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Pretreatment prognostic factors for children with hepatoblastoma — results from the International Society of Paediatric Oncology (SIOP) Study SIOPEL 1

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Abstract

The aim of this study was to investigate the prognostic significance of pretreatment patient and tumour characteristics for overall (OS) and event-free (EFS) survival in 154 children affected by hepatoblastoma (HB) in the first prospective liver tumour study run by the International Society of Paediatric Oncology. The pretreatment characteristics studied were age, α-fetoprotein, platelet count, histology; from radiology: intrahepatic tumour extension (PRETEXT), lung metastases, enlarged hilar lymph nodes, vena cava or extrahepatic vena porta tumour extension and tumour focality. Five-year OS was 75% (95% confidence interval (CI) 68–82%) and EFS 66% (95% CI 59–74%). Both were univariately associated with PRETEXT and the presence of metastases. Additionally tumour focality and enlargement of hilar lymph nodes at diagnosis were univariately associated with EFS. In multivariate analysis, PRETEXT was the only predictor of OS; PRETEXT and metastases were predictors of EFS. There is a need to investigate further these factors to confirm their validity.

Keywords: Hepatoblastoma; Prognostic factors; Overall survival; Liver tumours; Childhood

1. Introduction

Hepatoblastoma (HB) is one of the rarest solid tumours in children accounting for not more than 1% of all paediatric malignancies [1]. In the early 1970s, evidence that HB is a chemoresponsive tumour began to emerge, but overall survival was of the order of 20–30%. The introduction of cisplatin in the therapeutic armamentarium of childhood HB seems to have dramatically improved the prognosis of children affected by this tumour and survival has improved to 60–70% at 3 years [2–4]. There is now a need to identify the important prognostic factors in this disease so that treatment of paediatric HB can be tailored to the individual patient. Several groups have already attempted to identify prognostic factors mainly using small datasets and factors measured post-surgery, rather than at original diagnosis. This report examines the relationship between a few patient and tumour factors measured pretreatment and survival. In particular we have investigated whether the extent of disease pretreatment as assessed by the system adopted for the study can be used to predict prognosis. The analysis consists of 154 HB patients entered into the first collaborative study of the Liver Tumour Study Group of the International Society of Paediatric Oncology (SIOPEL 1). The study, reported elsewhere, investigated the role of pre-operative chemotherapy in the treatment of paediatric HB [5].

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2. Patients and methods

The SIOPEL 1 study was open for patient registration between January 1990 and February 1994. Children less than 16 years of age with HB not previously treated were eligible for the study. Biopsy was strongly recommended for all patients entering the study; however, it was not compulsory for those patients with unequivocal findings, i.e. patients aged between 6 months and 3 years, with raised α-fetoprotein (AFP) and a hepatic mass. Of the biopsies performed 80% (97/121) were also centrally reviewed. There was 98% agreement between the original diagnosis and the centrally reviewed diagnosis, thus it was felt appropriate to include the HB cases on original diagnosis in this paper. The study was prospective and non-randomised, based on the use of pre-operative chemotherapy. The intention was to treat all patients with four to six courses of pre-operative chemotherapy followed by resection of their primary tumour where feasible. The aim was for the pre-operative chemotherapy to consist of four courses of cisplatin 80 mg/m^2 administered in continuous infusion over 24 h (preceded and followed by adequate hyper-hydration) followed by doxorubicin (DOXO) 60 mg/m^2 in 48 h continuous infusion (PLADO). Tumour resectability was to be assessed after four courses of PLADO and, if feasible, delayed surgery was to be performed at that time. In case of macro- and microscopically complete resection, two further courses of PLADO were administered. After that, therapy was stopped. The time of delayed surgery and consequently the number of pre-operative courses of PLADO could vary upon the medical team's decision. In any case, no more than six courses of PLADO could be administered to each patient as per protocol guidelines. When the tumour was unresectable after a response to PLADO then liver transplantation was considered.

The process of obtaining informed consent from parents was left to the discretion of individual centres to be performed in accordance with their country's guidelines.

