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REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Incidence and long-term outcomes of surgically treated childhood hepatic malignancies in Finland

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Abstract

Aim: To analyse incidence, treatment and outcomes of paediatric liver malignancies in Finland during 1987-2017.

Methods: Medical records and national cancer registry data of 47 children with liver malignancies were reviewed. Survival was calculated with the Kaplan-Meier method.

Results: During follow-up, liver malignancy incidence remained stable at $1.1{:}10^6$. Altogether, 42 patients with hepatoblastoma (n = 24), hepatocellular carcinoma (n = 11) and undifferentiated embryonal sarcoma (n = 7) underwent surgery at median age 4.6 (interquartile range, 2.0-9.6) years and were followed up for 13 (7.0-19) years. Cumulative 5-year survival was 86% for hepatoblastoma, 41% for hepatocellular carcinoma and 67% for undifferentiated embryonal sarcoma. Five-year survival was decreased among hepatoblastoma patients aged ≥ 2.4 years (73% versus 100%, $P = .040$), with PRETreatment EXTent of disease IV (PRETEXT, 60% vs 100%, $P = .004$), and with recurrent disease (67% vs 88%, $P = .029$). Recurrent/residual disease associated with decreased 5-year survival in hepatocellular carcinoma (0% vs 83%, $P = .028$). Survival was similar among 19 transplanted and 23 resected patients. In total, 14 deaths occurred either for the underlying malignancy (n = 8), adverse effects of chemotherapy (n = 5) or unrelated reasons (n = 1).

Conclusion: Outcomes for PRETEXT I-III hepatoblastoma and un-metastasized hepatocellular carcinoma were encouraging. Adverse effects of chemotherapy significantly contributed to mortality.

KEYWORDS
children, hepatoblastoma, hepatocellular carcinoma, liver cancer, liver transplantation

Abbreviations: HB, hepatoblastoma; HCC, hepatocellular carcinoma; PRETEXT, pretreatment extent of disease.

1 | INTRODUCTION

Malignant liver tumours are the third most common abdominal malignancy among children, accounting for approximately 1% of all childhood solid tumours.[1] The most common paediatric liver cancer is hepatoblastoma (HB) with an incidence of 1.5 cases per million per year.[2] Survival rates for HB have improved drastically since introduction of cisplatin-based chemotherapy regimens combined to surgery, and currently approach 70%-90% at 5 years.[3] Hepatocellular carcinoma (HCC) is the second most common malignant liver tumour in children and much less responsive to chemotherapy with lower 5-year survival rates varying between 50%-65%.[4-6] Undifferentiated embryonal sarcoma is a rare liver malignancy sharing features with benign mesenchymal hamartoma. After complete resection, non-metastatic-undifferentiated embryonal sarcoma has an excellent prognosis in children.[7]

Neoadjuvant chemotherapy followed by surgical resection or liver transplantation has been the cornerstone of childhood liver malignancy treatment, although very low-risk tumours can be safely managed with upfront surgery.[2,8] Unfortunately, the majority of patients present with more advanced disease, and approximately, 15% of patients with HB and 20-35% of patients with HCC have a metastasized disease at diagnosis.[2,5,6] While chemotherapy in most cases renders extended HB suitable for resection or liver transplantation, HCC with extrahepatic disease extension usually remains beyond curative treatment. The international multicentre studies ran by cooperative trial groups have increased our understanding on the risk-stratification, optimal chemotherapy protocols and surgical approach for malignant liver tumours.[2,9,10] Histologic subtype, age, preoperative alpha-fetoprotein level, presence of metastases and radiological PRETEXT (PRETreatment EXTent of disease) staging are essential determinants of prognosis.[10]

Although large multicentre trials have improved and systematised management of paediatric liver malignancies, single-centre studies are also noteworthy in providing long-term follow-up data on surgical outcomes, adverse effects of chemotherapy and other consequences of the treatment, including growth impairment.[11,12] The incidence of HB appears to be increasing,[13] and population-based studies are needed to understand the epidemiology of paediatric malignancies. By combining reliable national cancer registry data with the hospital records, we evaluated the incidence, treatment outcomes and long-term follow-up results for childhood hepatic malignancies in all of Finland.

Key notes

- Incidence of paediatric liver malignancies remained stable over a 30-year follow-up.
- Improved treatment strategies are needed for PRETEXT IV hepatoblastoma and metastasized hepatocellular carcinoma.
- Adverse effect of chemotherapy significantly contributed to mortality.

