J Korean Surg Soc 2011;81:134-140
DOI: 10.4174/jkss.2011.81.2.134

JKSS
Journal of the Korean Surgical Society

pISSN 2233-7903 · eISSN 2093-0488

ORIGINAL ARTICLE

Hepatoblastoma: 15-year experience and role of surgical treatment

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Purpose: Hepatoblastoma is the most common malignant liver tumor in children. The aim of this study was to review our results of hepatoblastoma treatment and to determine the role of surgical treatment in hepatoblastoma. **Methods:** This is a retrospective clinical study. The medical records of patients with hepatoblastoma, treated between October 1994 and October 2009, were reviewed. The patients were classified according to the pretreatment extent of disease (PRETEXT) grouping system. The main outcome variable was survival. Secondary outcome variables were complete, partial and no response to chemotherapy and surgery, when indicated. **Results:** Twenty-seven patients were treated during the observation period. Eighteen were males. Five were PRETEXT group I, 8 group II, 13 group III and 1 group IV. Complete excision was achieved in all patients except in one case that underwent liver transplantation (group IV). Median follow-up and survival rate were 2.3 years and 100%, 6.6 years and 75%, 5.8 years and 92%, 7.7 years and 100%, for groups I to IV, respectively. Twenty patients are currently considered to be in complete response status and three patients are receiving postoperative chemotherapy. Four patients died; the causes of death were cytomegalovirus hepatitis, bone marrow suppression during adjuvant chemotherapy, primarynonfunction after the transplantation for recurrent tumor and metachronous rectal cancer, respectively. **Conclusion:** Favorable long-term outcome could be expected for hepatoblastoma with complete tumor excision and adjuvant chemotherapy.

Key Words: Hepatoblastoma, Surgery, Drug therapy, Transplantation

INTRODUCTION

Hepatoblastoma is the most common malignant liver tumor and the third most common intra-abdominal neoplasm in children. The survival of patients with a hepatoblastoma has markedly improved in recent years with the advances in chemotherapy and surgery. Several national and international cooperative studies have shown that the prognosis for hepatoblastoma can be improved dramatically by combining surgery with pre- and post-operative chemotherapeutic agents such as cisplatin and adriamycin [1,2]. Complete resection is the primary goal of surgical treatment and a prerequisite for cure, and effective neoadjuvant chemotherapy is important for complete re-

Received December 2, 2010, Accepted April 18, 2011

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This paper was presented as a oral presentation at the Asian Association of Pediatric Surgeons on Feb, 2010 in Kuala Lumpur, Malaysia.

section [3]. Recently, liver transplantation has been considered as an alternative option in cases with unresectable tumors and favorable outcomes have been reported [4]. The 5-year survival rate of hepatoblastoma has improved from 35% three decades ago to 75% in some recent series [5,6]. The aim of this study was to review our experience with the treatment of patients with hepatoblastoma and to determine the role of surgery in hepatoblastoma treatment.

METHODS

Patients

The medical records of 27 patients, treated at the Department of Surgery and Department of Pediatrics, Samsung Medical Center, between October 1994 and October 2009, were reviewed. The clinical, radiological, and surgical data were obtained. Tumor extension was assessed by computed tomography (CT) and by chest X-ray and CT for pulmonary lesions. Biopsy of the tumor was mandatory except in cases where the tumor seemed readily resectable. Tumor stage was established with the pretreatment extent of disease (PRETEXT) system, based on the radiological findings. As the PRETEXT system was developed at 2005 and we applied the system since then, patients who were treated before 2005 were classified retrospectively. High-risk patients were defined according to the previous study protocol [7].

