotherapy. Despite further treatment (tumor resection and adjuvant chemotherapy), he died because of disease progression. The other two patients who had undergone primary operations experienced recurrence after 5 and 43 months, respectively, but remain alive after operation on the recurred tumor or repeated TAE.

Eleven patients (68.8%) died; eight (72.7%) of the deaths were associated with disease progression, two (18.2%) with complications of liver cirrhosis (which presented as ascites, hematemesis, or hepatic encephalopathy) and one (9.0%) with sepsis after chemotherapy. The seven children who underwent a palliative operation or no operation died owing to disease progression. Of the eight patients who submitted to a curative operation, five remain alive, and three are dead. One died because of tumor recurrence and extension, another died because of complications of liver cirrhosis, and the third died

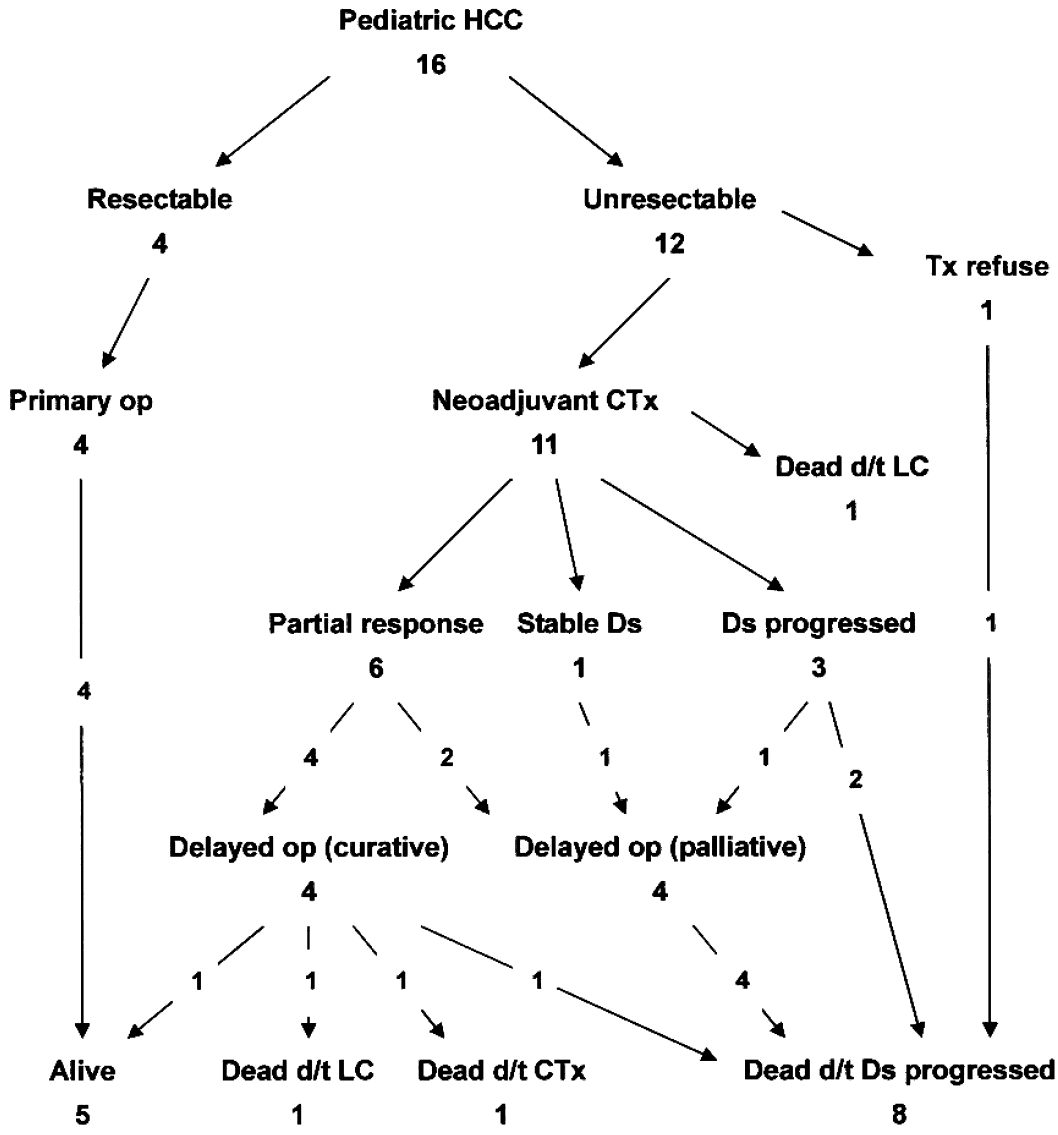

Figure 2. Clinical courses of 16 patients with pediatric HCC. Tx: treatment; Op: operation; CTx: chemotherapy; LC: liver cirrhosis; Ds: disease.

because of sepsis as an adverse effect of chemotherapy. Only three patients (18.8%) are alive, as they have not experienced recurrence after a curative operation. Based on the Kaplan-Meier plots, the 5-year survival rate for all of the patients was 27.3% (median survival 29 months, range 1–134 months). The