The THAI Journal of SURGERY 2002; 23:53-60.
*Official Publication of the Royal College of Surgeons of Thailand*

# *Primary Malignant Hepatic Tumors in Children: Fourteen-year Experience with 50 Cases*

**Maitree Anuntkosol, MD**
**Sukawat Watanatittan, MD, FACS**
**Rangsan Niramis, MD**
**Tongkao Rattanasuwan, MD**
*Department of Surgery, Queen Sirikit National Institute of Child Health*
*Bangkok, Thailand.*

*Abstract*

*Background :* **Primary liver tumors in children are uncommon but prevalently are malignant. This study was intended to review the experience in treating children with malignant liver tumors at the Children's Hospital.**

*Materials and Methods :* **A retrospective study of 50 children with primary malignant liver tumors admitted to the Children's Hospital, Queen Sirikit National Institute of Child Health, Bangkok, during a 14-year period (1987-2000) was made.**

*Results :* **There were 6 types of tumors, of which hepatoblastoma (HBL) was the most common (78 %). All but two patients with HBL were below 2 years of age at time of diagnosis. Resection was feasible in only one third of the cases (13/39), with 5 survivors. Chemotherapy in unresectable HBL showed no beneficial effect. Hepatocellular carcinoma (HCC) was seen in 14 percent of the patients, the last one in 1994. Nationwide hepatitis B immunization, launched in 1992, seemingly may have impact on the decline of HCC.**

*Conclusion :* **The results from this review which covered a long span of time, may represent the actual picture and its trend of malignant liver tumors in Thai children.**

Primary liver tumors account for approximately 7 per cent of abdominal masses in children.[1] Though they are uncommon but unfortunately are malignant in over two-thirds of cases.[2,3] The rarity of these tumors restricts a single center in gaining enough experience. This review outlines the pathology, clinical picture, management, and results of treatment of patients with primary malignant liver tumors at the Children's Hospital, Bangkok, during the last 14 years.

## Materials and Methods

The medical records of all children with liver tumors admitted to the Department of Surgery, Children's Hospital, Bangkok, during a 14-year period (January 1987 to December 2000) were reviewed. The final diagnoses were based on the histopathology of the tissue specimens obtained either from biopsy or from resection of the tumors. Metastases to the liver

from other primary malignancies were excluded. Particular attention was directed at hepatoblastoma (HBL) and hepatocellular carcinoma (HCC) since they were the two most common malignant liver tumors in children.

## Results

From 1987 through 2000, sixty four children with primary liver tumors were treated. Of these, 14 were benign (22 %), and 50 were malignant (78 %). Details of the histopathology are shown in Table 1. Only the 50 malignant cases were considered in this review.

### *Hepatoblastoma*

Of the 39 patients with HBL, 21 were males, and 18 were females, hence male to female ratio was 1.16: 1.

**Table 1** Analysis of 64 cases of liver tumors in children - Children's Hospital, Bangkok

| | | |
|---|---|---|
| **Benign tumors** | **14** | **(22%)** |
| Hemangioendothelioma | 10 | |
| Mesenchymal hamartoma | 2 | |
| Mature teratoma | 1 | |
| Cyst | 1 | |
| **Malignant tumors** | **50** | **(78%)** |
| Hepatoblastoma | 39 | |
| Hepatocellular carcinoma | 7 | |
| Angiosarcoma | 1 | |
| Undifferentiated sarcoma | 1 | |
| Rhabdomyosarcoma | 1 | |
| Endodermal sinus tumor | 1 | |

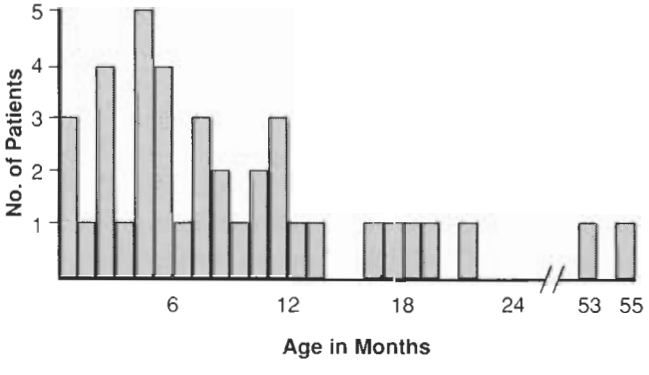


**Fig. 1** Age distribution of 39 patients with hepatoblastoma.

Most of the patients were younger than 2 years of age at the time of diagnosis (37/39, 95 %) (Figure 1).

