Pergamon

European Journal of Cancer, Vol. 34, No. 13, pp. 2064–2067, 1998

Printed in Great Britain
0959-8049/98/$—see front matter

PII: S0959-8049(98)00281-0

Original Paper

Survival and Distribution Pattern of Childhood Liver Cancer in Taiwan

C.-L. Lee[1] and Y.-C. Ko[2]

[1]Department of Paediatrics, Kaohsiung Veterans General Hospital; and [2]School of Public Health, Kaohsiung Medical College, No. 100, Shih-Chuan 1st Road, Kaohsiung, Taiwan

Studies of survival and distribution of liver cancer in children are scarce. In this study, using data from the cancer registry of Taiwan, from 1979 to 1992, we identified 377 young patients (0–15 years of age) suffering from liver cancer, coded 155 according to the International Classification of Diseases. Among these patients, 122 were histopathologically proven hepatocellular carcinoma (HCC) and 43 hepatoblastoma (HB). For survival analysis, we also searched for cases of liver cancer in 0–16 year old children in the Taiwan cancer registry for the period between 1988 and 1992. We found 109 cases with identification numbers and birth dates which allowed our cases to be linked with the death registry of the National Health Department of Taiwan enabling the calculation of 5-year survival rates using actuarial life tables. Between 1979 and 1992, for 122 HCC cases, there was a peak incidence at the age of 1 year, then a decline to a trough at the age of 4 years, after which the number of cases increased to the age of 15 years. After the age of 4 years boys outnumbered the girls by 2:1. 36 (84%) of 43 HB cases were under the age of 5 years and boys tended to outnumber girls by 2.9:1. Between 1988 and 1992, of the 109 patients, 49 were diagnosed histopathologically and 60 patients clinically. Their overall 5-year survival rate was 19%. The 5-year survival rate of the 28 HCC patients was 17%, whereas that of the 17 HB patients was 47%. In conclusion, our epidemiological findings indicate that the HCC distribution among children is different according to age and to some extent sex. The overall 5-year survival rate of children suffering from liver cancer was still unfavourable. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: survival rate, childhood, liver cancer, Taiwan, cancer registry
Eur J Cancer, Vol. 34, No. 13, pp. 2064–2067, 1998

INTRODUCTION

HEPATOBLASTOMA (HB) AND hepatocellular carcinoma (HCC) are the two commonest types of childhood liver cancer. Hepatitis B virus (HBV) can cause HCC and prevention of HBV infection can decrease the incidence of HCC [1]. In an HBV non-endemic area, childhood HB is more common than HCC [2], whereas in an HBV endemic area, childhood HCC is more common than HB [3]. The number of male cases is higher than female cases for both diseases [2, 3]. Because the affected cells are of different types, the prognosis for HCC is worse than for HB.

Studies of survival and distribution of children suffering from liver cancer especially HCC, are scarce. Hsu and colleagues described 42 children between 4 and 15 years of age suffering from HCC in Taiwan [4], but as they found no children younger than 4 years, they were unable to determine the distribution of HCC among children less than 4 years of age. However, in the U.S.A., Exelby and associates described a distribution of HCC among children with a peak before the age of 4 years [2].

To study the actual distribution and survival rate of childhood liver cancer, we needed a sufficiently large number of childhood patients. The Taiwan cancer registry was opened in 1979. Since then it has covered a sufficiently large population (20 million) and has been in existence long enough to have registered more than a handful of childhood liver cancer cases necessary for the proposed study.

Correspondence to Y.-C. Ko.
Received 2 Apr. 1998; revised 24 Jun. 1998; accepted 14 Jul. 1998.

MATERIALS AND METHODS

The National Taiwan Cancer Registry was opened in 1979, and is a population-based registry. The cancer registry-trained personnel review all discharge notes and all data concerning patients' primary diagnosis of cancer. Notification of deaths from cancer at hospitals housing at least 30 beds are forwarded to the National Health Department of Taiwan on a voluntary basis. Almost all such hospitals participate in the scheme (more than 142 hospitals). Cancer is diagnosed either clinically or histopathologically. Clinical diagnosis usually involves symptoms and signs, biochemistry, serum alpha fetoprotein, hepatic sonography, technetium and gallium scan, or hepatic angiography. The histopathological diagnosis is made from biopsy, surgical resection, or autopsies. Upon arrival at the National Health Department of Taiwan, the data are first checked for accuracy and completeness. If they are inaccurate they are returned to the sender for correction, otherwise they are entered into computer files and checked again to avoid duplication. All validated data are kept on computer files in the National Health Department of Taiwan. We estimated that the registry covered approximately 50% of adult liver cancer and 60% of childhood liver cancer in 1979, but in recent years this estimate has risen to approximately 95% of adult and childhood liver cancer.

