Comparison of childhood hepatic malignancies in a hepatitis B hyper-endemic area

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INTRODUCTION

Hepatocellular carcinomas (HCC) and hepatoblastomas (HB) are the most common primary hepatic malignancies in children. The two malignancies usually receive identical management. In the literature dealing with the two tumors, the main emphasis has often been on facilitating surgical management by more effective chemotherapy[1,2]. However, the two malignancies have lots of basic differences. Physicians should take these differences into consideration during the diagnostic work-up, before therapy is instituted. Because the tumors are rare, comparisons of their clinical behaviors have rarely been made in any detail. This study enrolled children with HCC or HB at Chang Gung Children's Hospital (CGCH) and National Taiwan University Hospital (NTUH), two major medical centers in northern Taiwan. Its purpose was to examine the differences of the clinical behaviors of these two malignancies.

MATERIALS AND METHODS

We collected the cases of children with HCC or HB at CGCH and NTUH from 1979 to 1997. A total of 127 children were eligible for inclusion in this study. Their diagnosis was confirmed by tissue obtained from laparotomy or needle biopsy. There were 73 cases of HCC and 54 cases of HB. Demographic data included gender and age at diagnosis. Laboratory investigations included alpha-fetoprotein (AFP), hepatitis B surface antigen (HBsAg), and Child's grading. Anti-hepatitis C antibody was checked after 1990 only in patients with HB.

RESULTS

HCC clinically differed from HB in mean age (10.6 vs 2.5 years; P < 0.001), status of hepatitis B infection (56/56 vs 4/435; P < 0.001) and accompanying liver cirrhosis (26/40 vs 0/30; P < 0.001), portal vein thrombi (22/56 vs 5/38; P = 0.006) and para-aortic lymphadenopathy (10/56 vs 1/38; P = 0.026). Due to a higher recurrence rate (7/12 vs 2/13; P = 0.041), stage I HCC compared poorly in survivals with stage I HB (P = 0.0183). Chemotherapy could only benefit HB as evidenced by 66.7% of resectability conversion and improve survivals for advanced HB, even with unsuccessful conversion. The survival difference between stage I HB and advanced HB with delayed complete resection was of borderline insignificance (P = 0.0507).

CONCLUSION

HCC and HB were preliminarily distinguishable by some clinical clues. Delayed resection after chemotherapy was only possible for HB. However, further studies are needed to strengthen our observation that appropriate reliance upon chemotherapy to subsequently resect advanced HB could achieve the comparable survival to that of stage I HB.

Key words: Chemotherapy; Children; Hepatitis B; Hepatoblastoma; Hepatocellular carcinoma
portal vein (PV) or inferior vena cava (IVC) thrombi, para-aortic lymphadenopathy, and hilar involvement. Those made tumors inadvisable to attempt from primary tumor extirpation. Chemotherapy would be administered only in the case of consent from the family. Its regimens were the combination of vincristine, cyclophosphamide, doxorubicin and 5-fluouracil before 1991 [4]. Cisplatin (or carboplatin) and doxorubicin (or epirubicin) were substituted for the former regimens after 1991 [1,2]. The resected specimens indicating the surgical surface and the location of sections were taken for microscopic examination to identify the presence or absence of tumor at the section margins. Cirrhosis was examined in all cases if possible. The histologic subtype of HB was also investigated. The two liver malignancies were staged according to intergroup staging system raised by Children’s Cancer Group (CCG) and the Pediatric Oncology Group (POG) [5], mainly based upon the initial operative findings and procedure, and the final pathologic examination. Stage I: Completely resected at initial surgery. Stage II: Resection with microscopic residual disease at margin. Stage III: Unresectable, tumor spillage or resection with gross residual disease but not metastatic. Stage IV: Metastatic disease, regardless of the status of primary tumor.