Abdominal mass was the most common presenting symptom, accounting for nearly 85 per cent, while jaundice and abdominal pain were much less frequent (Table 2).

Regarding the preoperative laboratory findings (Table 3), CBC was abnormal in nearly half of the patients. The abnormality was anemia. Of the 26 specimens of bone marrow aspiration studied, all but one were normal. The only one with abnormal finding showed hypocellularity in the specimen. Bilirubin and SGOT/SGPT were elevated in 4 and 3 patients respectively. Coagulogram was prolonged in 2 out of 9 patients.

**Table 2** Presenting symptoms in 39 patients with hepatoblastoma

| Symptom | No. of Patients (%) |
|---|---|
| Abdominal mass | 33 (84.6) |
| Abdominal enlargement | 1 (2.5) |
| Jaundice | 2 (5) |
| Abdominal pain | 2 (5) |
| Anorexia | 1 (2.5) |

**Table 3** Laboratory findings in 39 patients with hepatoblastoma

| | Normal | Abnormal | Not Done |
|---|---|---|---|
| CBC | 21 | 18 | - |
| Bone marrow | 25 | 1 | 13 |
| Bilirubin | 34 | 4 | 1 |
| SGOT/SGPT | 35 | 3 | 1 |
| Coagulogram | 7 | 2 | 30 |

**Table 4** Alpha-fetoprotein levels in 39 patients with hepatoblastoma

| Level (ng/ml) | No. of Patients |
|---|---|
| > 30,000 | 11 |
| 20,000 - 30,000 | 7 |
| 10,000 - 20,000 | 2 |
| < 100 | 11 |
| Negative | 1 |
| Not recorded | 6 |
| Not done | 1 |

The alpha-fetoprotein (AFP) levels were over 10,000 ng/ml in 20 patients. All these were of high levels with respect to the normal range of AFP for each age in infancy.[1] The details are shown in Table 4.

Concerning preoperative radiographic studies, 2 patients had nodules on chest X-rays, presumed to be lung metastasis (Figure 2). Three out of 28 children had lytic lesions detected upon bone surveys. Plain abdominal films showed calcification of the liver masses in 6 cases (15%) (Figure 3) . Abdominal ultrasonogram (US) and computerized tomogram (CT) were done in 37 and 26 patients respectively. All clearly delineated the liver tumors (Figure 4).

Upon operation, the tumor was found to be confined to the right lobe in 11 (28 %), to the left lobe in 5 (13 %), and found occupying both lobes in 23 cases (59 %). Resection of the tumor was feasible in only 13 patients, while in the majority two-thirds (26 patients) only biopsy of the tumor was done. Preoperative rupture of the tumor was noted in 2 patients.

Surgical complications occurred in 10 patients. The worst one was massive hemorrhage from inferior vena cava injury during hepatectomy of the right lobe in 3 cases, resulting in shock and postoperative deaths. Other complications were adhesive intestinal obstruction, small bowel intussusception, enterocutaneous fistula, wound evisceration of the tumor, and hepatic failure (Table 5).

Only one patient was given radiation to the liver in combination with chemotherapy who later succumbed to sepsis.

Regarding chemotherapy, vincristine (VCR), cyclophosphamide, and 5-fluorouracil (5-FU) were the combined mainstay during 1987-1997. Cisplatin and doxorubicin were given to one patient in 1998.