We searched the Taiwanese cancer registry from 1979 to 1992 and identified 377 patients aged 0–15 years who were suffering from liver cancer coded as 155 according to the International Classification of Diseases. None of the 377 patients was diagnosed by autopsy. 181 (48%) patients were clinically and 196 (52%) were histopathologically diagnosed. The characteristics of the 196 histopathologically proven liver cancer patients included 122 cases of HCC (62%) and 43 (22%) HB. We analysed the 122 HCC and 43 HB data to determine their distribution according to age and sex. The ratio of gender was tested by binomial probabilities performed with the SAS statistic software.

At the inception of the cancer registry in 1979, some data, such as identification numbers and birth dates, were available. It was not until 1988 that a database was kept that was reliable in all respects. Therefore, we collected data concerning liver cancer in 0–16 year old children for the period between 1988 and 1992. We found 115 cases of liver cancer, coded as 155 according to the International Classification of Diseases, 6 of which lacked identification numbers and birth dates, leaving 109 cases to be followed up (some of these cases, those under 16 years of age, were included in the 377 cases mentioned above). With the help of identification numbers and birth dates we linked our cases to the 1988–1994 National Deaths Registry of Taiwan kept by the Taiwanese National Department of Health. The latest follow-up data were up to the end of 1994. The duration of follow-up was between 2 and 7 years. Of the 109 cases, both identification number and birth date were available for 56 cases and birth date only for 53 cases, who therefore had to be matched to the deaths registry by cause of death and area of residence together. We used actuarial life tables to calculate the 5-year survival rate.

Table 1. *Five-year survival rate of* 109 *childhood liver cancer cases between* 1988 *and* 1992

	Period (5-year) survival (%)				
	1	2	3	4	5
All liver cancer ($n = 109$)	32	23	21	20	19
Diagnosis					
Pathological diagnosis ($n = 49$)	47	37	28	28	28
Hepatocellular carcinoma ($n = 28$)	32	25	17	17	17
Hepatoblastoma ($n = 17$)	76	47	47	47	47
Others ($n = 4$)	–	–	–	–	–
Clinical diagnosis ($n = 60$)	20	15	15	13	11

RESULTS

The age and sex distributions of the 122 histopathologically proven HCC patients from 1979 to 1992 are presented in Figure 1. Their age distribution was described by a rising curve with a peak at 1 year of age, then a trough at 4 years of age and rising again up to the age of 15 years. Boys (83) outnumbered girls (39) with a ratio of 2.1:1. However, there were 10 boys and 13 girls in the group younger than 4 years of age, although this trend was not significant ($P > 0.05$). Beyond the age of 4 years, boys (73) outnumbered girls (26) with a ratio of 2.8:1.

The age distribution of 43 histopathologically proven HB patients is presented in Figure 2. Eighty-four per cent ($n = 36$) of the 43 histopathologically proven HB patients were under the age of 5 years. Again boys (32) outnumbered girls (11) with a ratio of 2.9:1. Between 1988 and 1992, of the 109 childhood liver cancer cases, 49 cases were diagnosed histopathologically, with 28 cases of HCC, 17 HB and 4 others. 60 cases were diagnosed clinically. The 5-year survival rates are listed for all 109 patients in Table 1. Nineteen per cent of patients survived for longer than 5 years after diagnosis, as did 28% of histopathologically and 11% of clinically diagnosed cases. The 5-year survival rate among the 28 HCC cases was 17% and among the 17 HB cases was 47%.

Figure 1. Age distribution of hepatocellular carcinoma in children from 1979 to 1992.

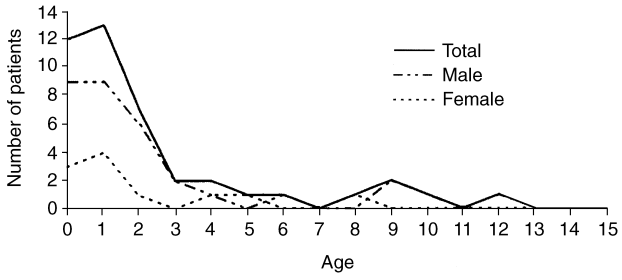

Figure 2. Age distribution of hepatoblastoma in children from 1979 to 1992.