2.1. Required patient information at diagnosis

At diagnosis, information was collected on physical examination, including demographic details and nutritional status, hepatic, renal, cardiac function (echocardiogram measurement of the left ventricular ejection fraction (EF) and shortening fraction (SF)) and serum AFP concentration. Pretreatment assessment of the extent of the primary tumour was by abdominal ultrasound, computer tomography (CT) scan and/or magnetic resonance imaging (MRI). Metastatic spread was assessed by chest X-ray (posterior, anterior and lateral) and/or lung CT scan. Hepatic angiography was optional. Central review of the original radiological findings was carried out. Based on the radiological findings a Pre Treatment Extent of Disease grouping system, PRETEXT, was adopted for the study which aimed to determine tumour extension before any therapeutic intervention and throughout therapy (Fig. 1).

It assessed: (a) the amount and anatomic location of normal liver tissue present, which would indicate whether the tumour could be resected and if so which type of resection could be applied; and (b) whether the tumour extended beyond the liver to veins, extrahepatic tissue or if metastases were present.

In the PRETEXT system the liver according to its surgical anatomy was divided into four sectors, namely an anterior and a posterior sector on the right and a medial and a lateral sector on the left. Thus, based on tumour extension within the liver, four groups were identified as follows: PRETEXT I, three adjoining sectors free (tumour only in one sector); PRETEXT II, two adjoining sectors free (tumour involves two sectors); PRETEXT III, one sector or two non-adjoining sectors free (tumour involves two or three sectors); and PRETEXT IV, no free sector (tumour in all four sectors).

In addition, the presence of extrahepatic tumour extension was expressed as: Hepatic vein (V), presence of hepatic vein involvement; Portal vein (P), presence of portal vein involvement; Extrahepatic (E), presence of extrahepatic direct spread, limited to enlargement of the hilar lymph nodes; and Metastases (M), presence of distant metastases.

2.2. Follow-up evaluation

Patients were to be followed-up monthly for a year, two-monthly for the second year and then three-monthly for the third year.

2.3. Statistical methods

There was a total of 38 deaths and 57 events in the study which meant there was adequate power to reliably investigate only three factors for their correlation with

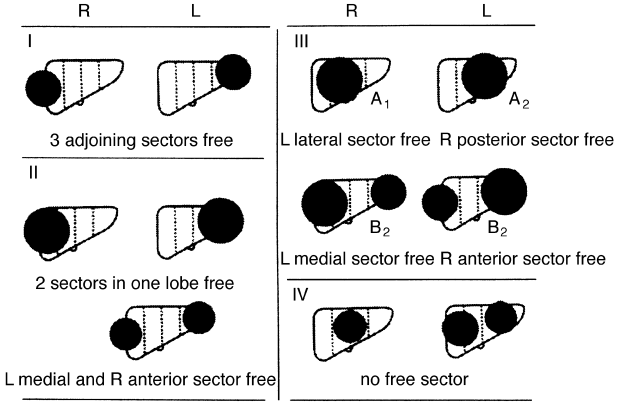


Fig. 1. PRETEXT grouping system.

overall survival (OS), and five factors for their correlation with event-free survival (EFS) [6]. However, 10 factors were investigated for both OS and EFS. This study should therefore be regarded as a hypothesis-generating study which requires confirmation in further studies.

Firstly, correlations between variables to be investigated were examined using Spearman's Rank Correlation Coefficient. None of the variables were correlated with a coefficient of >0.7 and an associated P-value of <0.01 [7].

Variables at diagnosis were then assessed univariately for their association with either OS or EFS. The Kaplan–Meier method was used to estimate the survival curves and the Logrank test was used to assess the prognostic effect of the factors. Ninety-five per cent confidence intervals (CI) were calculated for the survival estimates using Greenwood's method [8]. Where factors were believed to have a linear association with survival the Tarone–Ware test for trend was utilised [9]. Variables at this stage were considered to be statistically correlated with survival at the 10% level of significance.

Variables which were correlated with survival were then considered for further multivariate analysis. The multivariate stepwise Cox Proportional Hazards Model was used to model prognostic factors adjusted for the influence of each other. Both forward and backward selection procedures were used to identify factors for inclusion in the model with a 5% level of significance. The assumption of proportionality within the Cox model was checked by plotting the complementary log plot against log t for the grouped factors. Hazard ratios and their 95% confidence intervals are reported. The hazard ratio is the risk of the event for various values of the variable, e.g. for a binary variable coded 0 — male, 1 — female, a hazard ratio of 1.68 would imply that the risk of an event is 1.68 times greater for females than for males.