Chi-square test was used to compare the proportions. When the sample size in a 2x2 table was 20 or less, Fisher’s exact test was calculated. Student’s t test was used to compare the means. As for survival analysis, the survival time was defined by estimating the length of time from the date of initial diagnosis to the event of interest or the date of last follow-up. A patient who died was considered to have experienced an event. Otherwise, the patient was considered censored at last follow-up. Plots of survival time were constructed by Kaplan-Meier method. The log rank test was employed to compare survival curves. Differences were regarded as significant if \( P < 0.05 \).

**RESULTS**

The demographic characteristics and clinical features in this group of patients are summarized in Figure 1 and Table 2. The mean age (10.6 years) of HCC patients was significantly older than that (2.5 years) of HB patients (\( P < 0.001 \)). Both tumors were male predominant with a male to female ratio of 3.3:1 in HCC and 2.4:1 in HB, but the difference between them was not statistically significant (\( P = 0.420 \)).

The AFP level was elevated in 54 of 55 HCC patients

| Points scored for clinical and laboratory parameters in Pugh modification of Child’s classification of liver disease severity |
|-------------------------------------------------------------|
| Clinical and laboratory parameters                         | Points scored |
|-------------------------------------------------------------|
| Hepatic encephalopathy                                      | 1             |
| Ascites                                                     | 2             |
| Bilirubin (mg/dL)                                            | 3             |
| Albumin (g/dL)                                              |               |
| Prothrombin time prolongation (s)                           |               |
| Grade 0: normal consciousness, personality, neurological examination | 1             |
| Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired hand writing | 2             |
| Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia | 3             |
| Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity | 4             |
| Grade 4: unrousable coma, no personality/behavior, decerebrate |               |

\( ^* \text{Grade 0: normal consciousness, personality, neurological examination; Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired hand writing; Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia; Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity; Grade 4: unrousable coma, no personality/behavior, decerebrate.} \)

Table 2 Summary of clinical characteristics, laboratory investigations, cirrhosis, primary resectability, chemotherapeutic conversion and tumor recurrence in children with hepatic malignancies

| Clinical parameter | Hepatocellular carcinoma | Hepatoblastoma | \( P \) |
|--------------------|--------------------------|----------------|-------|
| Mean age in yr (SD) | 10.6 (3.3)               | 2.5 (3.5)      | <0.001 |
| Median age in yr   | 11.3                     | 1.0            |       |
| Sex                |                          |                | 0.420 |
| Male               | 56                       | 38             |       |
| Female             | 17                       | 16             |       |
| Serum alpha fetoprotein (\( \leq 20 \) ng/mL) | 1 | 3 | 0.299 |
| Serum alpha fetoprotein (\( >20 \) ng/mL) | 54 | 34 |       |
| Hepatitis B carrier |                          |                | <0.001 |
| Yes                | 56                       | 4              |       |
| No                 | 0                        | 31             |       |
| Child’s classification |                        |                | 0.673 |
| A                  | 41                       | 29             |       |
| B                  | 14                       | 8              |       |
| Liver cirrhosis    |                          |                | <0.001 |
| Yes                | 26                       | 0              |       |
| No                 | 14                       | 30             |       |
| Primary complete resection |                    |                | 0.285 |
| Yes                | 12                       | 13             |       |
| No                 | 61                       | 41             |       |
| Tumor recurrence after resection |              |                | 0.041 |
| Yes                | 7                        | 2              |       |
| No                 | 5                        | 11             |       |
| Complete resection after chemotherapy |          |                | <0.001 |
| Yes                | 0                        | 12             |       |
| No                 | 14                       | 6              |       |

\( ^* \text{Fisher’s exact test and } ^* \text{Two samples, independent-groups } t \text{ test.} \)
and 34 of 37 HB patients ($P = 0.299$). Among them, 66.7% of those with HCC and 61.8% of those with HB had the AFP level of more than 35,000 ng/mL. HBsAg was tested in 56 HCC patients and 35 HB patients. There was a significantly higher rate of positivity for HBsAg in HCC patients (100% vs 11.4%; $P < 0.001$). Among 55 HCC patients and 37 HB patients whose tumors could be completely graded by modified Child's classification, 41 HCC patients and 29 HB patients were in Child's group A, 14 HCC patients and 8 HB patients in Child's group B, and no patients in Child's group C. Both tumors appeared to have a Child's A predominance in an A to B ratio of 2.9:1 for HCC and 3.6:1 for HB without a statistically significant difference ($P = 0.673$).