Table 2. Studies of liver cancer 5-year survival rate

First author [ref.]	Year	Number	Resectable rate (%)	5-year survival rate (%)	Follow-up (years)
Population-based					
Present	1988–1992	HB:17		47	2–7
		HCC:28		17	2–7
		Liver Cancer:109*		19	2–7
Exelby [2]	1965–1974	HB:129	60	35	2–10
		HCC:98	33	13	2–10
Miller [16]	1973–1987	HB:53		58.5	5
Mott [17]	1977–1994	HB†		32–73	3
Ajiki [18]	1975–1984	HB:30		36	5
Stiller [19]	1971–1985	HB:120		8–40	5
Kaatsch [20]	1980–1992	Liver cancer:174‡		47	5
Hospital-based					
Chen [3]	1976–1985	HB:10	60	40	>1
		HCC:30	10	7	1–4.7
Wu [7]	1974–1985	HCC:20		0	1
Ni [9]	1964–1989	HCC:71§	9.8	4	5–7.5
Lack [10]	1924–1981	HCC:27	15	7	0.5–12
Haas [11]	1973–1984	HB:196	33	MST: 19 months	
		HCC:28	21	MST: 13 months	
		HCC:14	14	MST: 7 months	
Tagge [12]	1980–1990	HB:21		67	2.4±2.6
		HCC:21		29	2.4±2.6
Leuschner [13]	1972–1988	HCC:11		18	5
Lack [14]	1924–1981	HB:54	61	24	1.3–21
Stringer [15]	1981–1993	HB:41	34	68	0.1–12.2
Gururangan [21]	1981–1090	HB:7		72	1.3–8

*There were 28 HCC, 17 HB, 4 other types, and 60 clinically diagnosed patients. †Patient number was not mentioned. ‡Among them 80% were HB and 20% were HCC. §Among them 43 were HCC and 28 were clinically diagnosed. HCC, hepatocellular carcinoma; HB, hepatoblastoma; MST, mean survival time.

DISCUSSION

There are two characteristics of the age and sex distribution of childhood HCC. The first is the peculiar shape of the age distribution; a peak at 1 year, a trough at 4 years followed by a steady incline up to 15 years. A second characteristic is the predominance of boys, with a ratio of at least 2:1, after the age of 4 years. Our findings concerning HCC distribution according to age differed from those of Hsu and colleagues [4] and Exelby and associates [2]. Studying 4–15 year old children, Hsu and colleagues reported an age peak at 7–9 years and another at 12–15 years, compared with the straight inclining curve of ours. Hsu and colleagues may not have studied a sufficiently large number of patients and did not cover the age range below 4 years. Exelby and associates also reported two age peaks, one at under 4 years of age and another at 12–15 years of age. Their first peak coincides with ours and their second peak may be associated with the fact that their study took place in an HBV non-endemic area and their population up to the age of 12 years was not exposed to sufficient risks for the development of HCC.

The notion that the incubation period from HBV infection to clinically demonstrable HCC is more than 20 years is no longer true [5]. Many studies have found HBV to be correlated with childhood HCC. Shimoda and colleagues described a 6 year old boy suffering from HCC associated with HBsAg [5]. Beasley and associates reported an HBsAg carrier who developed HCC 7 years after perinatal infection [6]. A study of Hsu and colleagues showed that all the 42 HCC patients in their population sample were chronically infected with HBV [4], as were all of the 20 children (1 was only 8 months old) with HCC reported by Wu and colleagues [7]. Our previous study which showed that hepatitis B vaccination can reduce the incidence of HCC among 0–9 years old also supports the idea that HBV can cause childhood HCC [1]. Thus, we think that HBV is a major aetiological factor of HCC beyond the age of 4 years.

Newborns can be infected with HBV by their mothers and become chronically infected early in life [8]. How long it takes after that to develop HCC is unknown. Our epidemiological findings indicate the HCC distribution among children is different before and after 4 years of age. Further studies should be carried out to determine the association between HBV and children younger than 4 years of age. If positive HBsAg occurs among HCC children under 4 years of age at the same rate as in the general population, then HBV cannot be considered the major aetiological factor in children younger than 4 years old. However, if positive HBsAg occurs among HCC children under 4 years of age at a higher rate than in the general population, then HBV could be considered the major aetiological factor in all children.

Table 1 shows that the survival rate was 17% for the 28 HCC cases, 47% for the 17 HB cases and 11% for the 60 clinically diagnosed liver cancer cases, so it is likely that most of the clinically diagnosed cases were HCC patients.