OS time was defined as the time interval between date of diagnosis and date of death (death from any cause) or date of last follow-up; losses to follow-up were counted as censored events. EFS was defined as the time interval from date of diagnosis to date when alternative treatment to the study treatment was instigated as a result of failure of study treatment or date of relapse or date of death (any cause) or date of last follow-up, whichever occurred first. Patients lost to follow-up were censored in the analysis. Date of alternative treatment was used as a surrogate for date of progression since date of progression was not routinely or consistently recorded within the study. For the purposes of this analysis data were censored at three years from diagnosis.

13 patients had no pre-operative chemotherapy. Separate analyses were at first undertaken with and without those patients who had received primary surgery and no pre-operative chemotherapy. The two analyses gave very similar results, therefore the results from all patients considered together are presented in this report.

All statistical analyses were performed using SAS software.

3. Results

154 children were entered into the study from 91 centres and 30 countries. Median follow-up was 3.5 years (range 0–6 years). The median duration of follow-up of survivors was 5 years (range 7 months–9 years). The baseline characteristics of patients at diagnosis are summarised in Table 1. The 5-year OS was 75% (95% CI 68–82%) and EFS was 66% (95% CI 59–74%).

Table 1
Patient and tumour characteristics at diagnosis ($n=154$)

Characteristic	n (%)
Sex	
Male	97 (63)
Female	57 (37)
Age (years)	
Median (range)	1 (0–13)
Serum AFP (ng/ml)	
Median (range)	172 714 (2–40 000 000)
Platelet count ($\times 10^9$/l)	
>500	93 (60)
$\leqslant 500$	61 (40)
Pulmonary metastases (chest X-ray or lung CT scan)	
Yes	31 (20)
No	123 (80)
PRETEXT Group	
I	6 (4)
II	52 (34)
III	45 (29)
IV	39 (25)
Missing	12 (8)
Tumour focality	
Solitary	95 (62)
Multifocal	22 (14)
Missing	37 (24)
Presence of enlarged hilar nodes	
Yes	9 (6)
No	110 (71)
Missing	35 (23)
Vascular invasion	
Yes	14 (9)
No	65 (42)
Missing	75 (49)
Histology from central review (biopsy)	
Pure fetal	19 (12)
Other	78 (51)
Missing	57 (37)

CT, computed tomography; AFP, α-fetoprotein.

The following variables, which have been identified in previous studies, were included in our univariate analysis to see, firstly, if they were associated with OS and then, secondly, with EFS: serum AFP concentration at diagnosis, histological subtype and age of the patient at diagnosis [4,10–16]. Age was categorised into three groups: <6 months, 6–48 months and >48 months. Serum AFP was categorised in two ways: firstly as proposed by Ortega and colleagues [4] as <1000, 1000–100 000, $>100\,000$ ng/ml, and then as proposed by Van Tornout and associates [13] and Von Schweinitz and coworkers [14] as <100, 100–1 000 000, $>1\,000\,000$ ng/ml. Histological subtype obtained from the central review of biopsy was categorised as 'pure fetal' or other. Previous papers used subtypes categorised as 'pure fetal' or other based on resection [10,11,15,16]. We have made no attempt to subcategorise our histology further. We have attempted to be consistent with previous studies but recognise the limitations of material available at biopsy and the complexity of diagnosis. There is therefore a need for further *ad hoc* studies of this issue.

Other variables which have previously been shown to be important when measured histologically were investigated using the radiological findings at diagnosis: presence of lung metastases (identified from CT scan or chest X-ray), whether there was vascular invasion (identified from CT scan or ultrasound) and focality of tumour (identified from CT scan or ultrasound) [14–16]. The intrahepatic tumour extension as defined by the PRETEXT grouping of tumour was also investigated to see whether it could be as successful as surgical staging of tumour in identifying prognostic groupings [14,15].

Two further variables, not previously studied, were considered to be potentially clinically important and so were also included in the univariate analysis: whether there was enlargement of the hilar nodes (CT scan abdomen) and platelet count. Platelet count was categorised into two groups to mirror normal or abnormal range values at diagnosis, i.e. $\leqslant 500$ or $>500\times10^9$/l.

Of the ten factors considered univariately for their relationship with OS, two were statistically significant at the 10% level of significance: metastases at diagnosis and intrahepatic PRETEXT grouping at diagnosis. There was a statistically significant linear trend in the relationship between PRETEXT grouping and survival, $\chi^2=11.09$, $P=0.0009$. The results of the univariate analysis are given in Table 2. Since approximately half of the metastases identified at diagnosis were identified on CT only, the OS and EFS curves were compared between those patients identified on CT scan only and those identified by CT and chest X-ray. There was an indication of a difference, although not statistically significant, between the curves: 5-year overall survival for CT scan only was 77% (95% CI 54–99%), whereas for both was 42% (19–66%), EFS for CT only was 38% (12–65%) and for both was 21% (1–40%). However, the number of metastatic patients in this study was small and this will have to be investigated further in future studies.

