Hepatic tumors account for approximately 1% of child malignancies, with hepatoblastoma (HB) and hepatocellular carcinoma (HCC) constituting the majority. Because of their rarity, generalizations regarding the epidemiology are difficult. Worldwide, HB occurs almost twice as often as HCC in children. In Taiwan, as an endemic area for hepatitis B virus (HBV) infection, the incidence of HCC is higher than that of HB (4.4:1), which is different from the reports in Western countries. To control hepatitis B, Taiwan launched a nation-wide vaccination program in 1984. In 10 years, this program reduced the hepatitis B carrier rate in children from 10 percent to less than 1 percent, and the incidence of childhood HCC declined significantly. In this decade, the prognosis of HB has been improved because of the advances of surgery, chemotherapy and transplant. The aims of this study were to retrospectively compare the outcome of children with HB and HCC in 2 groups, according to the time of diagnosis and treatment.

**METHODS**

From August 1978 to June 2001, 48 pediatric patients with hepatic tumors were treated in the Division of Pediatric Surgery, Taipei Veterans General Hospital. The pathology was mainly HB and HCC (n = 20 and 15, respectively). Others included undifferentiated sarcoma (n = 1), malignant mesothelioma (n = 1), focal nodular hyperplasia (n = 1), traumatic liver cyst (n = 1), mesenchymal hamartoma (n = 2), hemangioendothelioma (n = 3) and stage IVs neuroblastoma (n = 4). Only the cases with HCC and HB were enrolled.

The patients were divided into 2 groups based on the time of diagnosis.
time of diagnosis and treatment. The group I was the 23 patients diagnosed from 1978 to 1990. Group II included the remaining 12 patients. Serum level of α-fetoprotein was checked in all patients. Abdominal ultrasonography and computed tomography (CT) were arranged to diagnose and stage the disease. CT scan of the chest was used to detect the presence of lung metastasis. This was supplemented by magnetic resonance imaging (MRI) in 9 patients after the technique became available in 1991.

Hepatic tumors were presumed to be unresectable if pulmonary metastasis was present or if the portal vein or inferior vena cava was involved at diagnosis. If the primary tumors were unresectable, preoperative systemic chemotherapy or hepatic artery chemoembolization would be given first, no matter if biopsy was not done. The regimens of chemotherapy in group I and II were different. In group I, the chemotherapy consisted of many drugs including vincristine, doxorubicin, cyclophosphamide and 5-fluorouracil. In group II, standard protocol comprising cisplatin, vincristine and 5-fluorouracil was prescribed.

Then the resectability was reevaluated after several courses of preoperative chemotherapy. Once the resectability was agreed upon, exploratory laparotomy was done. Formal operative resection of tumor was performed if the intraoperative findings still showed acceptable. Postoperative chemotherapy was administered according to the operative findings and the pathologic reports.

RESULTS

General data

Male predominance was noted in both HB and HCC (M:F was 12:8 and 9:6 respectively) and the age was younger in HB than in HCC (mean = 9, range = 2-36 months and mean = 10, range = 0.7-15 years, respectively). Alpha-fetoprotein level was elevated in all cases. The serum levels of α-fetoprotein in HB was higher than in HCC (mean = 320000, range = 18000-800000 ng/mL and mean = 140000, range = 60000-280000 ng/mL, respectively). All cases with HCC were hepatitis B carriers and none in HB. Palpable abdominal mass was the main clinical complaint in HB. Other symptoms included anemia, failure to thrive as well as vomiting in HB. In contrast, the patients with HCC complained with abdominal pain, poor appetite, jaundice and abdominal fullness. The ratio of HB: HCC increased from 11:12 in group I to 9:3 in group II.

Pretreatment tumor extents and resectability

The extents of tumors at diagnosis are shown in Table 1. Among these patients, 13 (37%) had a bilobar involvement, 11 (31%) involved the right lobe, and 11 (31%) involved the left lobe. Five (14%) cases had distant metastasis and 4 (11%) had hilum involvement. In the cases with multiple metastases or with portal vein thrombosis, unresectability was agreed initially. However, the resectability was uncertain in some cases at that time. Five patients in group I was determined unresectable by images due to huge tumor size but there was no metastasis or portal vein thrombosis. Two of them did not receive laparotomy. The other 3 cases without portal hilum involvement, according to the operative records, only received laparotomy and hepatic artery catheterization.