A number of studies of liver cancer are summarised in Table 2. The resectable rate of HCC varies between 10 and 30% [2, 3, 9–11] and accordingly their 5-year survival rates range between 0 and 29% [2, 3, 7, 9, 10, 12, 13]. The current treatment for advanced unresectable tumour involves chemotherapy initially, followed by surgery or liver transplanta-

tion. The 5-year survival rate following such treatment is still only 29% [12]. The resectable rate of HB ranges between 3 and 60% [2, 3, 11, 14, 15] and consequently the 5-year survival rate in the case of HB varies between 8 and 73 [2, 3, 12, 14–21]. Surgery is still the most common treatment.

In conclusion, our epidemiological findings indicate that the HCC distribution among children is different according to age and, to some extent, sex, and the overall 5-year survival rate of children suffering from liver cancer in our study was still unfavourable (19%).

1. Lee CL, Ko YC. Hepatitis B vaccination and hepatocellular carcinoma in Taiwan. *Pediatrics* 1997, **99**, 351–353.
2. Exelby PR, Filler RM, Grosfeld JL. Liver tumors in children in particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatrics Surgical Section Survey, 1974. *J Pediatr Surg* 1975, **10**, 329–337.
3. Chen WJ, Lee JC, Hung WT. Primary malignant tumor of liver in infants and children in Taiwan. *J Pediatr Surg* 1988, **23**, 457–461.
4. Hsu HC, Wu MZ, Chang MH, Su IJ, Chen DS. Childhood hepatocellular carcinoma develops exclusively in hepatitis B surface antigen carriers in three decades in Taiwan: report of 51 cases strongly associated with rapid development of liver cirrhosis. *J Hepatology* 1987, **5**, 260–267.
5. Shimoda T, Uchida T, Miyata H, *et al.* A 6-year-old boy having hepatocellular carcinoma associated with hepatitis B surface antigenemia. *Am J Clin Pathol* 1980, **74**, 827–841.
6. Beasley RP, Shiao IS, Wu TC, Hwang LY. Hepatoma in an HBsAg carrier—seven years after perinatal infection. *J Pediatr* 1982, **101**, 83–84.
7. Wu TC, Tong MJ, Hwang B, Lee SD, Hu MM. Primary hepatocellular carcinoma and hepatitis B infection during childhood. *Hepatology* 1987, 7, 46–48.
8. Stevens CE, Beasley RP, Tsui JJ, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. *N Engl J Med* 1975, **292**, 771–774.
9. Ni YH, Chang MH, Hsu HY, *et al.* Hepatocellular carcinoma in childhood: clinical manifestation and prognosis. *Cancer* 1991, **68**, 1737–1741.
10. Lack EE, Neave C, Vawter GF. Hepatocellular carcinoma: review of 32 cases in childhood and adolescence. *Cancer* 1983, **52**, 1510–1515.
11. Haas JE, Muczynski KA, Krailo M, *et al.* Histopathology and prognosis in childhood hepatoblastoma and hepatocarcinoma. *Cancer* 1989, **64**, 1082–1095.
12. Tagge EP, Tagge DU, Reyes J, *et al.* Resection, including transplantation, for hepatoblastoma and hepatocellular carcinoma: impact on survival. *J Pediatr Surg* 1992, **27**, 292–297.
13. Leuschner I, Harms D, Schmidt D. The association of carcinoma in childhood with hepatitis B virus infection. *Cancer* 1988, **62**, 2363–2369.
14. Lack EE, Neave C, Vawter GF. Hepatoblastoma: a clinical and pathologic study of 54 cases. *Am J Surg Pathol* 1982, **6**, 693–705.
15. Stringer MD, Hennayake S, Howard ER, *et al.* Improved outcome for children with hepatoblastoma. *Brit J Surg* 1995, **82**, 386–391.
16. Miller RW, Young JL, Novakovic B. Childhood cancer. *Cancer* 1994, **75**, 395–405.
17. Mott MG, Mann JR, Stiller CA. The United Kingdom Children's Cancer Study Group—the first 20 years of growth and development. *Eur J Cancer* 1997, **33**, 1448–1452.
18. Ajiki W, Hanai A, Tsukuma H, Hiyama T, Fujimoto I. Survival rate of childhood cancer patients in Osaka, Japan, 1975–1984. *Jpn J Cancer* 1995, **86**, 13–20.
19. Stiller CA, Bunch KJ. Trends in survival for childhood cancer in Britain diagnosed 1971–85. *Br J Cancer* 1990, **62**, 806–815.
20. Kaatsch P, Haaf G, Michaelis J. Childhood malignancies in Germany—methods and results of a nationwide registry. *Eur J Cancer* 1995, **31A**, 993–999.
21. Gururangan S, O'Meara A, Macmahon C, *et al.* Primary hepatic tumours in children: a 26-year review. *J Surg Oncol* 1992, **50**, 30–36.