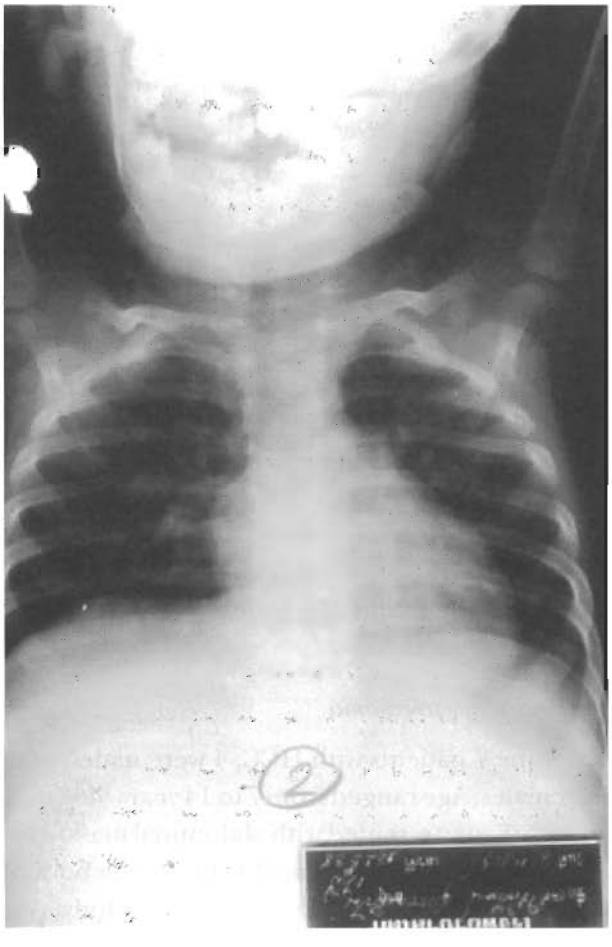

**Fig. 2** Chest film shows a nodule in the right lung in a patient with hepatoblastoma.

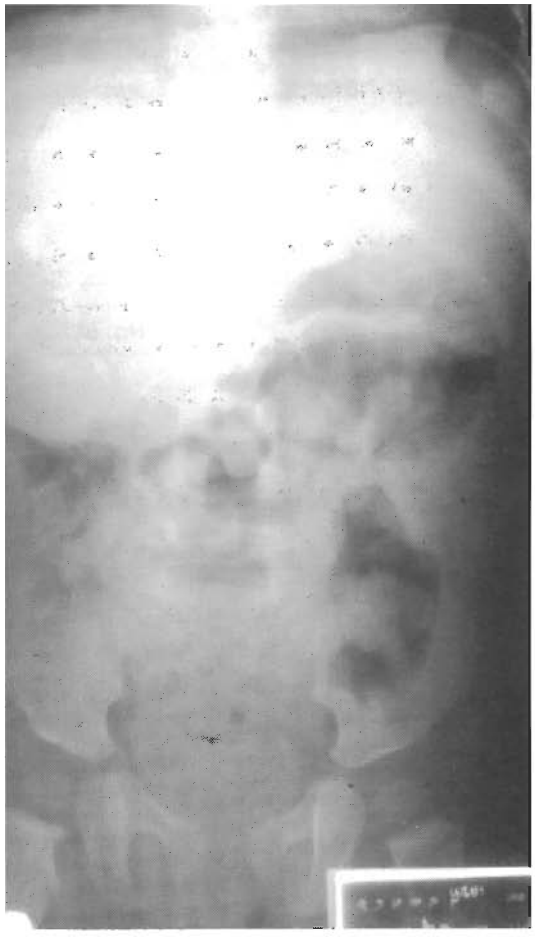

**Fig. 3** Abdominal film shows calcification of the liver mass in a patient with hepatoblastoma.

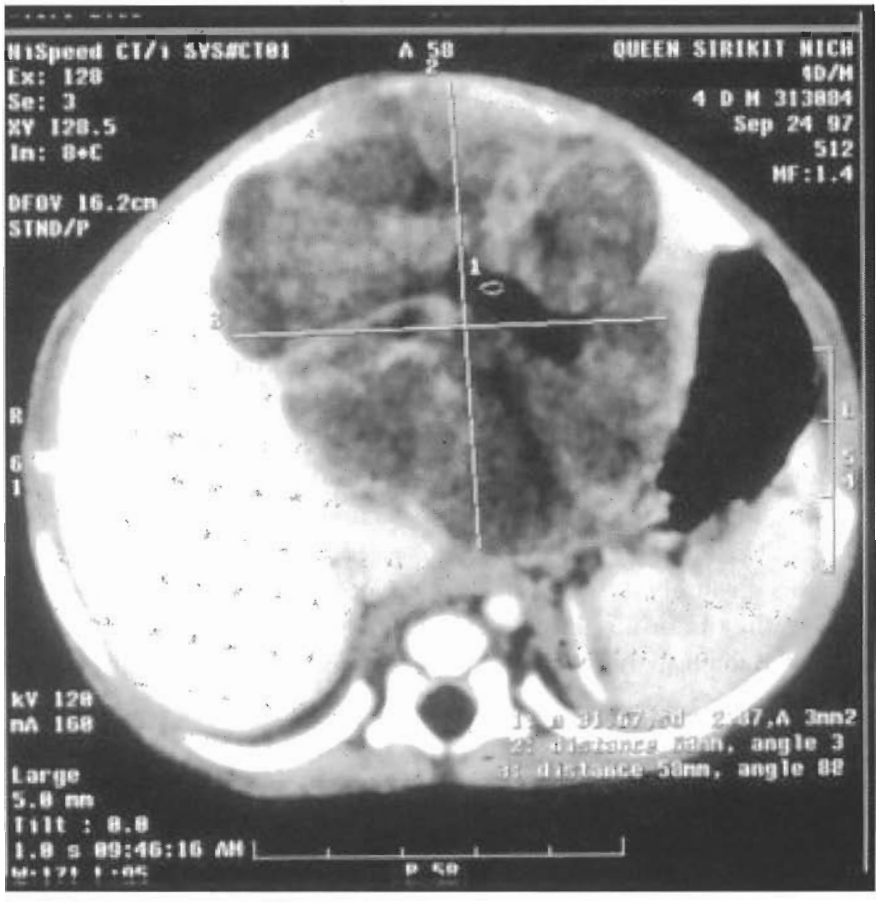


**Fig. 4** CT image shows tumor occupying the left lobe of liver.

**Table 5** Surgical complications in patients with hepatoblastoma

| | No. of Patients |
|---|---|
| Massive intraoperative hemorrhage | 3 |
| Adhesive intestinal obstruction | 3 |
| Small bowel intussusception | 1 |
| Enterocutaneous fistula | 1 |
| Wound evisceration of tumor | 1 |
| Hepatic failure | 1 |

Since 1999, cisplatin, VCR, and 5-FU have been administered instead.

In the 26 cases with biopsy only; 10 received no chemotherapy, in whom, one was dead from respiratory failure, and 9 were lost to follow-up, presumably dead; the other 16 were given chemotherapy, 2 were dead, one from sepsis, the other from pneumonia; 11 were not responsive to treatment, showing no tumor shrinkage, finally lost to follow-up, and 3 most recent cases continued to receive the antineoplastics.

In the 13 resection cases; 7 received no chemotherapy, in whom, 4 died postoperatively from surgical complications, one was lost to follow-up, and 2 survived without disease for 6 months before being lost to follow-up; the other 6 were given chemotherapy, one was dead, 2 survived without disease for 6 months before being lost to follow-up; one was disease-free eight years postoperatively, and 2 had tumor recurrence and metastasis. Results of treatment are summarized in Table 6.