median survival was 11 months in the palliative operation group and 1 month in the nonoperative group. The estimated 5-year survival rate for patients who underwent a curative operation was 62.5%. In contrast, the 5-year survival rate for patients who underwent palliative surgery and no operation was 0% (Fig. 3).

Univariate analysis by the Kaplan-Meier method identified the stage at diagnosis ($P = 0.0024$), metastasis ($P = 0.0398$), and curative operation ($P = 0.0039$) as significant prognostic factors that influenced the patients' survival. Although statistical significance was not attained, a good response to neoadjuvant chemotherapy tended to favor better survival ($P = 0.0550$). The presence of symptoms, HBV infection, or underlying cirrhosis was not found to be significantly associated with survival; and there was no statistical correlation between tumor diameter ($P = 0.957$) or V score ($P = 0.559$) and disease survival. Multivariate analysis could not be performed owing to an insufficient number of patients.

DISCUSSION

The incidence of HCC appears to be higher in HBV endemic areas, and HBV infection and liver cirrhosis are

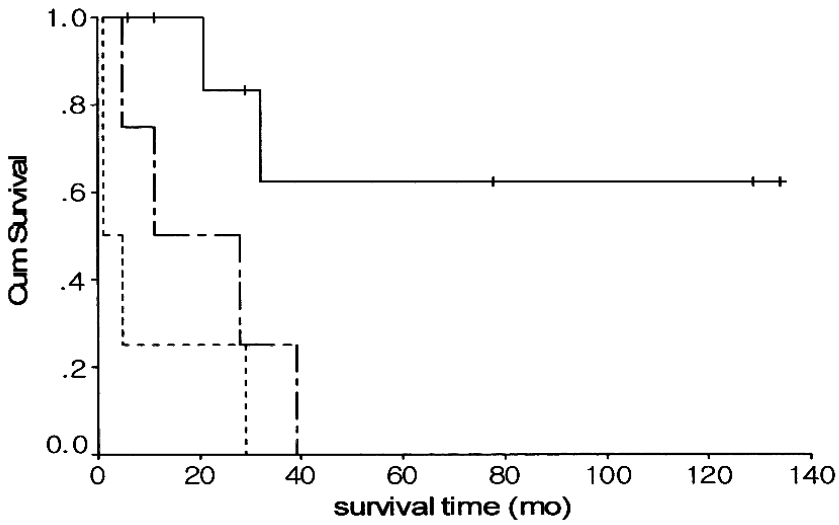

Figure 3. Survival of the complete tumor resection group by Kaplan-Meier analysis ($P = 0.0039$). Solid line: complete tumor resection; solid heavy line: palliative operation; dashed line: no operation.

