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Paediatric hepatoblastoma and hepatocellular carcinoma: retrospective study

兒科的肝胚細胞瘤和肝細胞癌：回顧研究

Objectives. To compare and contrast clinical characteristics and outcomes of hepatoblastoma or hepatocellular carcinoma in paediatric patients.
Design. Retrospective study.
Setting. University teaching hospital, Hong Kong.
Patients and methods. Medical records of 22 paediatric patients with hepatoblastoma (n=11) or hepatocellular carcinoma (n=11) admitted to Queen Mary Hospital between 1989 and 2000 were reviewed. Data gathered included demographic data, results of liver function tests, hepatitis A, B, and C titres, and α-foetoprotein levels, and imaging studies including chest X-ray, ultrasound study, computed tomography scan, and magnetic resonance imaging / hepatic angiogram for tumour staging and resectability.
Results. The mean age of patients with hepatoblastoma was 18 months (range, 5 months to 3 years), while that of patients with hepatocellular carcinoma was 10.2 years (range, 2 to 16 years). Females predominated in the hepatoblastoma group (female:male, 8:3) and males in the hepatocellular carcinoma group (male: female, 10:1). None of the patients with hepatoblastoma were hepatitis B surface antigen positive, in contrast to 64% of the hepatocellular carcinoma group. Only 45% of the hepatocellular carcinomas were resectable at presentation and this figure remained unchanged following chemotherapy. A total of 91% of hepatoblastomas were resectable, four at presentation, and a further six after chemotherapy. Tumour rupture was more common in patients with hepatoblastoma than in those with hepatocellular carcinoma (36% versus 9% of cases, respectively). Mortality rates were considerably higher among the hepatocellular carcinoma group than the hepatoblastoma group in this series.
Conclusion. Childhood hepatoblastoma and hepatocellular carcinoma differ with respect to age and tumour stage at presentation, hepatatis B surface antigen status, tendency to rupture, chemosensitivity, and prognosis.

目的：比較和對照兒童患者中肝胚細胞瘤或肝細胞癌的臨床特徵和結果。
設計：回顧性研究。
安排：大學教學醫院，香港。
患者及方法：回顧了 1989 至 2000 年間在瑪麗醫院就診的 22 名患有肝胚細胞瘤(n=11)或肝細胞癌(n=11)的兒童的醫療紀錄。所搜集的資料包括人口統計學數據，肝功能測試結果：甲、乙、丙種肝炎滴定度，α-胎球蛋白水平，包括胸X光、超聲波、電腦X線斷層攝影掃描的成像研究、磁共振成像/為腫瘤分段和可切除性的肝血管造影片。
結果：患肝胚細胞瘤的患者平均年齡是18個月(範圍，5個月至3歲)，而患肝細胞癌的患者平均年齡為10.2歲(範圍，2至16歲)。女性在肝胚細胞瘤患者組中佔大多數(女性與男性的比例是8比3)，而男性在肝細胞癌患者群中居絕對多數(男性與女性的比例為 10:1)。沒有一個肝胚細胞瘤患者呈乙型肝炎B表面抗原陽性，而與之相比，肝細胞癌患者群中有64%的患者呈陽性。在所介紹的病例中只有45%的肝細胞癌可切除，這百分數在化療後依然不變。總共91%的肝胚細胞瘤可切除，開始時4名，化療後又有6名。腫塊破裂在肝胚細胞瘤患者中比在肝細胞癌患者中更普遍(分別佔病例的36%和9%)。在這研究中肝細胞癌患者的死亡率大大高於肝胚細胞瘤患者。
結論：兒童肝胚細胞瘤和肝細胞癌在出現的年齡和腫塊階段，乙型肝炎表面抗原狀態，破裂趨勢，化療敏感性及預後等方面是不同的。

Key words:
Carcinoma, hepatocellular;
Child;
Hepatoblastoma;
Infant;
Liver neoplasms

關鍵詞：
肝細胞癌；
兒童；
肝胚細胞瘤；
嬰兒；
肝瘤

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Introduction

Primary neoplasms of the liver constitute 0.5% to 2.0% of paediatric tumours in large series, and malignant epithelial neoplasms constitute two thirds of the primary hepatic tumours in infancy and childhood.[1] Exelby et al[2] found that hepatoblastoma (HB) and hepatocellular carcinoma (HCC) were the most common primary epithelial liver tumours in children following a large questionnaire survey conducted in the US. A previous study at the Queen Mary Hospital suggested that HB and HCC may be equally common in the Hong Kong paediatric population.[3]

After studying 47 cases of HB and HCC, Ishak and Glunz[4] concluded in 1967 that patients with HCC had a poor prognosis regardless of the treatment offered but that surgical excision for HB did influence survival. Since this early study, there have been significant improvements in the results from hepatic resection[5] and with preoperative chemotherapy for initially unresectable HB.[6] Paediatric patients treated at Queen Mary Hospital for HB or HCC were reviewed in order to compare these tumours with respect to patient age and stage of tumour at presentation, associated factors, resectability, response to chemotherapy, and overall prognosis given recent advances in treatment.