2 | METHODS

2.1 | Patients and data collection

Helsinki University Hospital is a nationwide referral centre for paediatric liver malignancies in all of Finland with paediatric liver transplantation programme since 1987. All Finnish children under age of 18 years at diagnosis with malignant liver tumours between 1987 and 2016 were included. We obtained definitive diagnosis, tumour histology, cancer stage, recurrence and survival data from the nationwide Finnish Cancer Registry, which maintains records of all the cancer patients from every medical facility in Finland. The Finnish Cancer Registry practically covers the population completely and has high accuracy.[14] Retrospectively collected data from the medical patient records included associated diseases, imaging findings, histology reports, alpha-fetoprotein levels, details of oncological and surgical management, adverse effects and surgical complications. In addition, height, weight and liver biochemistry were recorded at last follow-up. Causes of death were confirmed from death certificates obtained from Statistics Finland. Malignancies diagnosed among the first-degree relatives of all patients and age-gender matched controls were recorded from the Finnish Cancer Registry. Normal population controls (five per patient) were collected from the Finnish Population Register Centre.

2.2 | Radiological staging and histology

All patients underwent pretreatment computed tomography (CT) and/or magnetic resonance imaging (MRI). An experienced paediatric radiologist blinded to clinical data reassessed the imaging findings retrospectively according to PRETEXT staging.[10] In addition, patients with HCC were classified by Milan and University of California San Francisco criteria.[15,16] Preoperative imaging was unavailable for one patient. Tumour histology was based on the most representative specimen analysed by experienced liver pathologists. In HB, small cell-undifferentiated tumours were considered to represent high-risk histology, foetal subtypes were defined as low-risk histology and other tumour subtypes as intermediate-risk histology.[2] HCC histology was divided into fibrolamellar and other subtypes.

2.3 | Chemotherapy

As shown in Table 1, patients with HB were mainly treated according to SIOPEL-2 and -4 protocols or by other cisplatin-doxorubicin–based combinations.[17,18] Patients with HCC received cisplatin-doxorubicin–based chemotherapy with or without sorafenib. Patients with undifferentiated embryonal sarcoma were treated by ifosfamide-vincristine–based neoadjuvant chemotherapy.

TABLE 1 Characteristics of surgically treated patients according to liver tumour types

	All patients, n = 42	HB, n = 24	HCC, n = 11	UES, n = 7
Boys, n (%)	20 (48)	13 (54)	5 (46)	2 (29)
Age at diagnosis, years	3.5 (1.6-8.3)	1.7 (0.85-3.3)	11 (8.3-14)	5.2 (2.7-6.6)
AFP at diagnosis, kU/l[a]	49 000 (440-180 000)	110 000 (59 000-370 000)	3000 (250-32 000)	1.0 (1.0-64)
AFP at time of primary surgery, kU/l[b]	150 (9-2100)	130 (17-1000)	270 (3-2400)	1.0 (1.0-1.0)
PRETEXT, n (%)[c]				
I	1 (2.3)	0 (-)	1 (9.1)	0 (-)
II	20 (48)	9 (38)	7 (64)	4 (57)
III	11 (26)	7 (29)	2 (18)	2 (29)
IV	9 (21)	8 (33)	1 (9.1)	0 (-)
Extrahepatic disease at diagnosis, n (%)	14 (33)	7 (29)	4 (36)	2 (29)
Distant metastases	8 (19)	3 (13)	3 (27)	1 (14)
Neoadjuvant chemotherapy				
Cisplatin-doxorubicin-based combinations	30 (71)	23 (96)	7 (64)	0 (-)
Cisplatin-doxorubicin-sorafenib	3 (7.1)	0 (-)	3 (27)	0 (-)
Ifosfamide-vincristine-based combinations	6 (14)	0 (-)	0 (-)	6 (86)
Doxorubicin-vincristine	1 (2.3)	0 (-)	0 (-)	1 (14)
No chemotherapy	2 (4.8)	1 (4.2)	1 (9.1)	0 (-)
Definitive surgical management, n (%)				
Resection	23 (55)	10 (42)	6 (55)	7 (100)
LT	13 (31)	9 (37)	4 (36)	0
Rescue LT	6 (14)	5 (21)	1 (9.1)	0

Abbreviations: AFP, alpha-fetoprotein; HB, hepatoblastoma; HCC, hepatocellular carcinoma; LT, liver transplantation; UES, undefined embryonal sarcoma.
[a]AFP at diagnosis missing for nine patients.
[b]AFP at time of surgery missing for eight patients.
[c]PRETEXT stage missing for one patient.

2.4 | Surgical treatment

Primary liver resections were mostly anatomical. Patients deemed unsuitable for curative resection due to local extension, central tumour location or vascular invasion were evaluated as liver transplantation candidates. Unlike lung metastases in HB resolving after surgical resection or chemotherapy, any extrahepatic HCC was considered as a contraindication for liver transplantation. Rescue liver transplantation was considered in case of local recurrence or residual disease after primary resection when no distant metastases were observed. Grafts for liver transplantation were harvested from deceased donors. Immunosuppression after liver transplantation consisted of cyclosporine, azathioprine and low-dose methylprednisolone. During the last decade, major liver resections were performed in cooperation with adult liver/transplant surgeons, who also performed harvesting and reductions of liver grafts.