Treatment

Patients were initially assessed for the tumor resectability. When the tumor was readily resectable (PRETEXT I), partial hepatectomy was attempted without preoperative chemotherapy. In contrast, for PRETEXT II and III tumors, neo-adjuvant chemotherapy was administered in an attempt to enable safe and complete resection. After histological diagnosis with a percutaneous biopsy, preoperative chemotherapy was administered with cisplatin, 90 mg/m^2 × 1 day and adriamycin, 20 mg/m^2 × 4 days. These courses were repeated every 4 weeks and the patients were re-assessed for the tumor resectability after 4 courses. If the tumor was deemed resectable, patients were referred to one of our authors (LSK) for complete resection. If deemed unresectable, patients were treated with another 2 courses followed by re-evaluation for resection. The liver transplantation was planned for patients deemed unresectable at this point. Regardless of the resectability, a maximum of 6 courses were given preoperatively. Standard anatomical resection was attempted, and clear resection margins were confirmed during the operation. Metastatic lesions that persisted after the preoperative chemotherapy were removed surgically, if possible. Complete resection was defined as no residual tumor by macroscopic or microscopic findings. All patients underwent postoperative chemotherapy with the same regimen, which was repeated up to a total of six courses until the serum α-fetoprotein (AFP) returned to the normal range.

Evaluation of treatment response

Assessment of response to the treatment was performed with AFP and CT after completion of the required treatment. The definitions used were as follow: complete response (CR) was no evidence of disease after complete resection and normal AFP; partial response (PR) was any tumor size decrease associated with decreased AFP (>1 log less than the original value); stable disease (SD) was no tumor size change and no change or less than 1 log decrease of AFP; and progressive disease (PD) was unequivocal increase in size of the tumor and/or any unequivocal increase of AFP.

Outcome measure

The main outcome measure was overall and event-free survival. Secondary outcome measures included CR, PR, SD, and PD. An event was defined as the disease-related patient death or disease relapse. Survival time was defined as the time from the diagnosis to the event.

RESULTS

Clinical features of the 27 patients with hepatoblastoma (Table 1)

The median age at the time of the diagnosis was 18 months (range, 2 months to 12.6 years), and the gender dis-

Table 1. Clinical features of 27 hepatoblastoma patients

Clinical features	Value
Age, median (range)	18 mo (2 mo-12.6 yr)
Sex (M:F)	18:9
Location	
Right	21
Left	5
Bilateral multiple	1
PRETEXT group	
I	5
II	8
III	13
IV	1
Metastasis	2 (lung)
Associated conditions	
BW syndrome	2
FAP	1
CMV hepatitis	1
No. of high-risk patients	5[a]
Serum AFP (ng/mL), median (range)	71,820 (1-426,332)
Surgical treatment	
Resection	26
Transplantation	2[b]
Pre-operative chemotherapy	20
Post-operative chemotherapy	26
Histology, n (%)	
Epithelial, pure fetal	7 (25.9)
Epithelical, fetal/embryonal	12 (44.4)
Mixed	8 (29.7)

PRETEXT, pretreatment extent of disease; BW, Beckwith- Wiedemann; FAP, familial adenomatous polyposis; CMV, cytomegalovirus; AFP, α-fetoprotein.
[a]Distant metastasis (n = 2), PRETEXT IV (n = 1), low serum AFP (n = 1), tumor rupture at presentation (n = 1). [b]One patient underwent living-related liver transplantation for the recurrent tumor after post-operative chemotherapy.

tribution was 18:9 (male:female). The tumor was located at the right hemiliver in 21 patients, left hemiliver in 5 patients, and throughout the whole liver in 1 patient. After PRETEXT classification, group I included 5 patients, group II 8 patients, group III 13 patients, and group IV 1 patient. Two patients had synchronous lung metastasis at the time of diagnosis (PRETEXT group II [multiple metastases] and III [solitary metastasis]). Associated conditions were as follow: Beckwith-Wiedemann syndrome (n = 2), familial adenomatous polyposis (FAP; n = 1), and cytomegalovirus (CMV) hepatitis (n = 1). Age-adjusted serum AFP levels were elevated in 26 patients except 1 patient (PRETEXT I, 1 ng/mL), with a median level of 71,820 ng/mL (range, 1 to 426,332 ng/mL). Twenty patients had preoperative chemotherapy, and postoperative chemotherapy was administered in 26 patients. For surgical treatment, complete tumor resection was achieved in 26 patients and 1 patient underwent primary living-related liver transplantation.