generally believed to be the most significant etiologic factors of adult-type HCC (70–90%).[4] Several reports have revealed that these factors are also significant in pediatric HCC and more frequent in HBV endemic areas.[1,5] In Western countries HBV infection and liver cirrhosis are present in 10% to 30% of those with pediatric HCC,[1,3] but in a Taiwanese study HBV infection was present in 100% of pediatric HCC patients and liver cirrhosis in 71%.[7] In our review, HBV infection was found in 68.8% and liver cirrhosis in 50.0%. These figures are higher than those reported in the West and reflect those of HBV endemic areas. In Taiwan, there has been a nationwide vaccination program since 1982, which has been highly effective in controlling chronic HBV infection and preventing liver cancer,[17] Similarly, it is believed that the incidence of HCC has been significantly reduced in recent years owing to the HBV vaccination in Korea.[8]

In this study, the median age at diagnosis was 10.5 years. Boys predominated, with a male/female ratio of 2.2:1.0. Abdominal pain, a mass, and distension were common presentations, which concurs with previous reports.[1,2,8] The AFP level was elevated in all of our 16 children. Many other studies have revealed that elevated AFP proves the diagnosis of HCC and reflects disease activity during the treatment and follow-up periods. There has been a trend toward improved survival among children who had normal AFP levels at diagnosis.[1–4,10,16] Furthermore, fibrolamellar-type HCC, which usually presents with a normal AFP level, is reported to have a good prognosis.[1,2] However, much debate exists, and some authors have proposed no difference in results when comparing outcomes of the various pathologic types of pediatric HCC.[18]

Pediatric HCC is frequently advanced and inoperable at diagnosis.[1,2] According to Czauderna *et al.*, in the SIOPEL study PRETEXT stages III and IV at diagnosis were present in 61%, lung metastases in 31%, extrahepatic tumor extension in 18%, and major vascular involvement in 21%.[3] Chen *et al.* reported in a Taiwanese review that 29.1% had distant metastasis at diagnosis, and only 18.2% were amenable to complete resection because of the advanced state of the disease and anatomic nonfeasibility.[5] In our study, multiple tumors were observed in 75.0%, advanced stages of SIOP III or IV in 50.0%, major vascular invasion in 50.0%, intraabdominal tumor extension in 12.5%, and distant metastasis in 37.5%. As in many other reports, most of our children had advanced disease, and 75.0% of tumors were inoperable at diagnosis.

Most reports concluded that curative resection is the most important prognostic factor and that it is essential for disease-free survival. In most previous reports, the curative resection rate was about 10% to 30%, which was relatively low because the disease was usually found to be advanced and inoperable at diagnosis.[7,19] In this study, 75.0% of our patients underwent operative treatment, and 50.0% had a curative operation with complete tumor resection. Most cases were advanced and had distant metastases at diagnosis, and only 25.0% underwent primary curative operation without neoadjuvant chemotherapy. Our results were somewhat better than others, perhaps because of the effect of the neoadjuvant chemotherapy.

At our institution, the Childrens Cancer Study Group (CCG) protocols of hepatoma were used for the chemotherapy. They consisted of cisplatin, doxorubicin, vincristine, and fluorouracil, among others, and were used in

different combinations and various infusion regimens. The CCG-823F protocol was used in most patients, although protocols CCG-8881A, 8881B, and 881c were also used.[8,10,14] A partial response was obtained in 54.5%; and according to the V scores, the reduction rate of the tumors was 80.7%. Moreover, the 36.4% of the tumors had been converted to a resectable state after neoadjuvant chemotherapy. Our results strongly suggest that the role of neoadjuvant chemotherapy is to reduce the size of the tumor, converting initially unresectable tumors to resectable ones. The SIOPEL study, a prospective study of PLADO neoadjuvant chemotherapy for pediatric HCC, reported a partial response in 49% of patients and a successful tumor excision rate of 36%.[3] Many studies have found that the partial response group has a better prognosis,[5,10,20] and our results were similar. However, there was no statistically significance in our study, perhaps because of the small number of patients.