Methods

The medical records of all paediatric patients with HB or HCC admitted to Queen Mary Hospital between 1989 and 2000 were reviewed. The diagnosis of HB or HCC was confirmed histologically. Laboratory investigations completed included liver function tests, hepatitis A, B, and C titres, and serum α-foetoprotein levels. Imaging studies included chest X-ray, ultrasonography, computed tomography (CT) scan, and hepatic angiography with or without magnetic resonance imaging for tumour staging and resectability. The International Society of Paediatric Oncology (SIOP) method of staging was used: Stage I, one liver segment involved; Stage II, two segments involved; Stage III, three segments involved or two isolated, separate segments involved; Stage IV, all four segments involved.[7,8] The segments were delineated using Couinaud's liver segments.[9] Substaging was indicated by subscripts to the above stages, such as 'm' for metastasis, or 'p' for portal vein involvement.

For unresectable tumours, biopsies were taken and systemic chemotherapy commenced to reduce tumour size, following the Paediatric Oncology Group regimens.[6,10] The induction drug used was carboplatin (500 mg/m^2), followed by a triple drug regimen of carboplatin (500 mg/m^2), vincristine (1.5 mg/m^2), and 5-fluorouracil (600 mg/m^2). Blood was taken from the patients after 3 weeks to assess recovery of leukocyte and platelet counts. The cycle of chemotherapy was repeated if leukocyte and platelet counts were normal. Transarterial oily chemoembolisation (TOCE) treatment with cisplatin was given to patients with inoperable, locally extensive HCC. Imaging studies were repeated regularly to assess tumour response and resectability.

Patients with ruptured tumours confirmed on CT scan underwent immediate cardiovascular resuscitation. Depending on the stage of the tumour as seen on the CT scan and the condition of the patient, stoppage of bleeding was accomplished by transcutaneous hepatic artery embolisation, selective hepatic artery ligation, or hepatic resection. Only clinically stable, small tumours were resected as an emergency procedure.

Results

Between 1989 and 2000, 22 patients were treated for HB (n=11) and HCC (n=11) in Queen Mary Hospital (Table 1). The mean age of patients with HB was 18 months (range, 5 months-3 years), while that of patients with HCC was 10.2 years (range, 2-16 years). Females predominated among the patients with HB (male:female, 3:8), and males among those with HCC (male:female, 10:1). While 64% (7/11) of the HCC patients were hepatitis B surface antigen (HBsAg) positive, none of the patients with HB were HBsAg positive. Younger patients with HCC (2, 5, and 8 years) also were negative for HBsAg. The mean serum α-foetoprotein level was higher for patients with HB (28 183 μg/L; normal level, <10 μg/L) than the HCC patients (4216 μg/L).

The tumour rupture rate was higher in the HB group (4/11, 36%) than in the HCC group (1/11, 9%). One patient in the HB group died within 1 day of admission before a diagnosis of ruptured tumour could be made, but all other patients with HB and ruptured tumour (n=4) had their bleeding stopped by embolisation (n=2), right hepatic artery ligation (n=1), or emergency lobectomy (n=1). These four patients were without evidence of disease after tumour resection and chemotherapy at the time of writing (mean survival, 3 years; range, 2-4 years). The only patient with a ruptured HCC underwent right lobectomy after stoppage of bleeding and died 5 months later due to tumour recurrence.