2.5 | Statistical methods

Continuous data are expressed as medians with interquartile ranges and categorical data as frequencies unless otherwise stated. Differences between groups were assessed with the chi-square or Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. The incidence of malignant paediatric liver tumours in Finland was estimated by relating the number of diagnosed patients to the number of children at risk (aged ≤ 18 years) over the same time period.[19] Incidence rate was expressed as the number of new cases/person years at risk over 5-year time periods.[20] Linear regression was used to analyse the observed change in incidence rate over follow-up time. The cumulative overall survival and disease-free survival rates were defined with Kaplan-Meier survival analyses, and the log-rank test was used to analyse differences between subgroups. Patients who received rescue liver transplantation were analysed in the liver transplantation group unless otherwise

TABLE 2 Comparison of HB and HCC patients managed with liver transplantation or liver resection

	HB, n = 24		HCC, n = 11	
	Transplantation, n = 14	Resection, n = 10	Transplantation, n = 5	Resection, n = 6
Age at diagnosis, years	2.1 (1.5-4.1)	1.0 (0.36-2.1)	11 (8.8-13)	11 (8.3-13)
AFP at diagnosis, kU/l[a]	360 000 (100 000-1 200 000)[b]	59 000 (14 000-180 000)[b]	9200 (2600-32 000)	670 (33-46 000)
PRETEXT, n (%)				
I	0 (-)[b]	0 (-)[b]	1 (20)[b]	0 (-)[b]
II	2 (14)	7 (70)	1 (20)	6 (100)
III	4 (29)	3 (30)	2 (40)	0 (-)
IV	8 (57)	0 (-)	1 (20)	0 (-)
Extrahepatic disease at diagnosis, n (%)	5 (36)	2 (20)	0 (-)	4 (67)
Local	3 (21)	1 [10]	0 (-)	1 (17)
Distant metastases	2 (14)	1 (10)	0 (-)	3 (50)
Age at surgery, years	3.9 (2.0-6.7)[b]	1.2 (0.69-2.4)[b]	12 (9.3-14)	12 (8.8-14)
Time from diagnosis to definitive surgery, months	6.8 (5.0-13)[b]	2.4 (1.3-3.9)[b]	7.4 (5.9-7.6)	5.0 (4.7-5.7)
Follow-up time after surgery, years	8.5 (4.3-17)	6.5 (2.7-14)	10 (1.7-15)	2.6 (0.39-3.6)
Palliative resection	-	0 (-)	-	4 (67)
Residual disease after definitive surgery, n (%)				
Local	0 (-)	0 (-)	0 (-)	2 (33)
Distal	0 (-)	0 (-)	0 (-)	1 (17)
Local and distal	0 (-)	0 (-)	0 (-)	1 (17)
Recurrent disease after definitive surgery, n (%)				
Local	0 (-)	0 (-)	0 (-)	0 (-)
Distal	3 (20)	0 (-)	1 (20)	0 (-)
Alive at last follow-up, n (%)	9 (64)	10 (100)	4 (80)	1 (17)

Note: *P*-values from the Mann-Whitney *U* test, Fisher exact test, or Chi-square test are reported.
Abbreviations: AFP, alpha-fetoprotein; HB, hepatoblastoma; HCC, hepatocellular carcinoma; LT, liver transplantation.
[a]AFP missing for eight patients (HB, n = 5; HCC, n = 3).
[b]*P*-value < .05 for the difference between resection and transplantation subgroups.

stated. A two-sided *P*-value of <.05 was considered statistically significant. Data analysis was performed using SPSS Statistics version 24.0 (IBM Corp, New York, USA).

2.6 | Ethics

The study protocol was approved by the Helsinki University Hospital's ethical committee as well as by the National Institute of Health and Welfare.

3 | RESULTS

3.1 | Epidemiology of childhood liver malignancies in Finland

Out of the 47 malignant liver tumours diagnosed in 47 patients during the study period, 27 (57%) were HB, 13 (28%) HCC and 7 (15%) undifferentiated embryonal sarcoma. Their incidence showed no significant change over time (Figure S1). Median incidence rate of all liver malignancies as well as HB was $1.1{:}10^6$ and $0.66{:}10^6$ during the whole follow-up period while $1.3{:}10^6$ and $0.66{:}10^6$ during the latest 5-year time period, respectively (Figure S1). The occurrence of malignancies among the first-degree relatives of the patients showed no difference when compared with cancer incidence in first-degree relatives of age-gender matched controls (4.6% vs 4.3%, *P* = .850).

