J Formos Med Assoc 2011;110(5):322–325

Contents lists available at ScienceDirect

Journal of the Formosan Medical Association

Journal homepage: http://www.jfma-online.com

Original Article

Treatment Outcomes for Hepatoblastoma: Experience of 35 Cases at a Single Institution

*Pei-Kwei Tsay,[1] Jin-Yao Lai,[2] Chao-Ping Yang,[3] Iou-Jih Hung,[3] Chuen Hsueh,[4] Ming-Horng Tsai,[3] Tang-Her Jaing[3]**

Background/Purpose: Hepatoblastoma is the most common malignant liver tumor in children. Comparative studies have elucidated the optimal pre- or postoperative chemotherapeutic regimens. The aim of this study was to investigate the prognostic significance of baseline tumor characteristics for overall survival and disease-free survival in children with hepatoblastoma.

Methods: There were 19 male and 16 female children with a median age of 19 months at diagnosis (range: 1–169 months) in our institution between February 1990 and June 2009. We reviewed the clinical presentation, serum α-fetoprotein level at diagnosis, histological subtype, treatment, and outcomes.

Results: Twenty-seven patients (78%) underwent neoadjuvant chemotherapy. The majority of patients subsequently underwent either hemihepatectomy (56%) or bisegmentectomy (16%). Only six patients underwent extended hepatic resection, and one of them required rescue liver transplantation. During follow-up, six patients died of progressive disease and two of perioperative mortality. Four of the six who died had pulmonary metastases at the time of diagnosis or follow-up. The median survival time was 28 months (range: 1–181 months). Five-year overall survival was 67.7% (95% confidence interval: 52.0–87.8%) and disease-free survival was 60.2% (95% confidence interval: 41.9–86.5%).

Conclusion: The potential down-staging effect of neoadjuvant chemotherapy on hepatoblastoma might facilitate remission and convert unresectable tumors into operable ones.

Key Words: hepatoblastoma, liver surgery, neoadjuvant chemotherapy, survival

Hepatoblastoma accounts for 79% of all liver tumors in children and almost two-thirds of primary malignant liver tumors in the pediatric age group. Surgical resection is the cornerstone of treatment for patients with hepatoblastoma.[1] Chemotherapy is used to reduce tumor size in lesions that appear unresectable at diagnosis and to control residual microscopic disease after definitive resection.[2] More recently, data from the International Childhood Liver Tumour Strategy Group (SIOPEL), which uses neoadjuvant chemotherapy, have demonstrated overall survival rates

[1]Department of Public Health and Center of Biostatistics, College of Medicine, Chang Gung University, [2]Department of Pediatric Surgery, [3]Division of Hematology and Oncology, Department of Pediatrics, and [4]Department of Pathology, Chang Gung Children's Hospital, Chang Gung University, Linkou, Taoyuan, Taiwan.

Received: April 7, 2010
Revised: May 29, 2010
Accepted: May 31, 2010

***Correspondence to:** Dr Tang-Her Jaing, Division of Hematology and Oncology, Department of Pediatrics, Chang Gung Children's Hospital, 5 Fu-Shin Street, Kwei-Shan 333, Taoyuan, Taiwan.
E-mail: jaing001@cgmh.org.tw

as high as 89% and event-free survival rates as high as 80%.[3] The objective of this study was to assess the assumed surgical advantages of neoadjuvant chemotherapy.

Subjects and Methods

Our objective was to review the experience of a leading tertiary referral center in treating hepatoblastoma in children over the past 19 years. We studied a cohort of 35 children with hepatoblastoma managed in our institution between February 1990 and June 2009. There were 19 male and 16 female children with a median age of 19 months at diagnosis (range: 1–169 months). The diagnosis was confirmed histologically in 32 of the 35 patients. The remaining three patients with age of onset between 13 and 30 months were diagnosed with hepatoblastoma based on serum α-fetoprotein (AFP) levels without histopathological confirmation, and obvious tumor regression after chemotherapy confirmed the diagnosis. One patient with a history of extremely low birth weight developed hepatoblastoma at the age of 2 years.

Recurrence was identified from unequivocal imaging and serially increasing AFP levels or biopsy confirmation. Kaplan–Meier survival analysis was conducted to determine actuarial survival. Ninety-five percent confidence intervals (CIs) were calculated for the survival estimation. The study was duly approved by the Faculty Ethics Committee. Written informed consent was obtained from parents or the legal guardian before each medical intervention.

Results

A palpable mass in the abdomen was the presenting symptom in 30 patients (85.7%). The median AFP level at diagnosis was 205,000 ng/mL (range: 467–2,420,000 ng/mL). Of those 35 patients, seven had documented pulmonary metastasis. Initial lung metastasis developed in four patients (11.4%). Chemotherapy regimens included the SIOPEL study protocols.