There were 19 HCC patients and 11 HB patients with lung metastasis at diagnosis. Additional brain metastasis was found in 1 HCC patient and additional skin metastasis in 1 HB patient. Radiological images of 94 patients (56 with HCC and 38 with HB) were available for review of tumor extent and invasiveness. A summary of these findings that were compared between HCC and HB is listed in Table 3. The variables to reach statistical significance were PV invasion (39.3% vs 13.2%; $P = 0.006$) and para-aortic lymphadenopathy (17.9% vs 2.6%; $P = 0.026$).

Cumulative survival curves for patients with liver malignancies in each intergroup stage are shown in Figure 2. Resection with a histologically clear margin (stage I) could be achieved in 12 HCC patients and 13 HB patients, contributing to primary resectability rates of 16.4% and 24.1%, respectively (Table 2, $P = 0.285$). Adjuvant chemotherapy was administered postoperatively to 2 HCC patients and 11 HB patients (both with chemotherapy). Therefore, HCC posed a higher recurrence rate than HB after curative resection (Table 2, $P = 0.041$). Repeated hepatectomy could only be performed in 2 HCC patients, one of whom remained alive at last follow-up exam (184 mo). Conclusively, stage I HB compared favorably in survival with stage I HCC with the 5-year survival rate of 32.4% for HCC and 82.5% for HB by the Kaplan-Meier survival curves ($P = 0.0183$). As for stage II tumor, there was none for HCC but 4 for HB. All the 4 HB patients died of recurrence, despite postoperative chemotherapy in one. Stage IV disease consisted of 19 HCC and 11 HB as evidenced by distant metastasis at diagnosis. Due to the heterogenous management for those advanced tumors (III and IV) ranging from no treatment, chemotherapy

**Table 3** Summary of tumor extent and invasiveness on imaging studies of children with hepatic malignancies

| Variable                                | Hepatocellular carcinoma (%) | Hepatoblastoma (%) | $P$   |
|-----------------------------------------|------------------------------|-------------------|-------|
| Bilobar involvement                     | 38/56 (67.9)                 | 20/38 (52.6)      | 0.136 |
| Portal vein invasion                    | 22/56 (39.3)                 | 5/38 (13.2)       | 0.006 |
| Inferior vena cava invasion             | 8/56 (14.3)                  | 3/38 (7.9)        | 0.516 |
| Para-aortic lymphadenopathy             | 10/56 (17.9)                 | 1/38 (2.6)        | 0.026 |
| Hepatic hilum involvement               | 3/56 (5.4)                   | 2/38 (5.3)        | 1.000 |
| Distant metastasis at diagnosis         | 19/73 (26.0)                 | 11/54 (20.4)      | 0.458 |

*Fisher's exact test.*

![Figure 1](image1.png) Age distribution of childhood hepatocellular carcinomas (HCC) and hepatoblastomas (HB).

![Figure 2](image2.png) Cumulative survival curves for patients with liver malignancies in each intergroup stage. A: HCC (I vs III, $P = 0.001$; III vs VI, $P = 0.0002$; log rank test); B: HB (I vs II, $P = 0.0019$; II vs III, $P = 0.8783$; III vs VI, $P = 0.5365$; log rank test).
alone, resection after chemotherapeutic conversion to resection with adjuvant chemotherapy, the comparison of survivals between HCC and HB within the same stage could not be free from bias. However, in view of the survivals of HCC or HB patients in different stages shown in Figure 2, differences among the stages of I, III and IV HCC could reach statistical significance (I vs III, 0.0011; III vs VI, 0.0002). As regards HB, this difference of survival curves was only seen between stages I and II (P = 0.0019) but not among stages II, III and VI (II vs III, P = 0.8783; III vs VI, P = 0.5365).