3.2 | Patient characteristics

Four patients with metastatic disease (HB, n = 3; HCC, n = 1) received chemotherapy and died without surgery. In addition, one patient was deemed inoperable due to large extrahepatically extended HCC with vascular invasion and extensive portal vein thrombosis. Including the unoperated patients, the cumulative overall 5-year

TABLE 3 Postoperative complications and follow-up characteristics of all surgically treated patients

	All patients, n = 42	Transplantation, n = 19	Resection, n = 23
Postoperative complications, n(%)	14 (33)	12 (63)[b]	2 (8.7)[b]
Relaparotomy for bowel obstruction/strangulation	2 (4.8)	1 (5.2)	1 (4.3)
Vascular complications	4 (10)	4 (21)	0 (-)
Biliary complications	3 (7.1)	3 (16)	0 (-)
Intra-abdominal infection	3 (7.1)	3 (16)	0 (-)
Gastrointestinal bleeding	2 (4.8)	1 (5.2)	1 (4.3)
Age at last follow- up (years)	13 (7.0-19)	15 (9.0-27)[b]	12 (6.2-15)[b]
Alive and disease-free at last follow-up, n (%)	28 (67)	13 (68)	15 (65)
Growth at last follow-up			
Height (z-score)	-0.45 (-1.0-1.0)	-1.0 (-2.0-0.50)	0.20 (-0.70-1.4)
Weight-for-height (%)	12 (-3.0-29)	27 (-6.0-40)	5.0 (0.0-18)
BMI (for patients aged > 18 years, n = 6)	19 (15-24)	16 (14-21)	28 (21-35)
Disturbed growth[a], n (%)	4 (10)	4 (21)[b]	0 (-)[b]
Liver biochemistry at last follow-up			
AFP, kU/l	2.0 (1.7-4.0)	3.0 (2.0-4.0)	2.0 (1.0-3.0)
Bilirubin, µmol/l	7.0 (6.0-17)	14 (7.0-23)	7.0 (6.0-10)
ALT, U/l	23 (17-42)	34 (19-41)	23 (16-48)
Adverse effects, n (%)	16 (38)	10 (53)[b]	6 (26)[b]
Transplant rejection	5 (12)	5 (26)	0 (-)
Sensorineural hearing loss	2 (4.8)	0 (-)	2 (8.7)
Neuropathy	1 (2.4)	0 (-)	1 (4.3)
Neutropenia	1 (2.4)	1 (5.2)	0 (-)
Cardiomyopathy	3 (7.1)	2 (11)	1 (4.3)
ALL	1 (2.4)	0 (-)	1 (4.3)
AML	2 (4.8)	1 (5.2)	1 (4.3)
Osteoporosis	1 (2.4)	1 (5.2)	0 (-)

Note: Continuous data given as median with interquartile ranges.
Abbreviations: AFP, alpha-fetoprotein; ALL, acute lymphoblastic leukaemia; ALT, alanine transaminase; AML, acute myeloid leukaemia.
[a]Disturbed growth defined as height < -2 z-scores, weight-for-height < -20% or BMI < 18.
[b]$P < .05$ for the difference between resection and LT subgroups.

survival was 80% (standard error 8.2%) for HB and 34% (standard error 14%) for HCC. Altogether, 42 patients underwent surgical management for their malignancy and were included in further analyses (Table 1).

Prematurity, familial adenomatous polyposis and possible neonatal hemochromatosis, according to earlier accepted diagnostic criteria, were associated disease states among five, two and one patient with HB, respectively. One patient with chronic intrahepatic cholestasis leading cirrhosis and two with possible neonatal hemochromatosis had developed HCC. Of patients with HB, eight out of 24 (33%) presented with PRETEXT IV disease, and apart from longer delay from diagnosis to definitive surgery (3.9 vs 9.1 months, $P = .006$) and higher alpha-fetoprotein levels at presentation (400 000 vs 66 000 kU/L, $P = .030$), their baseline characteristics were similar to other patients. Extrahepatic disease was present at diagnosis in four patients with HCC (36%) as well as in seven patients with HB (29%), of whom one had PRETEXT I, four PRETEXT III and two PRETEXT IV disease (Tables 1 and 2). Pulmonary metastases were found in three patients with HB (13%), of whom two had PRETEXT III and one PRETEXT IV disease. Lung metastases were treated with chemotherapy in two patients and the remaining patient with resection. None of the patients with HCC fulfilled the University of California of San Francisco or the Milan criteria.[19,20] Apart from one patient with HB (PRETEXT II) who underwent upfront surgery and one patient with HCC managed with preoperative