### *Hepatocellular carcinoma*

Of the 7 patients with HCC, 4 were males, and 3 were females. Age ranged from 7 to 14 years old (mean 10 years). Four presented with abdominal mass, 2 with pain, and one with abdominal fullness. Laboratory findings including CBC, bone marrow study, liver function test, and coagulogram were normal. AFP levels were negative in 2, over 4,000 ng/ml in 1, and

**Table 6** Results of treatment of 39 patients with hepatoblastoma

| Surgery | Chemotherapy | Result |
|---|---|---|
| Biopsy (26) | No (10) | Dead (1) |
| | | Lost to follow-up (9) |
| | Yes (16) | Dead (2) |
| | | Not responsive lost (11) |
| | | Still on chemotherapy (3) |
| Resection (13) | No (7) | Dead (4) |
| | | Lost to follow-up (1) |
| | | Survived (2) |
| | Yes (6) | Dead (1) |
| | | Recurrent, metastatic (2) |
| | | Survived (3) |

*( ) = No. of patients*

over 30,000 ng/ml in 3 cases. Hepatitis B surface antigens (HBsAg) were detectable in 2 patients. Concerning radiographic studies, one patient had a nodule in the left lung, another had bone metastasis. US and CT were done in 7 and 4 patients respectively.

According to the operative findings, the tumor was confined to the right lobe in one, to the left lobe but with cirrhosis of the right lobe in another, and occupied both lobes in 5 cases. All were considered unresectable, leading to biopsy only. No chemotherapy was commenced on any case. One patient was dead on arrival 1 month postoperatively. All the others presumably died of the malignancy. It is noteworthy that there has been no new case of HCC since the last patient was seen in January 1994.