Many prognostic factors have been mentioned in other reports, such as tumor size, vascular invasion, multifocality, tumor aneuploidy, histologic grade, tumor cell subtype, and estrogen receptor expression.[1,3,4] Most of the previous reports, however, agreed that curative operation is the most important factor; and so it was in our study. In this study, the 5-year survival rate after curative operation was 62.5%, but the patients who were not subjected to a curative operation all died. Other statistically significant prognostic factors identified were the stage and the presence of distant metastasis. These factors were also concerned with the resectability of the tumor. Our study proved that a curative operation with complete tumor resection is the major prognostic factor and an essential factor for long-term survival. We used the V score to represent the initial tumor volume, which is the size of a small rectangular hexahedron, not the actual tumor volume.[12] The V score was found not to be related to patient survival with any statistical significance. Although tumor size was assessed to be a prognostic factor, it is likely that tumor extent and tumor resectability are more important than the tumor volume itself.

The estimated 5-year survival rate of pediatric HCC patients was 27.3% in this review. Several previous reports noted that the survival rate of pediatric HCC was 10% to 30%.[1–5,8] Despite the numerous efforts to eradicate this disease, the results have been unsatisfactory owing to the difficulties of early detection, advanced and inoperable state of the tumor at diagnosis, and insufficient effecs of chemotherapy. Compared to hepatoblastoma, pediatric HCC has a poor prognosis because the effect of chemotherapy is poor and the rate of complete tumor resection is low.[1–10] Most reports revealed that the survival of patients with hepatoblastoma has been dramatically improved in recent years by the introduction of effective chemotherapeutic agents, such as cisplatin—hence the elevated chance of curative resection after neoadjuvant chemotherapy.[1,2] The survival rate after treatment of hepatoblastoma had been reported to be as high as 60% to 75%.[11,12] These results indicate that improved survival of pediatric HCC patients can be achieved by developing more effective chemotherapeutic regimens, which in turn would increase the curative resection rate.

In our hospital review of adult HCC, the overall survival rate was 29.7%, and the 5-year survival rate of patients who had undergone surgery with or without chemotherapy was about 40%. The major cause of death was liver failure, accounting for 50% to 60%, which was mostly due to aggravation of an underlying HBV infection and liver cirrhosis.[21] Compared with our pediatric cases, the overall survival rate was no different, but the results of operative treatment were much better. This might be due to the effect of neoadjuvant chemotherapy and the difference in the severity in liver cirrhosis.[4]

Especially in unresectable cases, liver transplantation has been widely substituted for resection, but the indications for transplantation remain controversial. The criteria for adult HCC are more definitive, usually including the presence of localized disease with no more than three tumor foci with a maximum diameter of 3 cm. Some authors believe that transplantation is a questionable treatment option for pediatric HCC because the disease is already advanced and metastatic at presentation.[4] Nevertheless, many reports have presented better results with this modality for unresectable pediatric HCC cases.[1,22] Superina and Bilk concluded that liver transplantation should be considered for all children who have unresectable hepatic malignancies, given the 83% survival rate with no evidence of tumor recurrence. They also insisted that control of the primary tumor with chemotherapy and the sterilization of all extrahepatic disease are prerequisites for achieving successful results.[22] Our institution had only one case of transplantation, which was necessary because of severe intractable liver cirrhosis despite a resectable tumor. It is expected that more cases will be undertaken. If it is impossible to perform complete resection of the tumor because of the locally advanced state without unresolved metastatic lesions or there is underlying intractable liver disease, transplantation can be considered a good choice of treatment.

As complementary treatment modalities, transarterial chemoembolization, intraarterial chemotherapy, percutaneous ethanol injection, radiofrequency ablation, and

cryosurgery may be considered in adult cases. Although not yet established, it is expected that these modalities will improve survival.[1,23,24] Recently, gene therapy has been studied with respect to improving response to chemotherapy. Some reports revealed that the resistance of HCC to chemotherapy may result from the presence of multidrug resistance (*MDR1*) genes, or some other mechanisms.[4,25]

This study confirmed that complete tumor resection plays the critical role for cure in pediatric HCC, and neoadjuvant chemotherapy is helpful in improving the tumor's resectability. To achieve improved resectability, the development of more effective chemotherapeutic agents and alternative therapeutic modalities are required. Simultaneously, orthotropic liver transplantation in unresectable cases must be emphasized. As a result, the incorporation of multiple treatment modalities may be necessary to obtain satisfactory survival results in pediatric patients with HCC.

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