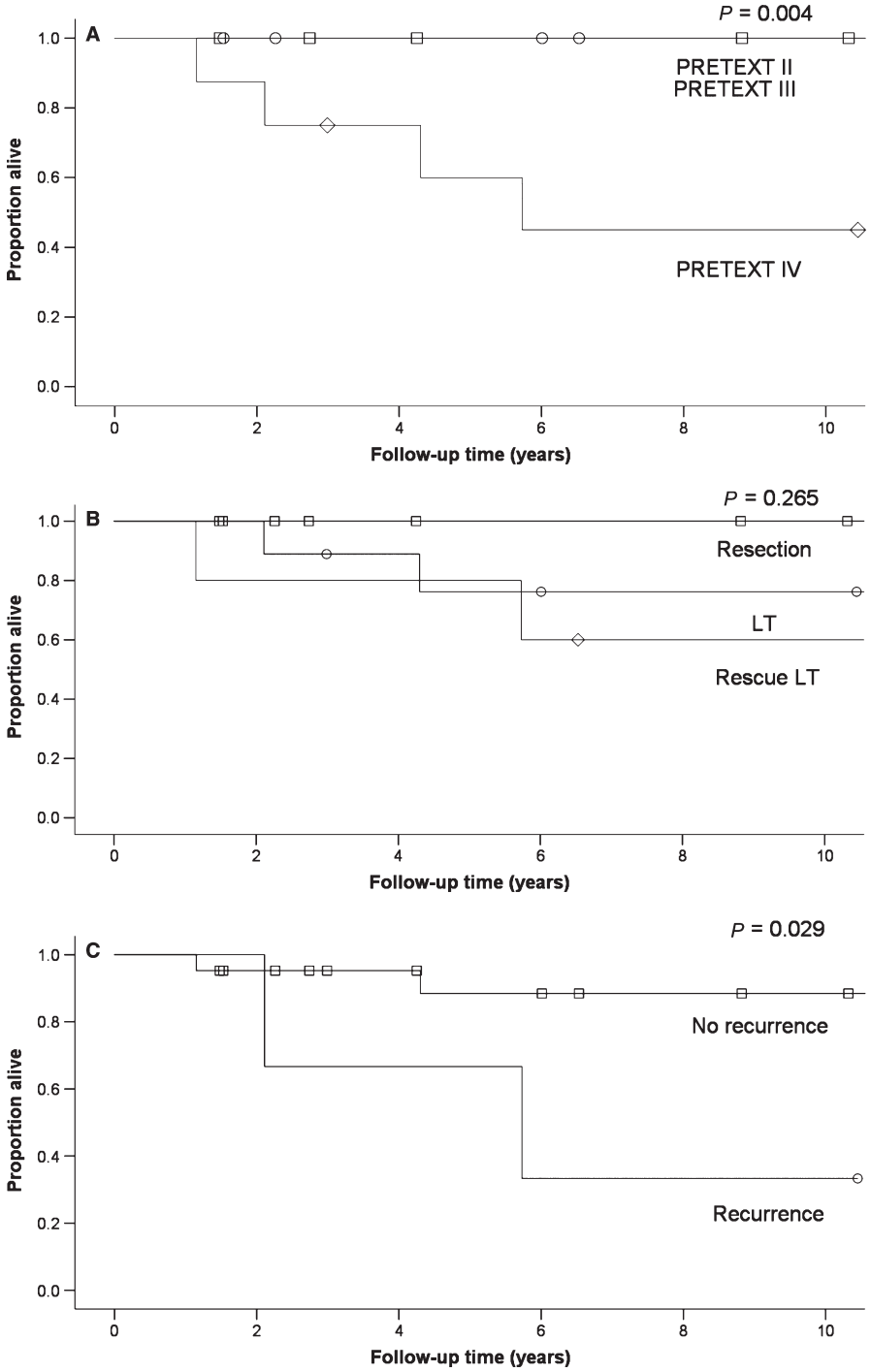

FIGURE 1 The cumulative survival of surgically treated hepatoblastoma patients according to PRETEXT stage, type of surgery and recurrence. LT, liver transplantation. *P*-values from the log-rank test are reported

transarterial chemoembolization, all others received neoadjuvant chemotherapy (Table 1).

3.3 | Surgical management

Primary resections included 11 right hepatic lobectomies, five extended right hepatic lobectomies, two left hepatic lobectomies, one extended left lobectomy and one left lateral segmentectomy (left trisegmentectomy). Patients with HB and HCC underwent liver transplantation or resection with relatively similar frequencies, while all patients with undifferentiated embryonal sarcoma were managed with liver resection (Table 2). Patients who underwent liver transplantation had a significantly longer delay from diagnosis to definitive surgery (Table 2). Six patients underwent rescue liver transplantation 6.0 (4.8-11) months after primary tumour resection (Table S1). Baseline characteristics, postoperative complications and recurrence rates were comparable after primary and rescue liver transplantation (p = ns for all). Surgical complications were more common after liver transplantation than resection (Table 3). Vascular complications occurred in four patients, two of whom had a thrombosis of the hepatic artery while two a portal vein stenosis (Table 3). One retransplantation was performed due to arterial thrombosis.

TABLE 4 Univariate analysis of 5-year Kaplan-Meier overall survival of surgically treated hepatoblastoma patients after liver malignancy diagnosis