Table 1. Characteristics of patients with hepatoblastoma or hepatocellular carcinoma at presentation

	Mean age (range)	Sex (male: female)	Hepatitis B surface antigen status positive No. (%)	Mean serum alpha-foeto-protein level (μg/L)	Resectable tumour at presentation or following chemotherapy No. (%)	Tumour rupture No. (%)
Hepatoblastoma (n=11)	18 months (5 months-3 years)	3:8	0 (0)	28 183	10 (91)	4 (36)
Hepatocellular carcinoma (n=11)	10.2 years (2-16 years)	10:1	7 (64)	4216	5 (45)	1 (9)

Table 2. Tumour stage at presentation according to the International Society of Paediatric Oncology staging method

Hepatoblastoma No. (%)		Hepatocellular carcinoma No. (%)	
Stage I	1 (9)	Stage I	1 (9)
Stage II	3 (27)	Stage II extension	1 (9)
Stage III	7 (64)	Stage III portal vein	1 (9)
		Stage III metastasis	1 (9)
		Stage IV	6 (55)
		Stage IV metastasis	1 (9)

The HCC tumours demonstrated a tendency to enlarge and infiltrate early in the clinical course (Table 2), with seven (64%) patients found to have Stage IV tumours at presentation. A Stage I HCC was identified in a patient with neonatal hepatitis, with follow-up ultrasound scanning locating a 2-cm nodule at the left lateral hepatic segment. This patient has since been tumour-free for 3 years following left lateral segmentectomy.

A total of 15 hepatic resections were performed: five for HCC (45%) and 10 for HB (91%). Six patients had HB tumours deemed suitable for resection following chemotherapy treatment, while such a response to chemotherapy was not seen in any patients with unresectable HCC. Operations included right lobectomy (n=6), right trisegmentectomy (n=2), right lateral segmentectomy (n=1), left trisegmentectomy (n=3), left lobectomy (n=1), left lateral segmentectomy (n=1), and left lateral segmentectomy with partial gastrectomy and transverse colectomy (n=1). The right lateral segmentectomy involved resection of segments six and seven only in order to preserve as much liver tissue as possible. Blood loss during surgery ranged from 250 cc to 1750 cc (mean, 525 cc). There was no operative mortality.

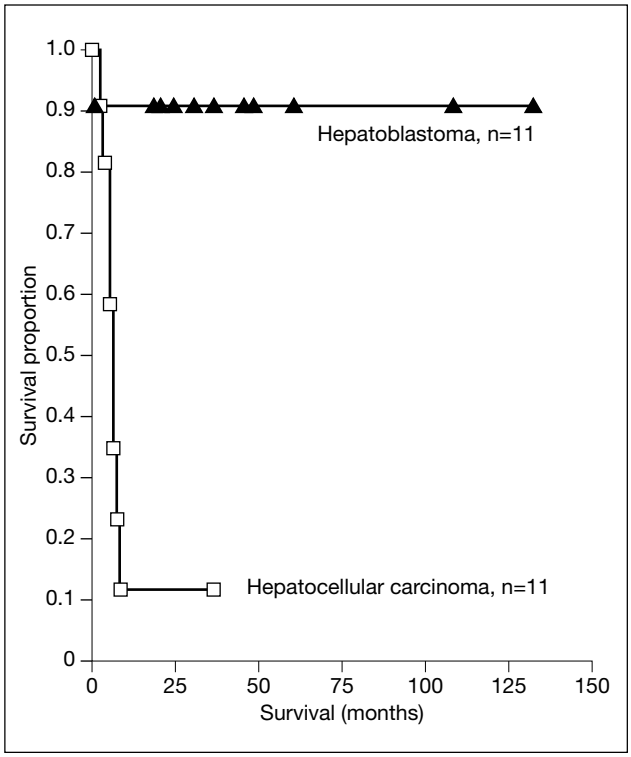

Fig. Survival curve for patients with hepatoblastoma and hepatocellular carcinoma

One patient experienced subphrenic haematoma formation and required a second operation for blood evacuation. All other patients had an uneventful recovery postsurgery.

Survival rates were higher overall for patients with HB than for those with HCC (Fig): median survival of 3 years versus 5 months, respectively (P=0.0001, log rank test). One patient with HB and tumour rupture (undiagnosed) died shortly after admission. Another patient with HB and raised α-foetoprotein levels 9 months after hepatic resection, was found to have three secondary tumours (one in the left lobe and two in the right lobe) on CT of the thorax. Left thoracotomy and partial pulmonary resection for the removal of the left nodule confirmed the secondary tumours histologically. The patient is awaiting further surgery to remove the right nodules. All other HB patients are well without evidence of disease. Of the patients with HCC, only three are still alive. One is without evidence of disease while two have persistent HCC and are undergoing TOCE treatment for tumour control.