In consideration of advanced tumors (III & IV), 38 HCC and 15 HB were left untreated. There were 14 HCC and 18 HB receiving intensive chemotherapy with the successful conversion into delayed complete resection in 12 of 18 HB but none of 14 HCC (Table 2, P<0.001). It contributed to the overall HB resectability of 46.3%, which compared favorably with that of HCC (P<0.001). Statistically, the survival difference between 13 stage I HB and 12 advanced HB with delayed complete resection after chemotherapy was of borderline insignificance (P = 0.0507). The remaining patients whose tumors failed to be chemotherapeutically converted (14 HCC and 6 HB) eventually succumbed to disease progression. It was found that advanced HB with unsuccessful conversion by chemotherapy had the significantly better survival than HB untreated (Figure 3, P = 0.0015). However, this beneficial effect of chemotherapy could not favor advanced HCC (Figure 3, P = 0.0690). HCC either with chemotherapy only or untreated had the better survival experience than HB untreated (Figure 3, P = 0.0015 and 0.0040, respectively). However, the differences of survivals could not reach statistical significance when compared with HB with chemotherapy only (Figure 3, P = 0.8139 and 0.0718, respectively).

Among 40 HCC specimens and 30 HB specimens available for pathologic evaluation, liver cirrhosis was demonstrated in 65.0% of HCC but none of HB (Table 2, P<0.001). It made no difference of sex ratio between cirrhotic and non-cirrhotic HCC (P = 0.281). There were 15 children whose HCC resection stayed margin-free (including 5 ruptured HCC). Of them, 6 had cirrhotic HCC and all succumbed to intrahepatic recurrence. HCC recurrence after complete resection was statistically associated with the presence of cirrhosis (P = 0.007). The survival of non-cirrhotic resected HCC was significantly better than cirrhotic resected HCC (Figure not shown, P = 0.0209). Among 22 resectable HB whose histologic subtypes could be traced, there were 13 with mixed epithelial-mesenchymal component and 9 with epithelial component, including mixed fetal and embryonal types in 3, pure fetal type in 2, embryonal type in 2 and macrotubular type in 2. Given the small number of HB patients in whom the histologic subtypes were known, comparisons of survivals between different histologic subtypes could not be done.

**DISCUSSION**

As shown in this study, childhood HCC and HB could be generally differentiated by some clinical data such as age, the status of hepatitis B virus (HBV) and the findings of imaging studies. HCC was mostly found in school age children, whereas HB was mainly diagnosed in infancy and rarely occurred after 3 years of age. The age distribution of HCC was somewhat skewing to the left with the peak age at around 12 years (Figure 1). It was in sharp contrast to the figure reported from Exelby et al., in which there are two age peaks, one below 4 years and a second peak between 12 and 15 years[8]. However, the age distribution of HB showed great resemblance to that of Exelby's series[8], looking rather asymmetric and skewing to the right (Figure 1). Imaging studies disclosed that HCC was more inclined to invade the PV and para-aortic lymph nodes than HB. As for AFP, its level was often extremely high, but not a reliable test to differentiate HCC from HB. However, it was a good marker for monitoring recurrence if its preoperative level was high.

In this series, HBV infection was found in 100% of the HCC patients who had been examined for HBsAg. A positive HBsAg status has long since been a critical marker for children with HCC in Taiwan[7]. As a hyper-endemic area of HBV infection, Taiwan launched a nationwide hepatitis B vaccination program in 1984. After a 10-year universal immunization, evidence showed that this program has effectively reduced both the HBV carrier rate[9] and the incidence of HCC in children[9]. As for hepatitis C virus (HCV), it has also been etiologically linked with HCC development[10]. Since specific serologic tests for HCV became available in 1989[11], only 13 cases in this cohort study have been checked for HCV and all showed negative results. Based upon the limited data, it was hard to conclude a causal relationship between HCV and childhood hepatic malignancies. Despite a low seroprevalence of HCV infection in children, HCV can be transmitted to infants and children either perinatally or through blood transfusion[12]. However, the progression from chronic hepatitis to cirrhosis and sometimes to HCC is most commonly a slow and silent process. It may take about 30 and occasionally even more years to reach its end point[10,13]. Therefore, those infected by HCV in childhood may be at risk of developing HCC at their young adult age. This may explain why HCV-related HCC has never been reported in children in spite of overwhelming evidence indicating a strong correlation...
between HCV and HCC in adults.

