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Survival of children with liver tumours in Europe 1978–1989

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Abstract

Hepatic tumours are rare in childhood. Within the frame of the EUROCARE II study, a total of 328 liver tumours in patients aged 0–14 years were reported during the period 1978–1989. The childhood cancer registries in UK and Germany contributed approximately a third of the cases each. Hepatoblastoma accounted for 71% of cases. The 5-year survival was 36% 95% confidence interval (CI) 28–46%, with no significant difference between the genders. Patients aged 10–14 years did worse, especially boys. Survival improved significantly during the study period. Survival in hepatocellular carcinoma was lower, 20% (95% CI 6–52%), and showed no improvement during the study period. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Hepatic tumours; Childhood cancer; Hepatoblastoma; Hepatocellular cancer; Survival study

1. Introduction

Primary malignant tumours of the liver are uncommon in childhood, with a relative frequency of 0.8–2.5% of childhood tumours [1]. Two main types can be clearly defined: hepatoblastoma and hepatocellular carcinoma.

Hepatoblastoma accounts for between 60 and 85% of all hepatic tumours, and is the most common type of liver tumour in children aged 0–4 years. Most cases appear to be sporadic, and the incidence throughout the world is fairly constant at 0.5–1.5 cases per million children [2,3]. Hepatoblastoma is an embryonic tumour containing hepatic epithelial parenchyma and, based on the epithelial components, four major histological subtypes can be identified. The liver parenchyma surrounding the tumour is usually normal. Interesting genetic findings are emerging [4,5].

Hepatocellular carcinoma is frequently associated with cirrhosis or other pre-existing parenchymal liver disorder, and the association of hepatitis B and C infection has been well documented [6–8]. Consequently, south-east Asia is a high prevalence area with an incidence of 2.1 cases per million in comparison to 0.2 per million in England and Wales [2,3]. The age at onset is higher than for hepatoblastoma — usually 10–14 years — and the incidence continues to rise in adolescence and adulthood.

The aim of the present analysis was to assess the survival of children with hepatoblastoma and hepatocellular carcinoma in Europe and search for variations over time and between different registries.

2. Patients and methods

During the period 1978–1989, 328 cases of hepatic tumours in the age group 0–14 years were reported to the EUROCARE II study by the participating registries [9]. The majority of cases were reported by the two childhood cancer registries of UK ($n=111$, 34%) and Germany ($n=115$, 35%). Hepatoblastoma accounted for 234 cases (71%), hepatocellular carcinoma for 90 (27%), and 4 cases (1%) were of an unspecified type (Table 1). These latter cases are not dealt with further.

Analyses were carried out separately for hepatoblastoma and hepatocellular carcinoma. Since the number of cases in each country was small, the material was further analysed only by gender and age group for all

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Table 1
Number of cases by morphological type and participating country 1978–1989[a]

	Hepatoblastoma *n* (%)	Hepatocellular carcinoma *n* (%)	Unspecified *n* (%)	Total *n* (%)
Northern Europe				
Iceland	–	–	–	–
Finland	13 (6)	4 (4)	1 (25)	18 (5)
Sweden[b]	1 (0.4)	3 (3)	–	4 (1)
Denmark	12 (5)	3 (3)	–	15 (5)
UK				
Scotland	6 (3)	6 (7)	–	12 (4)
England	83 (35)	28 (31)	–	111 (34)
Western and Central Europe				
The Netherlands[b]	2 (1)	1 (1)	1 (25)	4 (1)
Germany	86 (37)	29 (32)	–	115 (35)
Austria[b]	–	–	–	–
Switzerland[b]	–	–	–	–
France*	–	4 (4)	1 (25)	5 (2)
Southern Europe				
Spain[b]	–	–	–	–
Italy[b]	10 (4)	7 (8)	1 (25)	18 (5)
Eastern Europe				
Estonia	4 (2)	2 (2)	–	6 (2)
Poland[b]	1 (0.4)	–	–	1 (0.3)
Slovakia	16 (7)	3 (3)	–	19 (6)
Slovenia	–	–	–	–
Europe	234 (100)	90 (100)	4 (100)	328 (100)

[a] Source: EUROCARE II study.
[b] <20% of population covered.

countries together and for the entire time period. However, since the UK and German childhood cancer registries contributed approximately a third of all cases each, a comparison of survival was attempted between these two registries, Europe as a whole and the SEER data from the United States [10].