	HB patients (n = 24)					
Univariate	Patients (n)	5-year survival, %, mean (SE)	*P*-value	Patients (n)	5-year disease-free survival, %, mean (SE)	*P*-value
Management before 2005						
Yes	11	91 (9.0)	.817	11	79 (13)	.683
No	13	76 (16)		13	65 (18)	
Age at diagnosis[a,b]						
<High-risk age	21	88 (8.0)	.090	21	81 (10)	.290
≥High-risk age	3	67 (27)		3	33 (27)	
Age at surgery[c]						
<2.4 years	12	100 (-)	.040	12	76 (15)	.121
≥2.4 years	12	73 (13)		12	56 (15)	
PRETEXT						
I	0	-	.004	0	-	<.001
II	9	100 (-)		9	100 (-)	
III	7	100 (-)		7	100 (-)	
IV	8	60 (18)		8	31 (18)	
Histology[d]						
Low risk	9	76 (15)	.460	9	76 (15)	.926
Intermediate risk	11	100 (-)		11	63 (21)	
High risk	3	67 (27)		3	67 (27)	
Vascular invasion						
Yes	17	80 (11)	.490	17	58 (14)	.327
No	7	100 (-)		7	80 (18)	
Extrahepatic disease at diagnosis						
Yes	7	100 (-)	.162	7	80 (18)	.573
No	17	80 (12)		17	70 (13)	
Risk level[a]						
Very low	0	-	.552	0	-	.126
Low	2	100 (-)		2	100 (-)	
Intermediate	10	83 (15)		10	83 (15)	
High	11	81 (12)		11	56 (17)	
Surgical management						
LT	9	76 (15)	.265	9	65 (17)	.067
Rescue LT	5	80 (18)		5	38 (29)	
Resection	10	100 (-)		10	100 (-)	
Delay from diagnosis to definitive surgery[e]						
<4.9 months	12	100 (-)	.054	12	88 (11)	.096
≥4.9 months	12	74 (13)		12	61 (15)	
Any surgical complications						
Yes	6	83 (15)	.184	6	67 (19)	.886
No	18	85 (10)		18	76 (13)	
Recurrent/residual disease after surgery						
Yes	3	67 (27)	.029	3	0 (-)	<.001
No	21	88 (8.0)		21	87 (9.0)	

Note: P-values from the log-rank test are reported.

Abbreviations: AFP, alpha-fetoprotein; HB, hepatoblastoma; LT, liver transplantation; SE, standard error; SCU, small cell undifferentiated.

[a]Meyers RL, Maibach R, Hiyama E, et al. Risk-stratified staging in paediatric hepatoblastoma: a unified analysis from the Children's Hepatic Tumors International Collaboration. Lancet Oncol 2017;18(1):122-131.

[b]High-risk age at diagnosis according to PRETEXT group (>3 years for PRETEXT IV and > 8 years for PRETEXT I-III).

[c]Median age at surgery 2.4 (1.7-4.9) years.

[d]Low risk defined as foetal histology, high-risk as small cell undifferentiated, and intermediate as other histology.

[e]Median delay from diagnosis to surgery 4.9 (2.7-8.9) months.

3.4 | Outcomes of hepatoblastoma

Cumulative overall 5-year survival for operated patients with HB was 86% (standard error 7.8%) and 5-year disease-free survival 73% (standard error 11%). All patients with PRETEXT II and III survived, whereas the cumulative 5-year survival for PRETEXT IV was 60% (Figure 1). Five out of the 14 transplanted patients with HB had undergone rescue liver transplantation either because of residual disease or recurrence after resection (Table S1). Three patients with HB, all with PRETEXT IV, developed distant recurrence after liver transplantation and had a lower 5-year survival than patients without recurrent disease (Table 4, Figure 1). Recurrent HB metastases were managed with chemotherapy in one patient, resection in one patient or by both in one patient. Disease recurrence was successfully managed in both patients with familial adenomatous polyposis who are alive 17 and 25 years after liver transplantation. Causes of death were recurrence in two patients, leukaemia in one patient, septic infection in one patient and suicide in one patient (age 19 years). PRETEXT IV disease, age over 2.4 years at surgery, and recurrence associated with decreased survival, while patients with a shorter delay from diagnosis to definitive surgery tended to survive longer (Table 4).

3.5 | Outcomes of hepatocellular carcinoma

Five-year overall survival for operated patients with HCC was 41% (standard error 16%). The only factor predicting decreased survival for HCC was recurrent or residual disease (0% versus 83%, standard error 15%, $P = .028$), whereas other patient characteristics such as histology, PRETEXT stage and age were unrelated with survival (Figure 2). Four patients with disseminated HCC underwent a planned palliative resection. The patient with PRETEXT stage I HCC and underlying cirrhosis due to neonatal hepatitis underwent a primary liver transplantation. Residual extrahepatic disease in patients who had undergone palliative liver resection was managed with chemotherapy in three patients and redo liver resection in one patient, while recurrent HCC after liver transplantation in one patient was managed with chemotherapy. However, none of the patients with recurrent/residual disease survived. In addition, one patient with HCC died of cardiomyopathy after successful resection.

3.6 | Outcomes of embryonal carcinoma

Seven patients with undifferentiated embryonal sarcoma presented with PRETEXT stage II or III disease. Of them, two had extrahepatic disease at diagnosis and all were managed with liver resection at median age of 5.6 years (Table 1). Both cumulative overall survival and disease-free survival were 67% (standard error 19%) at 5 years. One patient developed pulmonary recurrence and eventually died despite lung resection. Two other patients with undifferentiated embryonal sarcoma died of leukaemia disease-free, diagnosed 1.1 and 7.1 years after successful liver resection.