Thirty-one patients underwent surgical resection. Four patients underwent primary surgery, and 27 patients underwent delayed surgery after super-PLADO chemotherapy. The regimen consisted of alternating cycles of 80 mg/m^2 cisplatin over 24 hours, 60 mg/m^2 doxorubicin over 48 hours, and 500 mg/m^2 carboplatin over 1 hour. Thirteen patients (40%) underwent right hepatectomy; five (16%) had left hepatectomy; eight (25%) had right extended hepatectomy; one (3%) had left extended hepatectomy; and five (16%) had bisegmentectomy. One patient subsequently required rescue liver transplantation for residual disease.

As shown in the Table, the post-chemotherapy histological types encountered as per the SIOPEL

Table. Summary of selected clinical data and histopathological characteristics of patients with hepatoblastoma

Characteristics	Value
Sex	
Male	19
Female	16
Age (mo)	
Median	19
Range	1–169
Serum α-fetoprotein (ng/L)	467–2,420,000
Pulmonary metastasis	
At diagnosis	4
Follow-up after diagnosis	2
Surgery	
Primary surgery	4
Delayed surgery (post-PLADO)*	27
Histotype	
Epithelial	14
Pure fetal	1
Embryonal/fetal	12
Macrotrabecular	1
Epithelial/mesenchymal	18
Not teratoid	16
Teratoid	2

**Alternating cycles of 80 mg/m^2 cisplatin over 24 hours, 60 mg/m^2 doxorubicin over 48 hours, and 500 mg/m^2 carboplatin over 1 hour.*

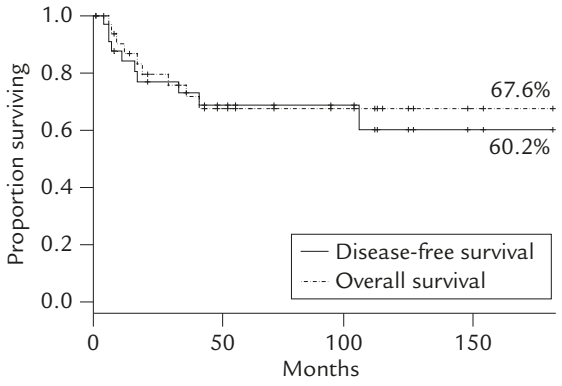

Figure. Overall and disease-free survival by Kaplan–Meier estimates.

Liver Study Group[4] were as follows: purely fetal type – 1; embryonal and mixed embryonal/fetal subtype – 12; macrotrabecular subtype – 1; mixed epithelial and mesenchymal type without teratoid features – 16; and mixed epithelial and mesenchymal type with teratoid features – 2. Two patients died during the perioperative period. Six patients died of progressive disease, and four of them had pulmonary metastases at the time of diagnosis or follow-up. The presence of pulmonary metastases might be a predictor of poor prognosis.

Although there were three recurrences, two patients had distant metastasis to the lung and one was local. The median survival time was 36 months (range: 1–181 months), and 5-year overall survival and disease-free survival rates were 67.7% (95% CI: 52.0–87.8%) and 60.2% (95% CI: 41.9–86.5%), respectively (Figure).

Discussion

Considerable controversy has surrounded the discrepancy between United States and international hepatoblastoma therapeutic protocols; surgery and staging are initially advised in the United States, whereas adjuvant therapy is strongly considered internationally.[5] Therefore, neoadjuvant chemotherapy followed by resection has become the mainstay in the treatment of hepatoblastoma.[6–8] With very effective preoperative chemotherapy for hepatoblastoma, many tumors can be shrunk to permit partial hepatectomy.[9] Total hepatectomy and liver transplantation has emerged as an effective treatment for the small proportion of children with unresectable hepatoblastoma that is limited to the liver. A 5-year survival rate of 70% can be achieved in such cases.[10,11] However, for patients with unresectable hepatoblastoma, neoadjuvant chemotherapy is the only means to convert them into resectable tumors, through down-staging of the tumors.

In our study, perioperative mortality in the early surgical era and the development of pulmonary metastasis had an ominous impact on survival outcome compared to other study groups.[12,13] However, with the advent of efficacious chemotherapy, survival has improved as compared to an early study in Taiwan.[14] It is noteworthy that patients in our group had satisfactory results at early follow-up. Complete tumor resection is a prerequisite for cure, therefore, any strategy that leads to an increased resection rate will result in improved survival.[15] Reoperation for positive resection margins does not necessarily have to be performed, because postoperative chemotherapy shows good results.[1]

Surgical removal of hepatoblastoma is never easy, and resection-related deaths still occur even with experienced surgeons.[16] The introduction of chemotherapy to the neoadjuvant setting has helped to improve surgical resection rates.[17–20] Our data also support an important role for preoperative neoadjuvant chemotherapy if the tumor is inoperable, or if the tumor is unlikely to undergo gross total resection at initial diagnosis.