In the Western countries, childhood HCC does not differ from the adult counterpart in terms of gross and microscopic features, except in the lack of an association with cirrhosis in most childhood HCC. We had found that liver cirrhosis occurred in 65% of HCC children, comparable to adult cases (70%) in Taiwan, while cirrhotic HB was never seen in this series. Undoubtedly, this strong association between childhood HCC and cirrhosis could be attributed to the preceding HBV infection. Cirrhosis represented as a pessimistic histologic feature with a worse outcome for resected HCC in adults and children, as evidenced by inevitable intrahepatic recurrence. Although HCC in both adults and children are frequently associated with liver cirrhosis, it is well recognized that adult patients more frequently decompensate or develop liver failure, if an overaggressive resection for cirrhotic HCC is attempted. Hence, it has been suggested that hepatectomy be performed in cirrhotic adult patients who have good-risk Child’s A grading. In considering the resection of childhood liver malignancies, liver function is rarely an unfavorable factor. Child’s A group accounted for over 70% in both types of tumors but Child’s C group was never observed in this series. Why liver function was better preserved in childhood liver malignancies was not well explained. However, it might have been due to a short duration of cirrhotic HCC and low incidence of cirrhotic HB in children.

Complete resection of liver malignancies is the only therapeutic modality that could offer patients long-term survival or even a cure. Primary resection could be achieved only in 16.4% of HCC and 24.1% of HB mainly because most liver malignancies presented with distant metastasis, PV thrombi, IVC thrombi, para-aortic lymphadenopathy, or hepatic hilar invasion at the time of diagnosis. Bilobar involvement was not always a hindrance to complete resection unless resection required compromise of critical vessels. Although HCC was more inclined to invade the PV and para-aortic lymph nodes in comparison with HB, this made no difference between the two tumors’ primary resectabilities. Tumor recurrence is the major cause of unsatisfactory results in adults with resectable HCC, occurring in around 50% of cases. A rather pessimistic background was observed in childhood HCC. Even with a successful resection, tumor recurrence in this series happened in over half of the HCC patients but only in 15% of the HB patients. Due to the higher intrahepatic recurrence of HCC, stage I HCC compared poorly in survival with stage I HB. Although repeated hepatectomy has been considered to remain the best treatment for tumor recurrence, it could only benefit two of 11 recurrent HCC in this series.

Our data were not sufficient to conclude the necessity of postoperative chemotherapy for stage I disease. However, HCC compared poorly with HB in response to chemotherapy. A better response of HB to chemotherapy might be attributed to the higher proliferation rate of HB. This could, on the other hand, reflect a more ominous natural course of disease as evidenced by the fact that if untreated, advanced HB apparently had a worse survival experience than advanced HCC. It was reported that delayed resection for childhood HCC after combined chemotherapy was the rare exceptions. We even never experienced any successful conversion of unresectable HCC by chemotherapy for these years despite the higher incidence of HCC in Taiwan. In contrast, we had 66.7% of successful rate to use chemotherapy as a detour leading to complete resection for initially unresectable HB. Even if chemotherapy failed to facilitate resection, it could substantially bring advanced HB to better survivals when compared with untreated HB.