Survival is given as crude observed survival rate, computed by the actuarial method [11], and stratified by age and gender. European survival estimates are given as the weighted average of crude survival rates from each participating country, with weights based on the corresponding proportion of people aged 0–14 years [12].

For the analysis of time trends in survival for hepatoblastoma, a Cox regression model was applied to data from registries with at least 12 reported cases. The variates included in the model were gender, age at diagnosis, registry and time period.

Table 2
Number of cases by gender and age group, Europe 1978–1989[a]

	Age group, years				
	<1 *n* (%)	1–4 *n* (%)	5–9 *n* (%)	10–14 *n* (%)	Σ *n* (%)
Hepatoblastoma	89 (38)	119 (51)	13 (6)	13 (6)	234 (100)
Boys	46	71	4	7	128
Girls	43	48	9	6	106
Hepatocellular carcinoma	6 (7)	17 (19)	27 (30)	40 (44)	90 (100)
Boys	4	11	13	24	52
Girls	2	6	14	16	38
Unspecified type	1 (25)	1 (25)	2 (50)	–	4 (100)
Boys	1	1	1	–	3
Girls	–	–	1	–	1

[a] Source: EUROCARE II study.

3. Results

3.1. Hepatoblastoma

A total of 234 cases, 128 boys (55%) and 106 girls (45%) were reported during 1978–1989. The mean age at diagnosis was approximately 2 years; 89 (38%) cases occurred before 1 year of age, and 119 (51%) in the age group 1–4 years (Table 2). 90% of the cases were microscopically verified.

The overall 1-year survival of all cases estimated from the weighted European pool was 48% (95% confidence interval (CI) 39–57%), 3-year survival 37% (95% CI 29–47%), and 5-year survival 36% (95% CI 28–46%)

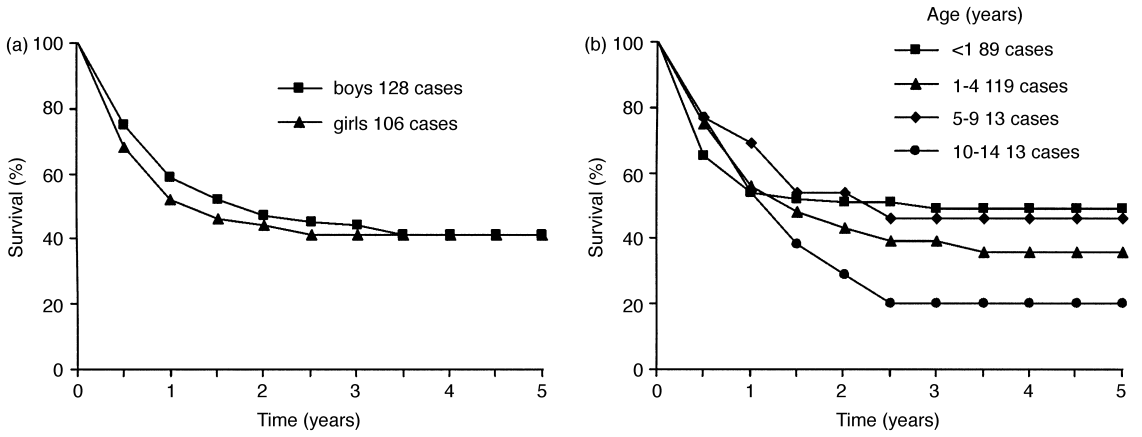

Fig. 1. Observed survival of patients with hepatoblastoma 1978–1989, from the EUROCARE II study. Unweighted European pool. (a) Survival by gender; (b) Survival by age group.

(Table 3a). There was no significant difference in survival between the genders, considering both the unweighted (Fig. 1a) and the weighted European pool (Table 3a). Survival was distinctly lower in the oldest age group (Fig. 1b), and especially marked for boys (Table 3a). The unweighted pool showed slightly higher survival rates than the weighted one, due to a few Italian cases with lower survival, especially for boys.

A significant increase in survival over time was observed: the hazard ratio (HR) for 1982–1985 being 0.57 (95% CI 0.36–0.91) and for 1986–1989 0.40 (95% CI 0.23–0.61) with the period 1978–1981 as a reference.