### *Sarcoma*

Two girls had sarcoma. One was 12 years old with undifferentiated sarcoma of the right lobe of liver. Biopsy was done, then VCR, actinomycin D, and cyclophosphamide were given without any response. She finally was lost to follow-up.

The other was a 6 years old with poorly differentiated angiosarcoma of the left lobe of liver. Left hepatectomy was done and no chemotherapy was given. She has been disease-free up to the present, 8 years postoperatively.

A 4-year-10-month-old boy had rhabdomyosarcoma involving both lobes of the liver. Biopsy was done, radiation to the liver was given, and VCR, actinomycin D, cyclophosphamide were administered. This patient is, at the time of this report, still on the course of treatment with chemotherapy for nearly one year postoperatively.

### *Endodermal sinus tumor*

A 2-year-old boy had endodermal sinus tumor involving both lobes of the liver without other primary lesion. Chemotherapy (cisplatin and doxorubicin × 4 courses, then cisplatin, bleomycin, and etoposide × 11 courses) was given after biopsy of the tumor established the diagnosis. His AFP level of over 60,000 ng/ml before treatment dropped to normal level soon thereafter. The liver mass shrank markedly, but small residual tumors were still present in both lobes on follow-up CT image. Second look laparotomy was not performed. The patient has been well and still attended the oncology clinic regularly for one and a half years after surgery.

## Discussion

### *Hepatoblastoma*

In this review, 78 per cent of primary liver tumors were malignant, and 78 per cent of these malignancies were HBL. The rates are higher than those of large compiled series.[2,3] HBL is the tumor of infants younger than 2 years of age, as evidenced by 95 per cent in our cases. The etiology of HBL is unknown, but there are clues that suggest genetic alterations in some patients. The associations between HBL and Beckwith-Wiedemann syndrome,[5] hemihypertrophy,[6,7] and familial adenomatous polyposis[8] have been reported. Nevertheless, there were no such associated conditions in our patients. Apart from abdominal mass, the children were usually asymptomatic. Preoperative laboratory findings were unremarkable except for anemia in nearly half of them. Most striking was the AFP level of over 10,000 ng/ml in more than half of the patients. It is useful as a marker in following the patient after tumor resection to ascertain that the tumor has been completely resected and has not recurred. Since AFP is a normal product of the fetus liver and embryonic yolk sac, its level is high in normal infants below 3 months of age.[1] Therefore its interpretation must be made with caution in those very young infants.

Preoperative radiographic studies had picked up at least 5 patients (12.8%) with disseminated disease at diagnosis, either to the lungs or to the bones. Calci-

fication of the tumor, readily discernible on plain radiograph, is of interest. Dachman et al[9] reviewed the radiologic-pathologic correlation of such findings and showed the relation between calcification and osteoid formation in the tumor. Since the osteoid tissue is a mesenchymal component, hence the tumor is categorized as a mixed HBL.[3] Many investigators have observed the favorable prognosis in pure fetal epithelial HBL and sine qua non.[3,10,11] Therefore, calcification of the tumor may suggest unfavorable behavior of HBL. In this review, all the six cases with calcification of the tumor did not respond well to treatment.

Since CT imaging can clearly define the tumor and probably its resectability, its role has replaced that of angiography. However, over- and underestimation of tumor involvement have been reported,[12,13] and some investigators have advocated magnetic resonance imaging as the method of choice for the assessment of resectability instead.[13]

Nearly 60 per cent of the patients had tumors involving both lobes of the liver, precluding the resection attempt. In the group with biopsy only and chemotherapy given, no tumor shrinkage had been observed.

In the group with tumor resection, two patients who had received post hepatectomy chemotherapy had tumor recurrence and metastasis, suggesting of the ineffectiveness of the antineoplastics. There were 5 survivors, all of whom were in the group with resection. Therefore, it is obvious that complete removal of the HBL is essential for survival.