3.7 | Follow-up patient characteristics

Overall, by the end of the follow-up at median age of 12.6 years, 28/42 patients (67%) were alive and disease-free (Table 3). Out of the 14 patients who died during follow-up, eight died of recurrent or residual primary liver malignancy, three of leukaemia, one of cardiomyopathy, one of septic infection and one as disease-free of suicide (age 19 years). At the latest follow-up visit, four patients (9.5%) had disturbed growth (defined as height < -2.0 z-scores, weight-for-height < -20%, or BMI < 18), of whom two had familial adenomatous polyposis, three had been successfully treated for recurrence and one later died of disease recurrence (Table 3). Other adverse effects of chemotherapy, including sensorineural hearing loss, neuropathy, neutropenia and cardiomyopathy, were detected in seven patients (17%). One patient (2.4%) diagnosed with chronic rejection had elevated ALT and bilirubin levels.

4 | DISCUSSION

This study entailed all patients treated in one country from an era (1987-2016) when liver transplantation was available and represents one of the longest follow-ups on paediatric liver malignancies.[21,22] Centralised management of paediatric liver cancer and use of accurate national registry data enabled reliable calculation of incidence, recurrence and survival rates as well as a detailed, long-term and complete patient follow-up. Our findings show encouraging long-term survival for HB excluding patients with PRETEXT IV disease, which associated with complications of chemotherapy, recurrence and decreased survival in the long-term.

The incidence of HB is increasing in the United States and although an increase was also observed in Europe between 1970s and 1990s, no similar trend exists in more recent epidemiological studies.[13,23,24] Accordingly, our results demonstrate steady incidence rates of $1.1{:}10^6$ for paediatric liver malignancies and $0.66{:}10^6$ for HB over a 30-year time period, corresponding a slightly lower incidence for HB while higher for HCC when compared with previously reported European numbers.[24] Cancer incidence among the first-degree relatives of liver malignancy patients was similar to controls, supporting the concept that most paediatric liver malignancies are explained by other factors than inherited conditions.[1] Whether the three patients with possible neonatal hemochromatosis, according to earlier accepted diagnostic criteria, who developed liver malignancy actually had gestational alloimmune liver disease remains unclear. Although young age at diagnosis associated with improved outcomes for HB, possibly due to the small sample size, the previously suggested age or alpha-fetoprotein cut-offs were insignificant among our patients.[2]

The observed 5-year overall survival of 86% for HB in the present study was similar to most recent reports.[3] However, while both overall and disease-free long-term survival was 100% for patients presenting with lower PRETEXT stages, the survival outcomes for PRETEXT IV HB were markedly inferior although comparable to