In the multivariate analysis, both metastases and PRETEXT grouping were included in the model. Only intrahepatic PRETEXT grouping was identified as an independent predictor of OS. The hazard ratio was 2.11 with a 95% confidence interval of 1.2–3.6, P-value $=0.005$, i.e. the risk of death approximately doubles for a PRETEXT group II patient compared with a PRETEXT group I patient, and for a PRETEXT group III patient compared with a PRETEXT group II patient, etc.

The ten factors were also considered univariately for their relationship with EFS. Four variables were statistically significant at the 10% level of significance: lung metastases, PRETEXT grouping, tumour focality and enlargement of the hilar nodes (all variables as assessed

Table 2
Summary of the univariate relationships with overall survival (OS)

Variable	χ^2	Degrees of freedom	P-value	5-year OS	95% confidence interval
PRETEXT grouping	16.17	3	0.001	I — 100%	
				II — 91%	82–100%
				III — 68%	55–82%
				IV — 57%	41–73%
(Test for trend)	11.09	1	0.0009		
Lung metastases	6.8	1	0.01	Yes — 57%	39–75%
				No — 81%	73–88%
Vascular invasion	0.03	1	0.87		
AFP — Ortega categorisation	0.42	2	0.81		
AFP — Van Tornout categorisation	1.01	1	0.31		
Histological subtype (from biopsy)	0.62	1	0.43		
Age	0.14	2	0.9		
Focality of tumour	1.6	1	0.21		
Platelet count	0.6	1	0.44		
Enlargement of hilar nodes	0.05	1	0.82		

AFP, α-fetoprotein.

Table 3
Summary of the univariate relationships with event-free survival (EFS)

Variable	χ^2	Degrees of freedom	*P*-value	5-year EFS	95% confidence interval
PRETEXT grouping	20.5	3	0.0001	I — 100%	
				II — 83%	72–93%
				III — 56%	41–71%
				IV — 46%	31–62%
Lung metastases	31.6	1	0.0001	Yes — 28%	12–44%
				No — 77%	69–85%
Vascular invasion	1.14	1	0.29		
AFP — Ortega categorisation	0.1	2	0.95		
AFP — Van Tornout categorisation	0.11	1	0.73		
Histological subtype (from biopsy)	0.04	1	0.85		
Age	1.5	2	0.48		
Focality of tumour	9.87	1	0.002	Multifocal — 40%	19–61%
				Solitary — 72%	63–81%
Platelet count	0.02	1	0.89		
Enlargement of hilar nodes	9.1	1	0.003	Yes — 33%	0–64%
				No — 74%	66–83%

AFP, α-fetoprotein.

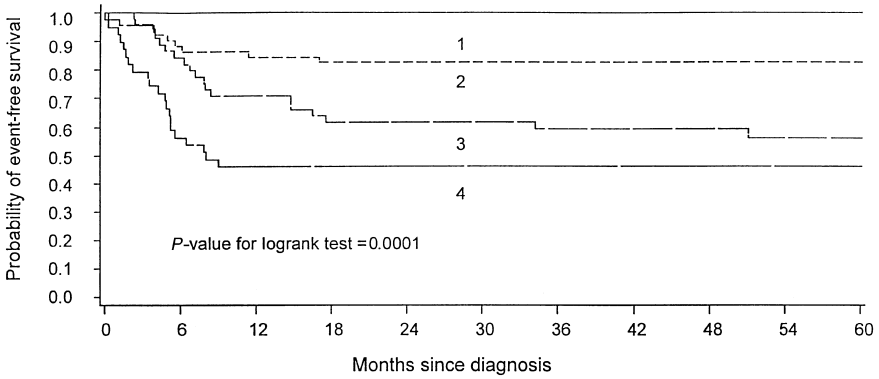
radiologically at diagnosis). There was a statistically significant linear trend in the relationship between PRETEXT grouping and survival, $\chi^2 = 20.5$, $P = 0.0001$. The results of the univariate analysis are given in Table 3.

