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ORIGINAL REPORT

Predictive Value of the Pretreatment Extent of Disease System in Hepatoblastoma: Results From the International Society of Pediatric Oncology Liver Tumor Study Group SIOPEL-1 Study

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose

Preoperative staging (pretreatment extent of disease [PRETEXT]) was developed for the first prospective liver tumor study by the International Society of Pediatric Oncology (SIOPEL-1 study; preoperative chemotherapy and delayed surgery). Study aims were to analyze the accuracy and interobserver agreement of PRETEXT and to compare the predictive impact of three currently used staging systems.

Patients and Methods

Hepatoblastoma (HB) patients younger than 16 years who underwent surgical resection (128 of 154 patients) were analyzed. The centrally reviewed preoperative staging was compared with postoperative pathology (accuracy) in 91 patients (81%), and the local center staging was compared with the central review (interobserver agreement) in 97 patients (86%), using the agreement beyond change method (weighted κ). The predictive values of the three staging systems were compared in 110 patients (97%) using survival curves and Cox proportional hazard ratio estimates.

Results

Preoperative PRETEXT staging compared with pathology was correct in 51%, overstaged in 37%, and understaged in 12% of patients (weighted κ = 0.44; 95% CI, 0.26 to 0.62). The weighted κ value of the interobserver agreement was 0.76 (95% CI, 0.64 to 0.88). The Children's Cancer Study Group/Pediatric Oncology Group–based staging system showed no predictive value for survival (P = .516), but the tumor-node-metastasis–based system and PRETEXT system showed good predictive values (P = .0021 and P = .0006, respectively). PRETEXT seemed to be superior in the statistical fit.

Conclusion

PRETEXT has moderate accuracy with a tendency to overstage patients, shows good interobserver agreement (reproducibility), shows superior predictive value for survival, offers the opportunity to monitor the effect of preoperative therapy, and can also be applied in patients who have not had operations. For comparability reasons, we recommend that all HB patients included in trials also be staged according to PRETEXT.

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INTRODUCTION

Hepatoblastoma (HB) is the most common malignant liver tumor in children.[1] In recent years, its prognosis has improved dramatically because of combined treatment strategies that used cisplatin-based chemotherapy combined with surgery, as shown in several studies.[2-4] The first prospective study that was launched by the Liver Tumor Study

Group of the International Society of Pediatric Oncology (SIOP), known as SIOPEL-1, combined preoperative cisplatin with doxorubicin (PLADO) followed by surgical resection. All patients were treated with preoperative chemotherapy to reduce the size of the tumor, improve the success of resection, and treat microscopic metastases. This resulted in a 5-year overall survival rate of 75% in SIOPEL-1, and new study protocols to improve these results (SIOPEL-2 and SIOPEL-3) were designed.[5-9]

In the SIOPEL-1 prospective trial, a preoperative surgical staging system, the pretreatment extent of disease (PRETEXT) system, which was based on the anatomy of the liver, was developed and adopted.[10,11] The main difference from other well-known liver tumor staging systems, such as the tumor-node-metastasis system of the International Union Against Cancer and the system used by the Children's Cancer Study Group (CCSG) and the Pediatric Oncology Group (POG),[2,4,12] is that the PRETEXT system was especially developed to compare the efficacy of various chemotherapeutic regimens in HB and to stage the tumor before surgical treatment, whereas the other two systems stage the tumor postoperatively. PRETEXT was used as a relatively objective but noninvasive method to assess tumor extent at diagnosis and subsequent chemotherapy response and to determine the optimal time and type of resection. Its ultimate goal was to ascertain preoperatively whether it would be possible to perform a radical resection.

In 1997, von Schweinitz et al[13] investigated the predictive impact of the different staging systems (mentioned in the previous paragraph) in 72 patients treated in the German Pediatric Liver Tumor Study HB89 and proposed using the tumor-node-metastasis system to compare treatment results in HB. The aims of the SIOPEL-1 study group in this article were to evaluate the accuracy of the PRETEXT staging system against surgery (gold standard), to study the interobserver agreement of PRETEXT, and to compare the predictive values of the different staging systems among patients who underwent delayed surgical resection of their tumor and subsequently followed the SIOPEL-1 protocol.[7]

PATIENTS AND METHODS

PRETEXT Staging System

The PRETEXT system, which is based exclusively on imaging at diagnosis and, thus, before (surgical) therapy, divides the liver into four parts, called sectors. The left lobe of the liver consists of a lateral (Couinaud segments 2 and 3) and medial sector (segment 4), whereas the right lobe is divided into an anterior (segments 5 and 8) and posterior sector (segments 6 and 7).[11,14] Couinaud segment 1 is identical with the caudate lobe and is not included in this division. The tumor is classified into one of the following four PRETEXT categories depending on the number of liver sectors that are free of tumor (Fig 1): PRETEXT I, three adjacent sectors free of tumor; PRETEXT II, two adjacent sectors free of tumor (or one sector in each hemi-liver); PRETEXT III, one sector free of