The stage of tumors was reported as the most important criterion for determining the prognosis of HCC and HB in children. In this study, stage I HCC or HB still represented the best prognosis. However, the differences among the survival curves of stages II-IV HB became indistinguishable from one another due to delayed complete resection of advanced HB, which had become an attainable goal since the advent of chemotherapy. Another important issue in dealing with an advanced HB was whether the survival of those tumors with delayed complete resection could catch up with that of stage I HB. As we knew, diagnostic imaging studies are important in assessing the resectability of hepatic malignancies. Although better imaging techniques have improved the accuracy, they do not provide an absolutely reliable evaluation of resectability. The error rate may reach 20% with a combination of sonography and either CT or MRI. Whenever there is the indeterminable resectability of HB on imaging studies, pediatric surgeons will be in a dilemma as to whether they should show boundless enthusiasm for an aggressive surgical approach or rely upon preoperative chemotherapy to subsequently perform a delayed resection. We found that the survival difference between stage I HB and advanced HB resected after chemotherapy could only reach borderline insignificance with a P value of 0.0507. Although it was not solid enough in consideration of survival to support appropriate reliance upon chemotherapy in advance to deal with a potentially risky surgical problem for strategically located HB, this approach could render a delayed but safe hepatectomy with less blood loss, minimal operative complications and more substantial preservation of normal hepatic tissue. There was also evidence showing that if an attempted primary resection for HB ended up as incompleteness and was then boosted by postoperative chemotherapy, such a therapeutic modality did not necessarily achieve a more favorable outcome than initial chemotherapy with delayed resection. Thus, the therapeutic philosophy of “stage creep” from the enrollment of more stage III HB and then preoperative reliance upon chemotherapeutic cytoreduction can be justified in some aspects, but requires further investigations for its impact on survival. As for strategically located HCC, pediatric surgeons should show the enthusiasm for aggressive surgical intervention in view of their unresponsiveness to chemotherapy because primary resection of HCC is undoubtedly the only chance for a cure or long-term survival. Although liver transplantation can be an alternative for advanced HCC, it was rarely pursued in Taiwan due to unfavorable factors including large tumor size, near absolute HBV carrier status, nonfibrolamellar histology, and a high frequency of local and metastatic spread.

REFERENCES

1. King DR, Ortega J, Campbell J, Haas JE, Ablin AR, Lloyd D, Newman K, Quinn J, Krailo M, Feusner J, Hammond D. The
surgical management of children with incompletely resected hepatic cancer is facilitated by intensive chemotherapy. J Pediatr Surg 1991; 26: 1074-1081

2 Ortega JA, Kralio MD, Haas JE, King DR, Ablin AR, Quinn JJ, Feusner J, Campbell JR, Lloyd DA, Cherlow J. Effective treatment of unresectable or metastatic hepatoblastoma with cisplatin and continuous infusion doxorubicin chemotherapy: a report from the Children’s Cancer Group Study. J Clin Oncol 1991; 9: 2167-2176

3 Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-649

4 Evans AE, Land VJ, Newton WA, Randolph JG, Sather HN, Tefft M. Combination chemotherapy (vincristine, adriamycin, cyclophosphamide, and 5-fluorouracil) in the treatment of children with malignant hepatoma. Cancer 1982; 50: 821-826

5 Children’s Cancer Group-8881. Intergroup protocol for the treatment of childhood hepatoblastoma and hepatocellular carcinoma, Arcadia, Calif, 1989, Children’s Cancer Group

6 Exelby PR, Filler RM, Grosfeld JL. Liver tumors in children in the particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatrics Surgical Section Survey-1974. J Pediatr Surg 1975; 10: 329-337

7 Chen WJ, Lee JC, Hung WT. Primary malignant tumor of liver in infants and children in Taiwan. J Pediatr Surg 1988; 23: 457-461

8 Chen HL, Chang MH, Ni YH, Hsu HY, Lee PI, Lee CY, Chen DS. Seroepidemiology of hepatitis B virus infection in children: ten years of mass vaccination in Taiwan. JAMA 1996; 276: 906-908

9 Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, Liang DC, Shau WY, Chen DS. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. N Engl J Med 1997; 336: 1855-1859