References

1. Schnater JM, Aronson DC, Plaschkes J, et al. Surgical view of the treatment of patients with hepatoblastoma: results from the first prospective trial of the International Society of Pediatric Oncology Liver Tumor Study Group. *Cancer* 2002;94:1111–20.
2. Shukla PJ, Barreto SG, Qureshi SS, et al. Hepatoblastoma: a single institutional experience of 18 cases. *Pediatr Surg Int* 2008;24:799–802.
3. Aronson DC, Schnater JM, Staalman CR, et al. Predictive value of the pretreatment extent of disease system in

hepatoblastoma: results from the International Society of Pediatric Oncology Liver Tumor Study Group SIOPEL-1 study. *J Clin Oncol* 2005;23:1245–52.
4. Zimmermann A. The emerging family of hepatoblastoma tumours: from ontogenesis to oncogenesis. *Eur J Cancer* 2005;41:1503–14.
5. Brown J, Perilongo G, Shafford E, et al. Pretreatment prognostic factors for children with hepatoblastoma—results from the International Society of Paediatric Oncology (SIOP) study SIOPEL 1. *Eur J Cancer* 2000;36:1418–25.
6. Schnater JM, Köhler SE, Lamers WH, et al. Where do we stand with hepatoblastoma? A review. *Cancer* 2003;98: 668–78.
7. Bajpai M, Pal K, Agarwala S, et al. Midterm results with hepatectomy after preoperative chemotherapy in hepatoblastoma. *Pediatr Surg Int* 2005;21:364–8.
8. Wang LL, Filippi RZ, Zurakowski D, et al. Effects of neoadjuvant chemotherapy on hepatoblastoma: a morphologic and immunohistochemical study. *Am J Surg Pathol* 2010; 34:287–99.
9. Finegold MJ, Egler RA, Goss JA, et al. Liver tumors: pediatric population. *Liver Transpl* 2008;14:1545–56.
10. Stringer MD. The role of liver transplantation in the management of paediatric liver tumours. *Ann R Coll Surg Engl* 2007;89:12–21.
11. Tiao GM, Bobey N, Allen S, et al. The current management of hepatoblastoma: a combination of chemotherapy, conventional resection, and liver transplantation. *J Pediatr* 2005;146:204–11.
12. Hou JY, Liu HC, Yeh TC, et al. Long-term treatment results of hepatoblastoma at a single institution in Taiwan. *J Pediatr Hematol Oncol* 2009;31:718–22.
13. Meyers RL, Rowland JR, Krailo M, et al. Predictive power of pretreatment prognostic factors in children with hepatoblastoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer* 2009;53:1016–22.
14. Chiu SN, Ni YH, Lu MY, et al. A trend of improved survival of childhood hepatoblastoma treated with cisplatin and doxorubicin in Taiwanese children. *Pediatr Surg Int* 2003; 19:593–7.
15. Rana AN, Qidwai A, Pritchard J, Ashraf MS. Successful treatment of multifocal unresectable hepatoblastoma with chemotherapy only. *Pediatr Hematol Oncol* 2006;23: 153–8.
16. Ang JP, Heath JA, Donath S, et al. Treatment outcomes for hepatoblastoma: an institution's experience over two decades. *Pediatr Surg Int* 2007;23:103–9.
17. Kusano T, Aoki H, Kinjo T, et al. Successful resection for advanced hepatoblastoma, combined with perioperative chemotherapy. *J Hepatobiliary Pancreat Surg* 2000;7: 410–6.
18. Suita S, Tajiri T, Takamatsu H, et al. Improved survival outcome for hepatoblastoma based on an optimal chemotherapeutic regimen—a report from the study group for pediatric solid malignant tumors in the Kyushu area. *J Pediatr Surg* 2004;39:195–8.
19. Towu E, Kiely E, Pierro A, Spitz L. Outcome and complications after resection of hepatoblastoma. *J Pediatr Surg* 2004;39:199–202.
20. Davies JQ, de la Hall PM, Kaschula RO, et al. Hepatoblastoma—evolution of management and outcome and significance of histology of the resected tumor. A 31-year experience with 40 cases. *J Pediatr Surg* 2004;39: 1321–7.