Surgical and pathological results

Six patients underwent complete surgical excision as primary therapy without preoperative chemotherapy: five patients in group I for readily resectable tumors (3 sectionectomies, 2 right hemihepatectomies) and one patient in group II for a ruptured tumor (emergency surgery, right hemihepatectomy). One patient (group IV) underwent primary liver transplantation for bilateral multiple hepatoblastomas, which was initially misdiagnosed as hepatocellular carcinoma after percutaneous biopsy. For the remaining 20 patients (7 group II patients and 13 group III patients), preoperative chemotherapy was administered and complete tumor excision was achieved thereafter. There were 6 hemihepatectomies and 1 sectionectomy in group II patients, and 4 trisectioinectomies, 7 hemihepatectomies, 2 sectionectomies in group III patients. In group III, seven unresectable cases were rendered resectable after preoperative chemotherapy (Fig. 1). Postoperative chemotherapy was administered in all patients regardless of the PRETEXT classification except in the one patient who underwent primary liver transplantation. The pathological results and the treatment courses are summarized in Table 1 and Table 2, respectively.

Treatment outcome according to the PRETEXT classification (Table 2)

The median follow-up duration was 6.5 years (range, 3 months to 15 years) after the diagnosis. Twenty patients have a CR status, three patients are receiving postoperative chemotherapy, and four patients died. Two patients, in group II, died of medical complications postoperatively. In one patient, although biochemical liver function test was abnormal preoperatively, CMV hepatitis was not suspected and no evaluation on viral hepatitis other than hepatitis B was performed. Pathological examination revealed the CMV infection on operative specimen,

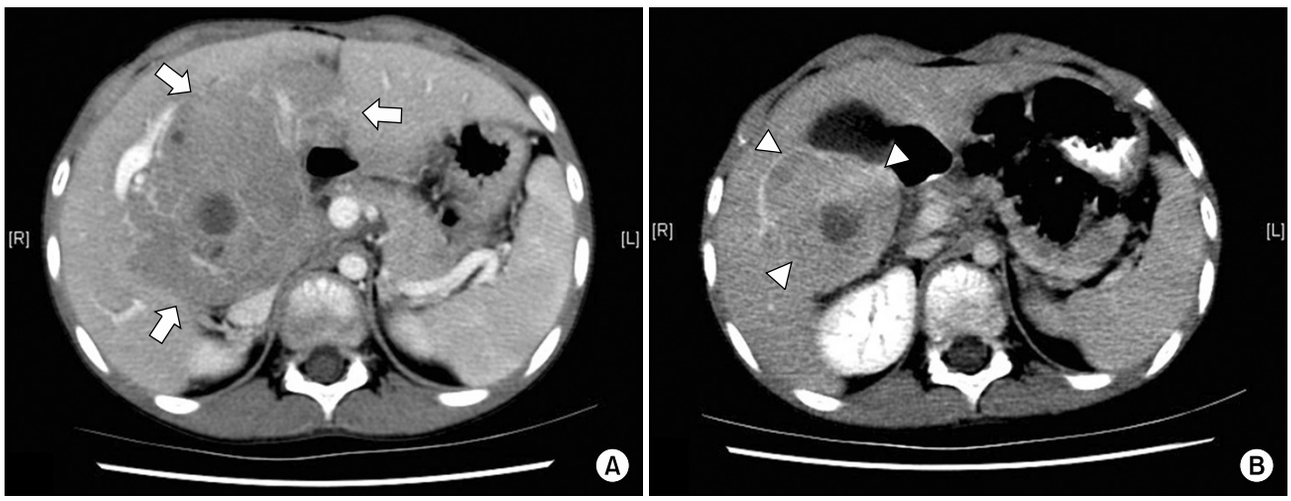

Fig. 1. (A) Tumor involved three adjacent sections (arrow) and complete resection with safe margins seems unlikely. (B) After 6 courses of neoadjuvant chemotherapy, extent of tumor decreased markedly (arrowhead) and was treated successfully with right hemihepatectomy.