Currently, it has been suggested that, for children with HBL in which the tumor is completely resected, long-term survival can be achieved by adding cisplatin-based therapy after surgery.[11] Some investigators have advocated surgery alone for the very young patients with pure fetal histology, who would have excellent prognosis with complete tumor resection.[10] For children with unresectable tumors, biopsy is performed followed by chemotherapy and secondary resection.[15-18] Intraarterial chemoembolization of the tumor followed by subsequent hepatic resection is another alternative.[19] Finally, liver transplantation may be considered as a last resort for nonresponsive cases.[20]

### *Hepatocellular carcinoma*

HCC accounted for only 14 per cent of the liver malignancies which was much less frequent than HBL. The age incidence was quite different, occurring at a later age (mean age,10 years). AFP level was elevated in more than half of the patients. HCC commonly presents with advanced disease at diagnosis. It is frequently multifocal or metastasized. Two of our patients had either lung or bone metastasis, five had tumors in both lobes of the liver, and all of the seven were considered unresectable.

Concerning the etiology of HCC, it has been closely related to hepatitis B (HB) virus, particularly among the Asians, as evidenced by the high rate of HBsAg positivity (70-100%) in the liver tissue of HCC patients.[21,22] Beasley et al[23] had shown, in a prospective study of 22,707 men in Taiwan, the incidence of HCC among HBsAg carriers to be 1,158:100,000 as opposed to 5:100,000 of those non-carriers, a relative risk of 223. They concluded that HB virus has a primary role in the etiology of HCC. In Thailand, many investigators had also shown such correlation between HB virus and HCC both in adults[24,25] and in children.[26] In the past, the incidence of HBsAg carriers in Thai population was 9.8 per cent,[21] which was regarded as an important public health problem. In 1988, the Ministry of Public Health hence launched HB immunization among children in two provinces, Chiengmai and Chonburi, as a pilot field trial. Ten more provinces were included into the project in 1990. Finally, a nationwide HB vaccination has been integrated into the Extended Program of Immunization in 1992. Such effort has resulted in the decline of HBsAg carrier rate among younger population.[27] Consequently, the incidence of pediatric HCC is expected to be decreased, as no new case was seen since 1994 in this review. In the future, HCC should be rare among Thai children.

### *Sarcoma*

Sarcoma of the liver is very rare. There are no large compiled series to reflect meaningful experience of its treatment.

Regarding angiosarcoma, there were reports of malignant degeneration from hemangioendothelioma.[28,29] Resection of the tumor offers the only hope for survival since chemotherapy has not been proven effective.[29] The only one patient in our series have been disease-free up to the present, 8 years after left hepatectomy, without receiving chemotherapy.

For rhabdomyosarcoma, the only patient is still

on the course of treatment and the result is to be evaluated.

### *Endodermal sinus tumor*

This tumor is also very rare. Hart reported the first case in 1975.[30] In our patient, chemotherapy had dramatically reduced the tumor size and the AFP level. The long term outcome is being followed.

## Conclusion

In conclusion, the lessons learned from this review are : (1) HBL was the common liver malignant tumor of infants below 2 years of age, (2) resection of HBL should be attempted when feasible, if survival is to be attained, (3) preresection chemotherapy in unresectable HBL has not thus far shown any beneficial effect, (4) the incidence of HCC in children is expected to decline as the HB immunization has been covered nationwide, and (5) limited experience in angiosarcoma indicated the curative result of tumor resection.