All four of the univariately statistically significant variables were included in the multivariate analysis. Both PRETEXT grouping and presence of metastases at diagnosis were identified as independent predictors of EFS. The hazard ratios were 1.63 (95% confidence interval of 1.05–2.50), *P*-value = 0.0002 and 0.26 (0.12, 0.52), *P*-value = 0.02, respectively, i.e. the risk of an event is approximately half as much again as more sectors of the liver are involved at diagnosis and is reduced by one-third if the patient does not have lung metastases at diagnosis. The Kaplan–Meier curves for these variables clearly illustrate their relationship with EFS (Figs. 2, 3).

4. Discussion

The SIOPEL 1 Liver Tumour Study has represented, along with other almost concurrent clinical trials conducted in the USA and Germany, an attempt to set the present standard of care for childhood HB [2,3,4,17,18]. Five-year OS and EFS of 75% (95% CI 68–82%) and 66% (95% CI 59–74%), respectively have been achieved in this study.

There have been a few attempts to demonstrate prognostic factors in childhood HB. The major factor identified to date has been the completeness of the surgical resection. Very few have attempted to assess the importance of factors measured pretreatment. The identification of pretreatment tumour characteristics is becoming more important now that an increasing number of study groups are adopting treatment strategies based on pre-



Number at risk

1	6	6	6	6	6	5	5	4	3	3	3
2	52	46	44	43	41	38	34	33	31	27	22
3	45	38	31	27	27	27	25	24	19	18	14
4	39	22	18	18	18	18	17	16	14	14	13

Fig. 2. Event-free survival probability according to PRETEXT grouping at diagnosis. 1–4 represent PRETEXT groups I–IV, respectively.

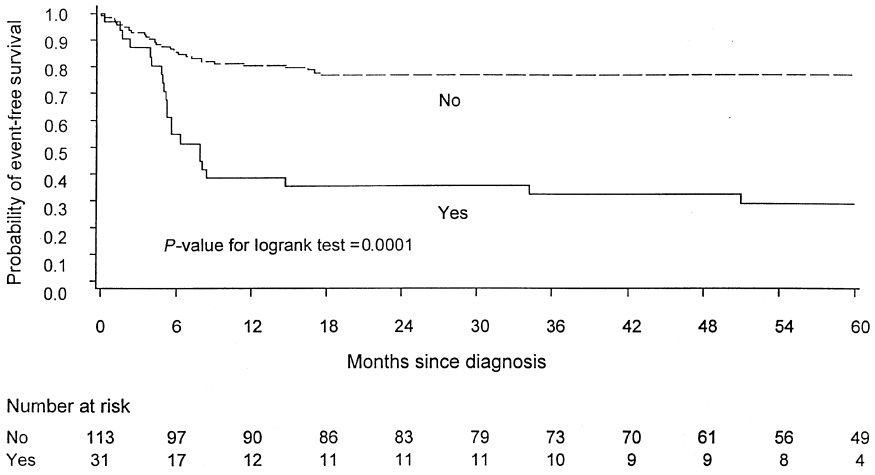


Fig. 3. Event-free survival probability according to presence of metastases at diagnosis.

operative chemotherapy. It is also crucial that a common system to evaluate pretreatment tumour extension is available in order that comparisons of results between studies can be made.

In this study, amongst the ten different variables considered, intrahepatic pretreatment tumour extension as defined by the evaluation system adopted for the study (PRETEXT) has been shown to be an independent prognostic factor both for OS and EFS. The PRETEXT system was mainly introduced to try to predict surgical resectability, however, its prognostic significance does not seem to be simply a matter of prediction of resectability in itself. The PRETEXT categories I, II and III should, in theory, all identify resectable HB and hence be associated with the same survival rates. Our results indicate that instead, the risk of death is approximately half as much again as one moves along PRETEXT categories.

Von Schweinitz and colleagues [15,16] investigated in a retrospective study of childhood HB the prognostic value of the pathological tumour, node and metastases (TNM) staging system proposed by the International Union Against Cancer (UICC) for hepatocellular carcinoma [19]. In the first study, amongst the 22 patient characteristics that were then entered into a multivariate analysis, the pathological primary tumour status emerged as an independent prognostic factor. The heterogeneity of the treatments received by the patients, the small size of the population they studied and the design of the study significantly weaken the validity of this observation. In the second study, they found that post-surgical staging and the conventional TNM system for liver cancer have a high predictive value in contrast to the UICC TNM system. However, these systems as applied are post-treatment tumour staging. The intrahepatic PRETEXT category is the only pretreatment evaluation system ever investigated prospectively in a large cohort of homogeneously treated HB patients. Thus, our data seem to indicate that the PRETEXT system provides a way forward for pretreatment categorisation of childhood HB.