10 Kiyosawa K, Sodeyama T, Tanaka E, Gibo Y, Yoshizawa K, Nakano Y, Furuta S, Akahane Y, Nishioka K, Purcell RH. Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: analysis by detection of antibody to hepatitis C virus. Hepatology 1990; 12: 671-675

11 Kuo G, Choo QL, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, Miyamura T, Dienstag JL, Alter MJ, Stevens CE. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. Science 1989; 244: 362-364

12 American Academy of Pediatrics. Committee on Infectious Diseases: Hepatitis C virus infection. Pediatrics 1998; 101: 481-485

13 Tong MJ, El-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 1995; 332: 1463-1466

14 Weinberg AG, Finegold MJ. Primary hepatic tumors of childhood. Hum Pathol 1983; 14: 512-537

15 Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus: a prospective study of 22,707 men in Taiwan. Lancet 1981; 2: 1129-1133

16 Hsu HC, Wu TT, Wu MZ, Sheu JC, Lee CS, Chen DS. Tumor invasiveness and prognosis in resected hepatocellular carcinoma: clinical and pathogenetic implications. Cancer 1988; 61: 2095-2099

17 Chen JC, Chen CC, Chen WJ, Lai HS, Hung WT, Lee PH. Hepatocellular carcinoma in children: clinical review and comparison with adult cases. J Pediatr Surg 1998; 33: 1350-1354

18 Kubota K, Makukuchi M, Kusaka K, Kobayashi T, Miki K, Hasegawa K, Harihara Y, Takayama T. Measurement of liver volume and hepatic function reserve as a guide to decision-making in resectional surgery for hepatic tumors. Hepatology 1997; 26: 1176-1181

19 Randolph JG, Altman RP, Arensman RM, Matlak ME, Leikin SL. Liver resection in children with hepatic neoplasms. Ann Surg 1978; 187: 599-605

20 Pazdur R, Bready B, Cangir A. Pediatric hepatic tumors: clinical trials conducted in the United States. J Surg Oncol Suppl 1993; 3: 127-130

21 Lee PH, Lin WJ, Tsang YM, Hu RH, Sheu JC, Lai MY, Hsu HC, May W, Lee CS. Clinical management of recurrent hepatocellular carcinoma. Ann Surg 1995; 222: 670-676

22 Sakairi T, Kobayashi K, Goto K, Okada M, Kusakabe M, Tsuchiya T, Sugimoto J, Sano F, Mutai M. Greater expression of transforming growth factor alpha and proliferating cell nuclear antigen staining in mouse hepatoblastomas and hepatocellular carcinomas induced by a diethylnitrosamine-sodium phenobarbital regimen. Toxicol Pathol 2001; 29: 479-482

23 Stocker JT. An approach to handling pediatric liver tumors. Am J Clin Pathol 1998; 109(Suppl 1): S67-72

24 von Schweinitz D, Burger D, Moldenberger H. Is laparotomy the first step in treatment of childhood liver tumors? The experience from the German Cooperative Pediatric Liver Tumor Study HB-89. Eur J Pediatr Surg 1994; 4: 82-86

25 Seo T, Ando H, Watanabe Y, Harada T, Ito F, Kaneko K, Horibe K, Sugito T, Ito T. Treatment of hepatoblastoma: less extensive hepatectomy after effective preoperative chemotherapy with cisplatin and adriamycin. Surgery 1998; 123: 407-414

26 von Schweinitz D, Hecker H, Harms D, Bode U, Weinel P, Burger D, Erttmann R, Moldenberger H. Complete resection before development of drug resistance is essential for survival from advanced hepatoblastoma—a report from the Germany Cooperative Pediatric Liver Tumor Study HB-89. J Pediatr Surg 1995; 30: 845-852

27 Tagge EP, Tagge DU, Reyes J, Tzakis A, Iwatsuki S, Starzl TE, Wiener ES. Resection, including transplantation, for hepatoblastoma and hepatocellular carcinoma: impact on survival. J Pediatr Surg 1992; 27: 292-297