Table 2. Treatment course and outcome according to the PRETEXT classification

PRETEXT	Treatment course	Outcome	5-yr EFS (%)
I (n = 5)	Hepatectomy → CTx (n = 5)	3 CR, 2 PR[c)]	100.0
II (n = 8)	Hepatectomy → CTx (n = 1)[a)]	6 CR, 2 died[d)]	75.0
	CTx → hepatectomy → CTx (n = 7)		
III (n = 13)	CTx → hepatectomy → CTx (n = 13)[b)]	10 CR, 1 PR[c)], 2 died[e)]	91.6
IV (n = 1)	Primary transplantation (living-related)	CR	100.0

PRETEXT, pretreatment extent of disease; EFS, event-free survival; CTx, chemotherapy; CR, complete response; PR, partial response.
[a)]This patient underwent emergency operation for the ruptured tumor. [b)]One patient underwent living-related liver transplantation for the recurrent tumor after partial hepatectomy. [c)]These patients are currently under postoperative chemotherapy. [d)]The cause of death was CMV hepatitis and bone marrow suppression during the postoperative CTx, respectively. [e)]The cause of death was metachronous rectal cancer and primary nonfunction after liver transplantation, respectively.

which was not evident on preoperative biopsy. Postoperative ganciclovir treatment failed to recover the liver function and the patient died of hepatic failure 8 months after the operation. The other patient showed persistent pancytopenia after completion of 3 courses of postoperative chemotherapy. The patient recovered well from the preceding 2 courses of chemotherapy. Bone marrow examination revealed the myelodysplastic syndrome, and the patient died of sepsis and multi-organ failure 2 months after the diagnosis of myelodysplastic syndrome. One patient, who was in group III, died of rectal cancer with multiple lung and liver metastases 15 years after the diagnosis of hepatoblastoma. In this case, numerous polyps were noted throughout the whole colon and rectum; there was no family history of colorectal cancer, but the *adenomatous pol-*

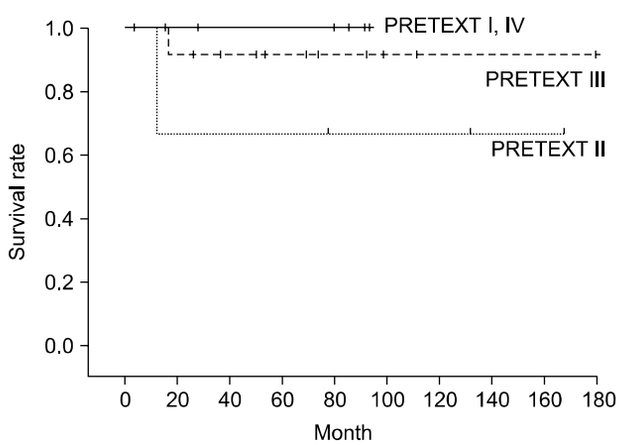

Fig. 2. The event-free survival according to the PRETEXT classification.

yposis coli (APC) gene mutation test was positive and the sporadic FAP was confirmed. One patient, who was also in group III, showed intrahepatic relapse 11 months after hepatectomy and was treated with a living-related liver transplantation; however, the patient died of primary non-function eight days after the transplantation. Both of the patients with initial lung metastases currently have a CR status. The overall 5-year event-free survival (EFS) was 87.8%, while 5-year EFS by PRETEXT grouping was 100%, 75%, 92% and 100% for group I to IV, respectively (Fig. 2).