## References


1. Watanatittan S, Sangcham K. Palpable abdominal masses in children. Bull Dept Med Serv 1988; 13: 93-103 (in Thai).
2. 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: 329-37.
3. Weinberg AG, Finegold MJ. Primary hepatic tumors of childhood. Hum Pathol 1983; 14: 512-37.
4. Tsuchida Y, Endo Y, Saito S, et al. Evaluation of alpha-fetoprotein in early infancy. J Pediatr Surg 1978; 13: 155-6.
5. Haas JE, Muczynski KA, Krailo M, et al. Histopathology and prognosis in childhood hepatoblastoma and hepatocarcinoma. Cancer 1989; 64: 1082-95.
6. Ishak KG, Glunz PR. Hepatoblastoma and hepatocarcinoma in infancy and childhood. Report of 47 cases. Cancer 1967; 20: 396-422.
7. Geiser CF, Baez A, Schindler AM, Shih VE. Epithelial hepatoblastoma associated with congenital hemihypertrophy and cystathionuria. Pediatrics 1970; 46: 66-73.
8. Kingston JE, Herbert A, Draper GJ, Mann JR. Association between hepatoblastoma and polyposis coli. Arch Dis Child 1983; 58: 959-62.
9. Dachman AH, Pakter RL, Ros PR, Fishman EK, Goodman ZD, Lichtenstein JE. Hepatoblastoma: radiologic - pathologic correlation in 50 cases. Radiology 1987; 164: 15-9.
10. Newman KD. Hepatic tumors in children. Semin Pediatr Surg 1997; 6: 38-41.
11. Kasai M, Watanabe I. Histologic classification of liver-cell carcinoma in infancy and childhood and its clinical evaluation : a study of 70 cases collected in Japan. Cancer 1970; 25: 551-63.
12. Amendola MA, Blanc CE, Amendola BE, Glazer GM. CT findings in hepatoblastoma. J Comput Assist Tomogr 1984; 8: 1105-9.
13. Finn JP, Hall-Craggs MA, Dicks-Mireaux C, et al. Primary malignant liver tumors in childhood: assessment of resectability with high-field MR and comparison with CT. Pediatr Radiol 1990, 21: 34-8.
14. Douglass EC, Reynolds M, Finegold M, et al. Cisplatin, vincristine, and fluorouracil therapy for hepatoblastoma: a Pediatric Oncology Group study. J Clin Oncol 1993; 2: 96-9.
15. King DR, Ortega JA, Campbell J, et al. The surgical management of children with incompletely resected hepatic cancer is facilitated by intensive chemotherapy. J Pediatr Surg 1991; 26: 1074-81.
16. Ortega JA, Krailo MD, Haas JE, et al. Effective treatment of unresectable or metastatic hepatoblastoma with cisplatin and continuous infusion doxorubicin chemotherapy: a report from the Children's Cancer Study Group. J Clin Oncol 1991; 9: 2167-76.
17. Reynolds M, Douglass EC, Finegold M, Cantor A, Glickman A. Chemotherapy can convert unresectable hepatoblastoma. J Pediatr Surg 1992; 27: 1080-4.
18. Black CT, Cangir A, Choroszy CM, Andrassy RJ. Marked response to preoperative high-dose cis-platinum in children with unresectable hepatoblastoma. J Pediatr Surg 1991; 26: 1070-3.
19. Yokomori K, Hori T, Asoh S, Tuji A, Takemura T. Complete disappearance of unresectable hepatoblastoma by continuous infusion therapy through hepatic artery. J Pediatr Surg 1991; 26: 844-6.
20. Tagge EP, Tagge DU, Reyes J, et al. Resection, including transplantation for hepatoblastoma and hepatocellular carcinoma : impact on survival. J Pediatr Surg 1992; 27: 292-7.
21. Obata H, Nishioka K. Prevalence of hepatitis B virus and primary hepatocellular carcinoma in Asia. Southeast Asian J Trop Med Pub Hlth 1979; 10: 621-6.
22. Chen WJ, Lee JC, Hung WT. Primary malignant tumor of liver in infants and children in Taiwan. J Pediatr Surg 1988; 23: 457-61.
23. Beasley RP, Lin CC, Hwang LY, Chien CS. Hepatocellular carcinoma and hepatitis B virus. ø prospective study of 22,707 men in Taiwan. Lancet 1981; 2: 1129-32.
24. Bunyaratvej S, Rochanawutanon M, Chaimuangraj S. Hepatitis B surface antigen in liver tissue and primary liver carcinomas in Thailand. J Med Assoc Thai 1979; 62: 414-21.
25. Panyathanya R, Thakerngpol K, Chinda K, Stitnimankarn T.

The incidence of hepatitis B surface antigen in liver tissues of liver diseases in Thailand. J Med Assoc Thai 1982; 65: 246-51.
26. Hemsrichart V, Ammawat K. Primary hepatic neoplasms in Children's Hospital: the pathological study of 30 cases. Thai Cancer J 1992; 18: 49-55.
27. Poovorawan Y, Theamboonlers A, Vimolket T, et al. Impact of hepatitis B immunization as part of the EPI. Vaccine 2001; 19: 943-9.
28. Kirchner SG, Heller RM, Kasselberg AG, Greene HL. Infantile hepatic hemangioendothelioma with subsequent malignant degeneration. Pediatr Radiol 1981; 11: 42-5.
29. Awan S, Davenport M, Portmann B, Howard ER. Angiosarcoma of the liver in children. J Pediatr Surg 1996; 31: 1729-32.
30. Hart WR. Primary endodermal sinus (yolk sac) tumor of the liver. First reported case. Cancer 1975; 35: 1453-8.