Table 1. Extent of tumor in 35 patients with hepatoblastoma or hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Primary location</th>
<th>n</th>
<th>Metastasis</th>
<th>Resectability</th>
</tr>
</thead>
<tbody>
<tr>
<td>R’t lobe</td>
<td>8</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>L’t lobe</td>
<td>9</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>L’t lobe+Seg 5 or 8</td>
<td>3</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>R’t lobe+Seg 1</td>
<td>1</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>R’ lobe</td>
<td>3*</td>
<td>Lung and bone</td>
<td>No</td>
</tr>
<tr>
<td>L’t lobe</td>
<td>2</td>
<td>Lung</td>
<td>No</td>
</tr>
<tr>
<td>R’ lobe+Seg 4</td>
<td>5</td>
<td>No**</td>
<td>No</td>
</tr>
<tr>
<td>L’t lobe+Seg 5+Seg 6 or 8</td>
<td>4</td>
<td>No#</td>
<td>No</td>
</tr>
</tbody>
</table>

* = one patient died of hemorrhage after open biopsy; ** = two had portal vein thrombosis; # = two had portal vein thrombosis; Seg = segment.
rized in Fig. 1. One patient died of tumor rupture and hemorrhage after biopsy and subcutaneous port implantation. Thirteen patients were treated with preoperative chemotherapy for primary unresectable tumors. Ten of 13 were treated with systemic chemotherapy and the remaining 3 patients received hepatic artery chemoembolization. Four of the 10 patients had sufficient response to systemic chemotherapy to allow complete surgical resection of their tumors and were all in group II, as a satisfactory reduction in tumor size in 3 children and lung metastasis disappearance in 1. The other 6 children treated with systemic chemotherapy died of the disease and the complications of systemic chemotherapy although tumor response was observed in 4. Among the 3 patients treated with chemoembolization, 2 died of cachexia in conjunction with successful tumor response and 1 died of respiratory failure caused by multiple lung metastases.

The survival rate of HB in group I was zero compared with 56% in group II (0 of 11 vs 5 of 9). The survival rate of HCC persisted as zero. Operative mortality was 9% in group I compared with zero in group II (2 of 23 vs 0 of 12).

Twenty patients suffering from HB underwent primary (n = 8) or secondary (n = 4) hepatic resection as illustrated in Fig. 2. The patients with diagnosed unresectable HB received chemotherapy but all got poor response. In group II, the conversion rate was 100%. Grossly incomplete tumor resection and vascular invasion in microscopy were provided with chemotherapy after the surgical procedure. There was only 1 case of 3-year survival, who was treated with complete tumor resection only.

**DISCUSSION**

Hepatic tumors account for approximately 0.5% to 2.0% of all neoplasms in children and, excluding leukemia and lymphoma, about 1% to 4% of all solid tumors. In our study, the components of the first 23 cases (group I) (1978-1990) were distinct from the next 12 cases (group II) (1991-2001). The ratio of HB: HCC increased. All patients in this study diagnosed with HCC were HBV carriers. It strongly supports that hepatitis B virus infection had been the most important underlying cause of HCC of pediatric patients in Taiwan. After 10 years of the hepatitis B mass-vaccination program, which started

![Fig. 1. Outcome of the 35 patients with hepatoblastoma or hepatocellular carcinoma.](image)
in 1984, HCC reduced significantly. Chang et al.\textsuperscript{7} even predicted that there should be no HCC in children if the efficacy of the program is 100% with excellent coverage. In fact, only 3 cases of HCC in children were found, who were all born after July 1984.

Male predominance has been pointed out in the report of Chen et al.\textsuperscript{2} and our study disclosed a similar result, no matter in HB or HCC. However, the real causes are still unknown. The age of diagnosis in HCC was older than in HB, because the HCC is a specific malignancy to vertical HBV infection and gradually deriving. The elevated α-fetoprotein was noted in all patients and the level of HB was higher than that of HCC. The serum α-fetoprotein level was used as a measure of disease activity as well as sonography screening in carrier children who sustained HCC.\textsuperscript{8} In our review of some studies, HB arises from the right lobe more frequently.\textsuperscript{9} The left lobe is supplied with oxygenated blood entirely from the umbilical vein, whereas the right lobe is supplied with portal vein blood containing lower oxygen saturation.\textsuperscript{10} Pre-

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**Fig. 2.** Outcome of the 20 patients with hepatoblastoma. (A) is group I. (B) is group II.