DISCUSSION

The goal of this study was to review our experience with the treatment of hepatoblastoma and to determine the role of surgical treatment in hepatoblastoma. The pre- or post-operative chemotherapy protocol using a combination of cisplatin and adriamycin has been the standard treatment for hepatoblastoma in Japan since 1991 (Japanese Study Group for Pediatric Liver Tumors Protocol-1 [JPLT-1]); the results of the JPLT-1 trial were similar to those from Europe and United States [8]. However, the Japanese trial used staging criteria somewhat different from those of the PRETEXT classification, and therefore a direct comparison with our results cannot be made. Suita et al. [9] recently published the findings of improved survival with the JPLT-1 protocol with results similar to this study. They concluded that the combination of cisplatin-adriamycin could improve survival by increasing the resectability of the tumor or by improving the cure rate in cases with incomplete tumor resection. In this study, most of the patients in group III benefitted from neoadjuvant chemotherapy with a similar regimen and could achieve complete tumor resection, thus showing the usefulness of the regimen as a preoperative treatment. However, as there were no cases with an incomplete resection in this study, the benefit of this regimen on residual tumor could not be evaluated.

The survival of patients with hepatoblastoma is usually correlated with the PRETEXT classification; group I being the best and group IV the worst [9,10]. By contrast, our results showed the worst survival in group II and the best survival in groups I and IV. We speculate that this is probably due to low patient number. Moreover, the causes of death in the group II patients might have been prevented by different medical management; although the post-chemotherapy myelodysplastic syndrome was difficult to predict and fatal if affected, CMV hepatitis could have been treated preoperatively by careful patient evaluation and the patient death would have been prevented. Therefore, the survival of group II patients might have been similar or even better than group III with different medical intervention. Most recently published paper showed the improved survival in PRETEXT IV patients with dose-intensive chemotherapy and surgery [7], and similar results were obtained with total hepatectomy and liver transplantation [11]. In our study, only one case in group IV was successfully treated with a liver transplantation and the chemotherapeutic regimen was different. Therefore, the comparison of the survival would seem inappropriate, but we expect long-term disease-free survival in this patient.

Transplantation after tumor recurrence, the so called "rescue transplantation", has a much worse survival rate compared to primary transplantation [11,12]. Some investigators have suggested that recurrence of a tumor after a primary resection is a relative contraindication to transplantation [13]. Although this series had only two cases of transplantation (one primary and one rescue) for hepatoblastoma, our experience is consistent with previously reported results. Most of the causes of death after rescue transplantation have been related to the recurrence of disease within the first year after the transplantation. The patient who underwent rescue transplantation in this study, however, died of primary nonfunction after rescue transplantation. This might be explained in part by the anastomosis between the portal vein of the liver graft and the recipient renal vein, which showed insufficient blood flow; the patient had portal vein thrombosis.

Adjuvant chemotherapy after primary transplantation has been the subject of debate. Many investigators have recommended posttransplantation chemotherapy whenever possible for reducing the frequency of tumor recurrence and improving the rate of survival [14]. However, the risk of chemotherapy must be balanced between the

posttransplantion complication and the risk of immunosuppression. Although only one patient was cured by transplantation without adjuvant chemotherapy, considering the risk of disease relapse in the transplanted liver, posttransplantation chemotherapy should be considered for prevention in similar cases.

FAP is a well-known autosomal dominant cancer predisposition syndrome caused by germline mutations in the tumor suppression gene *APC*. Since first described in 1982, the association of FAP with hepatoblastoma has steadily been reported and the estimated risk of hepatoblastoma is 750 to 7500 times higher in children predisposed to FAP than in the general population [15]. Conversely, however, the frequency of FAP in cases of hepatoblastoma without a family history of FAP is unknown. Phillips et al. [16] reported only one case of FAP in 20 (5%) patients with hepatoblastoma and Aretz et al.[15] found *APC* germline mutations in five patients after screening of 50 patients (10%) with apparently sporadic hepatoblastoma. Some investigators have suggested routine germline mutation screening of the *APC* gene in every child with hepatoblastoma [17]. Although we have not routinely performed *APC* mutation testing in patients with hepatoblastoma, it might be appropriate to perform *APC* mutation testing at the time of the diagnosis of a hepatoblastoma.

In summary, favorable survival outcome could be achieved with complete tumor excision and adjuvant chemotherapy. For initially unresectable tumor, neoadjuvant chemotherapy based on the combination of cisplatin-adriamycin was effective for tumor down-sizing and improving the resectability in group II and III patients. The *APC* mutation should be ruled out in all hepatoblastoma patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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