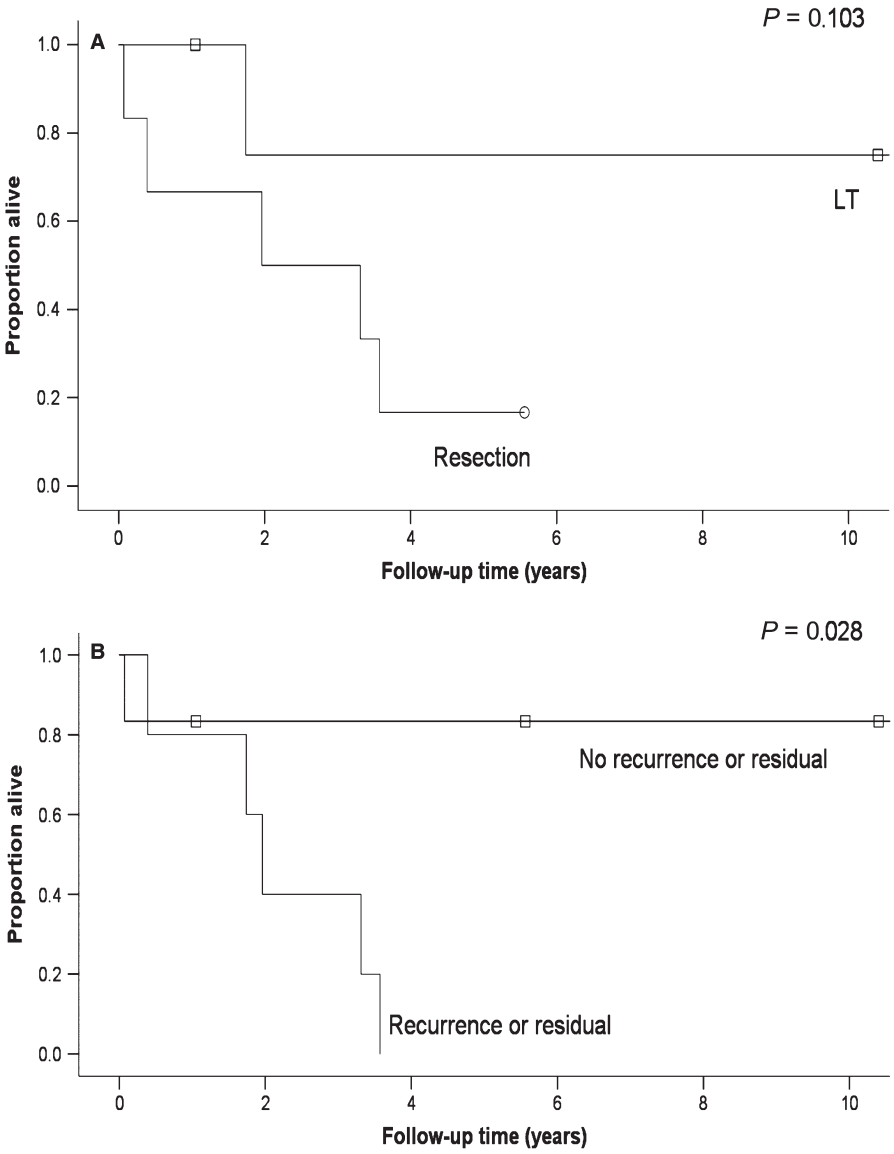

FIGURE 2 The cumulative survival of surgically treated hepatocellular carcinoma patients according to type of surgery, and recurrence/residual disease. LT, liver transplantation. *P*-values from the log-rank test are reported

larger contemporary reports.[2,22] As many as one-third of our patients with HB presented with either PRETEXT IV or extrahepatic disease, clearly exceeding the proportions of such high-risk patients in most large HB series.[2,3,9] One factor possibly contributing to suboptimal outcomes for PRETEXT IV HB may be the longer delay from diagnosis to definitive surgery compared with lower PRETEXT stages, leading to increased exposure to chemotherapy[22]; however, this was not a statistically significant predictor of survival. The median delay of 7 months from diagnosis to liver transplantation was similar than previously reported in the United States; however, considerably better HB survival has been reported after very short transplant waiting list times.[22] In Finland, no living-donor liver transplantation is currently performed, influencing transplant list waiting times and cumulative chemotherapy exposure. The need for rescue liver transplantation in five patients with HB also contributed to increased chemotherapy exposure.

Although the 41% 5-year survival for HCC is dismal, it compares favourably to larger studies including similar proportions of patients with metastatic disease.[5,6] Likely due to the small number of patients with HCC, no statistically significant predictors of survival apart from recurrent and residual disease were identified. Nevertheless, only one liver transplantation recipient with HCC experienced recurrence and died, supporting the benefit of liver transplantation for children with inoperable HCC without extrahepatic involvement even when the Milan or University of California of San Francisco criteria are not fulfilled.[25] Metastatic HCC, instead, remains a major challenge and was the main cause of mortality also among most of our patients with HCC. While regular screening of children with inherited liver diseases may help to detect HCC in time, sporadic liver malignancies presenting with vague, nonspecific symptoms are seldom detected in early stage.[4,5] Promisingly, novel treatments such as sorafenib and transarterial chemoembolization may both improve tumour resectability and decrease postoperative recurrence rates.[26] Such management options emerged at the end of our 30-year follow-up, and larger cohorts are needed to evaluate their benefit in paediatric HCC.

Our overall postoperative complication rate of 33% was comparable with previous studies.[21] Any vascular complications, occurring in one-fifth of our patients after liver transplantation, have been previously reported to affect up to 25%-40% of paediatric liver transplantation recipients and to be more common in patients transplanted for malignant than benign conditions.[21,22] In the present series, only one patient was retransplanted due to arterial thrombosis leading to biliary necrosis. Despite the low rate of severe operative complications, over one-third of all deceased patients and half of deceased patients with HB died of adverse effects related to chemotherapy or immunosuppression. Secondary cancer, possibly induced by the use of alkylating agents, also contributes to our modest 5-year survival of 67% for undifferentiated embryonal sarcoma.[7] Since toxicity of cisplatin, anthracyclines and alkylating agents is dose-dependent, lower overall exposure to chemotherapy could reduce their severe side effects.[27-29] Long-term survival could increase by improving patient selection for primary liver transplantation and the timely availability of optimal transplants thereby reducing the need for preoperative chemotherapy[22]. The latest rescue liver transplantation for residual malignancy in our centre was performed more than a decade ago.

The main limitations of this study included our inability to record reliably the exact cumulative dosage of chemotherapy, the low number of patients due to rarity of childhood liver malignancies and the various chemotherapy protocols and surgical approaches applied during the long study period. During the last decade, PRETEXT IV patients have undergone primary LT instead of tumour resection.

5 | CONCLUSIONS

Apart from PRETEXT IV disease, the national outcomes for surgically treated HB are encouraging. Outcomes of HCC and undifferentiated embryonal sarcoma are largely determined by the presence of extrahepatic disease. Diagnosing paediatric liver malignancies at earlier stage as well as reducing exposure to chemotherapy appears challenging but attainable means to improve survival.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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