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sumably lower oxygen tension impedes the embryonic differentiation of the hepatoblast in certain conditions, thus predisposing to the development of HB in the right lobe predominantly. Similar theories regarding oxygen tension and hepatic tumor development have been postulated for the pathogenesis. However, the extent of tumor in this study showed equivalent frequency in either lobe. Newman found that 10% of children with HB had pulmonary metastasis at the time of diagnosis which was similar to ours (14%).

The concept of multimodality therapy has improved the survival for childhood malignancies, including hepatic malignant tumors. Complete resection of primary tumor remains the most important prognostic determinant of survival. The term “resectable” is now used to describe a tumor based on radiographic criteria or surgical evaluation of laparotomy findings and technical consideration. Some investigators have shown that pretreatment CT findings may overestimate tumor involvement and erroneously predict resectability. The 9 patients with initially unresectable tumors who had received preoperative chemotherapy with poor response, were later taken into consideration of exploratory laparotomy. If “unresectable” was agreed upon intra-operatively, total hepatectomy and liver transplant could be another choice.

In the 1960s and 1970s, it became evident that HB was a chemosensitive tumor, but early survival rate was low, in the range of 20% to 30%. Agents shown to be effective included vincristine, 5-fluorouracil and doxorubicin. Since late 1980s, the introduction of cisplatin into chemotherapy regimens for HB has markedly improved survival in unresectable tumors. The Intergroup HB/HCC Study is a cooperative effort initiated in 1989 between the CCG (Children’s Cancer Group, Europe) and POG (Pediatric Oncology Group, USA) that was initiated in 1989. They have made conclusion that the cisplatin-based regimen combined with vincristine makes good response rate and less side effect no matter in neoadjuvant or adjuvant chemotherapy. Owing to the recent clinical studies in preoperative chemotherapy, doctors can convert the “potentially unresectable” HB to a “resectable” tumor and achieve complete resection. The 4 patients who received preoperative cisplatin-based chemotherapy and then underwent hepatic resection were all in group II. This indicates that systemic chemotherapy has gained better results during the recent decade.

Unfortunately, dismal results are still obtained in the management of children with HCC. Because of the high incidence of unresectable HCC, a number of adjuvant measures have been developed to deal with persistent or recurrent disease. Much of the information regarding these measures has been acquired from adult cancer studies. In our series, the children with HCC were diagnosed at late stage and combined with severe liver cirrhosis. The 3-year survival rate persisted zero in group I and II. Although the treatment of HCC is disappointing, we can prevent children from this disease by vaccination.

In the recent decade, improved anesthetic and surgical techniques and perioperative care have reduced the operative mortality to 0-3%. The post-operative intensive care in children also plays an important role. The surgical techniques that are based on experience and modern facilities minimize the surgical mortality and make extensive resection feasible. Several factors may have reduced operative hemorrhage, including preoperative tumor shrinkage by chemotherapy, awareness of hepatic segmental anatomy, use of the ultrasonic dissector and fibrin sealant. Multiple surgical resections, along with chemotherapy and radiation therapy, also have been successful in treating pulmonary and brain metastases years after the initial resection of a HB. Aggressive treatment of recurrent disease using both aggressive chemotherapy and multiple resections would have been applied to the 18 patients who received hepatic resection but died of recurrent diseases.

Routine newborn screening by pediatrician with physical exam is the only way to find the abdominal mass but it is always too late for high stages. In the pediatric literature, several cases have been diagnosed post-natally, within 6 weeks after delivery, suggesting that HB may arise during fetal life. But only a case report could be found about antenatal diagnosis of congenital HB in uterus as initial presentation of enlarged fetal abdominal circumference at 36 weeks of gestation. Now, the prenatal sonogram is prevalent and may help to an early diagnosis of liver tumors.
In conclusion, HCC in children has become rare on account of universal hepatitis B vaccination in Taiwan. HB presently is the most common liver tumor in children. The integration of surgery and chemotherapy is the way to achieve the best outcome.

REFERENCES