Discussion

Surgical techniques designed to reduce intraoperative blood loss, blood transfusion, and ischaemic injury to the liver remnant following hepatectomy, together with postoperative care, have been improving and are reducing hospital mortality associated with hepatectomy towards zero.[5,11,12] Paediatric patients have a small blood volume, and have been found to have better results than older patients.[13,14] In the 15 hepatectomies reported here, there was no surgical mortality and the only morbidity was a single instance of subphrenic haematoma requiring a second operation for blood evacuation. With careful surgical techniques and good postoperative care, hepatectomy has been shown to be a safe procedure for paediatric patients in this series, with a mean blood loss of 525 cc.

Late presentation posed a major management problem for the patients in this study. In this series, only 45% (Table 1) of patients with HCC and 36% of patients with HB had resectable tumours at presentation. Fortunately, the HB tumours were chemosensitive, with six patients able to undergo resection after chemotherapy. All patients with HB therefore underwent hepatectomy, except the patient who died prior to diagnosis. One patient had secondary pulmonary tumours and was treated with thoracotomy and lung resection. A similar patient has been reported in the literature to have long-term survival.[15] Because of the chemosensitivity of HB, more aggressive treatment for more extensive tumours has been attempted, including transarterial chemotherapy and liver transplantation.[15-17] The results for HCC treatment, in contrast, have been poor. No patient in this series was able to undergo surgical resection of the tumour following chemotherapy. Transarterial oily chemoembolisation has been reported for the prolongation of life, though the mean survival achieved was only 5 months.[18] Hepatitis B surface antigen–positive patients with HCC have a higher

mortality rate, suggesting that they make poor candidates for liver transplantation.[19] In this study, the only patient who survived for 3 years was one identified on a screening ultrasound study for postneonatal hepatitis. Screening for early disease may enhance the survival rate of patients with HCC.[20]

The SIOP staging system for paediatric hepatic tumours has been confirmed as useful for comparing results of different treatment options.[7,8] It is a preoperative clinical staging system, with the emphasis on local extension and vascular invasion. The system differs from the International Union Against Cancer (UICC) TNM staging system commonly used in adults. Modification of the adult UICC TNM staging system, placing greater emphasis on vascular invasion has been suggested by Izumi et al[21] and Staudacher et al[22] following their studies investigating treatment results of patients with HCC. The SIOP staging system addresses the infiltrative status of tumours and this may explain its prognostic accuracy with respect to paediatric hepatic tumours, especially paediatric HCC which is very infiltrative and aggressive (Table 2).

Rupture has not been included as a variable in the SIOP staging system. In selected patients and with appropriate treatment, survival is possible.[23] The mechanism of spontaneous rupture of liver tumour is unknown. It may be related to venous congestion, haemorrhage, central necrosis, or trauma.[24] Embolisation, emergency hepatectomy, and selective hepatic artery ligation are reported treatments[25-28] and were successfully applied in this study to arrest postrupture bleeding. The preferred treatment depends on the general condition of the patient, tumour size, and the experience of the surgeon. Selective hepatic artery ligation did not appear to affect postligation chemotherapy for the patients in this study. There were apparently sufficient collateral vessels remaining to allow postoperative chemotherapy to control the tumour. Rupture in HB did not appear to negatively influence patient survival, except in the patient in whom the diagnosis of ruptured HB was not made.

The prognosis for paediatric patients with HCC appears poor (Fig).[29] The resection rate in this study was 45%, and the median survival time in this series only 5 months. Hepatitis B surface antigen tests were positive in 64% of the patients overall. Those who tested positive were the older patients in the group. In younger patients, the development of HCC has been attributed to a variety of conditions, including tyrosinaemia, biliary atresia, idiopathic neonatal hepatitis, and neonatal iron storage disease.[30] Idiopathic neonatal hepatitis was found in one of the current patients. Universal hepatitis B vaccination is known to decrease the incidence of HCC.[31] Since hepatitis vaccination has commenced in Hong Kong, the local incidence of HCC is expected to decrease.

The aetiology of HB is currently unknown. All of the patients with HB in the current series were HBsAg negative. Prematurity has been shown to be associated with HB,[32,33] but the exact mechanism is unclear. The alteration of genes involved with cell cycle control and cell growth, as well as chromatin modification, have been noted in patients with HB.[34] Similar genetic aberrations, such as p53 mutations, have also been found in patients with HCC.[35,36] The use of molecular techniques to investigate these tumours and the differences between them still remains to be addressed in research studies.

Conclusion

Paediatric HB and HCC demonstrate marked differences in their clinical course. These differences should be kept in mind when planning management for paediatric patients with HB or HCC, and counselling patients and their families.

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