3.2. Hepatocellular carcinoma

During the same period, 90 cases of hepatocellular cancer, 52 boys (58%) and 38 girls (42%) were reported. The mean age at diagnosis was approximately 8 years with 27 (30%) cases in the age group 5–9 years and 40 (44%) in the age group 10–14 years (Table 2). 97% of the cases were verified microscopically.

Survival in hepatocellular carcinoma was generally lower than for hepatoblastoma. The overall 1-year survival of all cases estimated from the weighted European pool was 47% (95% CI 32–63%), 3-year survival 29% (95% CI 16–47%), and 5-year survival 20% (95% CI 6–52%) (Table 3b). The unweighted European pool showed a steep decrease in survival during the first 2 years from diagnosis (data not shown). Survival of girls was higher than for boys (Fig. 2a). The youngest age group (0–4 years) had a better prognosis than the two older age groups (Fig. 2b). No improvement in survival during the study period was observed (data not shown).

3.3. Comparison between registries

In Table 4, the 5-year survival rates for Europe and for the UK and German childhood registries are given, together with survival data from SEER [10]. As can be seen, there is an improvement in survival in the latter part of the study period for hepatoblastoma, but not for hepatocellular carcinoma. In Europe, Germany had a

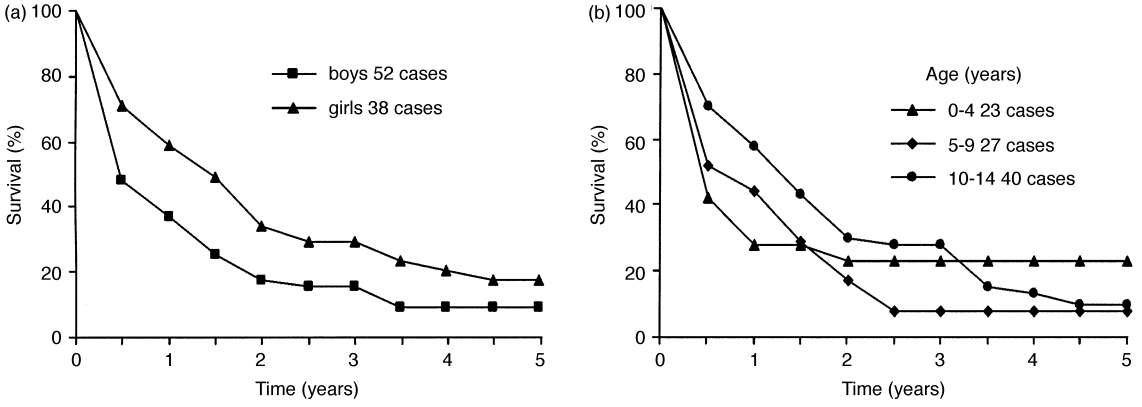

Fig. 2. Observed survival of patients with hepatocellular carcinoma 1978–1989, from the EUROCARE II study. Unweighted European pool. (a) Survival by gender; (b) (b) Survival by age group.

Table 3
Observed survival (Obs%) and corresponding 95% confidence limits (95% CI) by age and gender. European weighted data[a]
a. Hepatoblastoma 1978–1989

	Age group (years)				
	<1 Obs% (95% CI)	1–4 Obs% (95% CI)	5–9 Obs% (95% CI)	10–14 Obs% (95% CI)	ALL Obs% (95% CI)
Boys					
1 year	50 (29–71)	57 (37–75)	70 (24–94)	72 (30–94)	50 (37–63)
2 years	50 (29–71)	47 (27–67)	39 (10–80)	9 (0–74)	39 (26–53)
3 years	48 (27–70)	44 (25–65)	30 (5–78)	0 (0–35)	37 (25–52)
5 years	48 (27–70)	37 (25–51)	30 (5–78)	0 (0–35)	35 (23–50)
Girls					
1 year	56 (40–70)	45 (30–61)	73 (32–94)	38 (6–85)	46 (34–58)
2 years	53 (38–68)	36 (22–53)	52 (21–82)	38 (6–85)	40 (29–53)
3 years	53 (38–68)	34 (20–51)	52 (21–82)	20 (1–82)	38 (27–51)
5 years	54 (38–69)	34 (20–51)	50 (19–81)	4 (0–96)	38 (27–51)
Overall					
1 year	53 (39–66)	51 (38–64)	71 (38–91)	55 (23–84)	48 (39–57)
2 years	51 (38–65)	42 (29–55)	46 (20–73)	24 (5–67)	40 (31–49)
3 years	51 (37–64)	39 (27–53)	41 (16–71)	10 (1–62)	37 (29–47)
5 years	51 (37–65)	35 (26–46)	40 (16–71)	2 (0–93)	36 (28–46)