In this study, the presence of lung metastases was also an independent prognostic factor for EFS but not for OS. The negative impact on long-term survival of the presence of lung metastases has been shown in previous studies [14–16]. In the first study, no long-term survivors were reported amongst the 4 metastatic HB patients, whilst in the second study, the OS curve of the 16 children presenting with metastases dropped to less than 20% at 45 months. In the modern cisplatin era the 3-year OS of metastatic patients varies between 0 and 33% [2,3,20]. The reason why lung metastases were not identified as an independent prognostic indicator for OS in our multivariate analysis is unclear. One possible explanation may be that some of the patients presenting with lung disease, despite PLADO failure, have very protracted courses which aggressive multidisciplinary therapeutic approaches may maintain for a long period of time [20]. Consequently, it may be that lung metastases would be identified as significantly associated with OS in a multivariate analysis with longer follow-up.

In our study, it is interesting to note that there was a difference in survival and event-free survival for those patients whose metastases were identified from CT only or CT and chest X-ray. Both sets of patients had similar PRETEXT groupings at diagnosis; however, there were more single metastases in the group identified by CT only. It is difficult to interpret this finding given the small number of patients involved. However, this should be investigated in future studies.

Von Schweinitz and colleagues [14] in a cohort of 37 advanced HB (patients with unresectable disease, macroscopical residuals or metastases) found that patients with AFP values less than 100 ng/ml or higher than 1 000 000 ng/ml had a worse prognosis. In the low AFP group they had 7 patients (including one with rhabdoid and some with undifferentiated features); the other

group included 5 children, all with large HB or metastases. The relevance of this observation deserves further investigation and, particularly for the low or normal AFP group, a better understanding of the possible relationship with potentially unfavourable histological features is warranted. This association with AFP was also found upon further analysis of this study [16]. In addition, Von Tornout and associates [13] has shown that the timing and magnitude of decline of AFP is important.

Von Schweinitz and colleagues [14,16] also identified other histological tumour characteristics as possible prognostic factors such as: tumour growth within the liver (tumour disseminated throughout the liver versus solid mass or several well-defined nodules), hilar lymph node enlargement and tumour invasion of the inferior vena cava, main liver and/or portal veins. It should be noted that there are differences in the definition of lymph node enlargement and tumour invasion in this study and our study and these categorisations need to be carefully defined in future studies. However, in a multivariate analyses the completeness of tumour resection remained the only significant prognostic factor.

There is at least one report claiming that children less than 1 year old have a better outcome than older ones [12]. At least two studies have investigated the existence of unfavourable histological features for childhood HB [10,11], although no consistent results have been produced on this to date. The rare pure fetal HB has been claimed to have an excellent prognosis if the tumour can be completely resected [10]. Single observations have indicated that undifferentiated HB are very poorly chemosensitive tumours capable of aggressive biological and clinical behaviour [21]. It has not been possible to investigate this more thoroughly in our study. The issue of the possible existence of unfavourable histological features for childhood HB is a complex problem that deserves dedicated studies.

In conclusion, in this paper, we have attempted to confirm prognostic associations as found in previous studies, to try and investigate factors which can be used pretreatment and to limit our exploration of potentially new factors to just two factors. Frequently, results from prognostic factor studies are not borne out in further studies and should therefore be treated with caution and scepticism for this reason until confirmatory studies have been carried out. Certainly the previous studies which have looked at factors for childhood HB have had too few events and hence limited power to reliably detect prognostic relationships; continuous variables have been arbitrarily categorised and the same set of patients has been analysed on more than one occasion. In addition, with the exception of Von Schweinitz and colleagues [14,15] and Conran and colleagues [11], previous studies have not considered factors in a multivariate analysis.

In this study we have shown that our pretreatment grouping system, PRETEXT, correlates with prognosis (both OS and EFS) and that the system retains its importance in multivariate analysis. We would propose that the PRETEXT grouping system provides a way forward for pretreatment categorisation of tumour. Metastases at diagnosis has also been confirmed as an indicator of poor EFS.

There is now a need to investigate further these prognostic factors in future studies in order to confirm their validity. This information can then be used to aid in the design of future trials. We are already beginning to use such data in our current SIOPEL research programme.

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