b. Hepatocellular carcinoma 1978–1989

	Age group (years)			
	0–4 Obs% (95% CI)	5–9 Obs% (95% CI)	10–14 Obs% (95% CI)	ALL Obs% (95% CI)
Boys				
1 year	17 (3–59)	23 (6–59)	62 (30–86)	31 (16–52)
2 years	16 (2–59)	2 (0–98)	44 (19–73)	20 (7–42)
3 years	16 (2–59)	0 (0–23)	44 (19–73)	19 (7–43)
5 years	16 (2–59)	0 (0–23)	30 (5–77)	11 (2–39)
Girls				
1 year	47 (5–93)	40 (17–69)	71 (40–90)	63 (37–83)
2 years	47 (5–93)	12 (1–66)	38 (16–65)	41 (20–66)
3 years	47 (5–93)	8 (0–66)	37 (16–64)	39 (18–65)
5 years	47 (5–93)	8 (0–66)	8 (0–66)	29 (5–75)
Overall				
1 year	32 (6–76)	31 (15–55)	67 (43–84)	47 (32–63)
2 years	31 (6–76)	7 (0–83)	41 (23–62)	30 (17–48)
3 years	31 (6–76)	4 (0–46)	40 (22–61)	29 (16–47)
5 years	31 (6–76)	4 (0–46)	19 (4-58)	20 (6–52)

[a] Source: Eurocare II study.

Table 4
Comparison of selected European hepatic tumour survival data from the EUROCARE II study with survival data from SEER: 5-year survival in per cent

Data set	Time period	Hepatoblastoma	Hepatocellular carcinoma
EUROCARE II European pooled	1978–1989	36	20
EUROCARE II European pooled	1985–1989	51	18
England	1978–1989	34	18
England	1985–1989	43	21
Germany	1978–1989	51	4
Germany	1985–1989	59	8
SEER, USA	1975–1984	51	31
SEER, USA	1985–1994	59	42

high survival rate for hepatoblastoma, but a very low one for hepatocellular carcinoma. The European rates for hepatoblastoma are approximately the same as in the United States, but clearly inferior for hepatocellular carcinoma.

4. Discussion

A rough estimate of incidence of hepatic tumours in Europe based on the present material gives similar levels to those reported in the literature. Geographical variations within Europe could not be assessed due to small numbers. The age distribution was markedly different for the two main types of liver tumours. In the youngest age groups (0–4 years) hepatoblastoma was the dominant type with 89%, while in the oldest age group (10–14 years) hepatocellular carcinoma accounted for 44% of cases. Overall, hepatoblastoma accounted for 71% of all cases, similar to the figure of 79% in the SEER study. This may indirectly indicate that hepatocellular carcinoma secondary to hepatitis B and C is not a predominant issue in Europe, although it has been suggested that hepatitis C virus might be responsible, at least partly, for the increase in liver cancer mortality observed in recent years in Italy and Central Europe [13]. The small number of cases below the age of 5 years could presumably be attributed to predisposing congenital diseases like the Alagille's syndrome (arteriohepatic dysplasia) [14,15]. The male/female ratio was 1.2 for hepatoblastoma and 1.4 for hepatocellular carcinoma. Similar figures were reported in the SEER programme.

The present data does not allow any in-depth analysis of survival. However, some conclusions might be warranted. The survival in hepatocellular carcinoma was very low without any tendency towards improvement during the study period. The survival in Europe was significantly lower than in the United States. This could probably be attributed to the rareness of this tumour in Europe, and lack of an established, common treatment programme. Underlying liver disease might also have a negative influence on survival.

Survival in hepatoblastoma, however, was higher and showed a clear improvement during the study period, the figures in Europe approaching those of the United States. This trend continued in the period 1990–1992 with a hazard rate of 0.29 (95% CI 0.16–0.50) (data not shown). One explanation for this could be the implementation of improved staging procedures and treatment programmes combining surgery and chemotherapy [4,5].

In contrast to other childhood tumours, liver tumours, and particularly hepatocellular carcinoma, carry a bad prognosis and improvements in diagnosis and treatment are still awaited.

5. The EUROCARE Working Group for this study

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