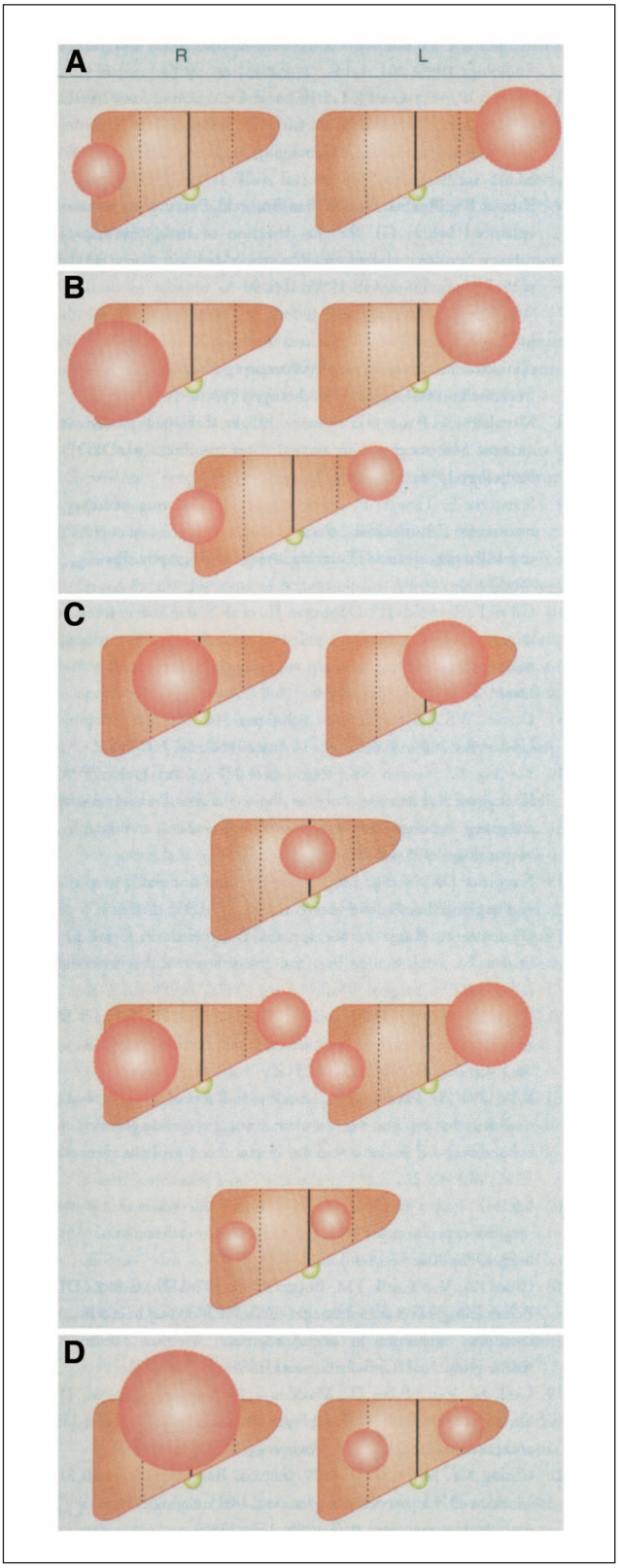

Fig 1. The Liver Tumor Study Group of the International Society of Pediatric Oncology (SIOP) SIOPEL-1 pretreatment extent of disease grouping system. (A) Pretreatment extent of disease (PRETEXT) group I, (B) PRETEXT group II, (C) PRETEXT group III, (D) PRETEXT group IV. R, right; L, left.

tumor (or two sectors in one hemi-liver and one nonadjacent sector in the other hemi-liver); and PRETEXT IV, no tumor-free sectors. Extrahepatic growth is indicated by adding one or more of the following characters: V, vena cava and/or main tributaries (caval attachments); P, portal vein and/or main tributaries (hilar); E, extrahepatic excluding extrahepatic V or P (rare); and M, distant metastases (mostly lungs, otherwise specify). The assessment of the extent of the primary tumor is performed by abdominal ultrasound and computed tomography (CT). Magnetic resonance imaging or hepatic angiography is only performed if thought necessary by the local center. A lung CT scan is indicated to assess metastatic spread only if the chest x-ray is suspect.

Patients were staged according to the PRETEXT system at diagnosis, during neoadjuvant chemotherapy, and before surgery. The original radiologic films were centrally reviewed by one radiologist (C.R.S.). For the comparison study between PRETEXT and pathology, the postchemotherapy PRETEXT taken before surgery was used.

Patients

Between January 1990 and February 1994, patients younger than 16 years old with HB were registered onto the SIOPEL-1 study. See Brown et al[5] and Pritchard et al[6] for a detailed description of study design, data collection, and definitions of event-free survival and overall survival. In short, all patients were treated preoperatively with PLADO after a biopsy had been taken according to the intent-to-treat principle. In case of unequivocal clinical findings, a biopsy was recommended but was mandatory in patients aged less than 6 months and more than 3 years because of the increased prevalence of other tumor types in these age groups. After four courses of PLADO, tumor resectability was assessed by imaging, and definitive surgery was performed if considered feasible. Tumor resection was then followed by two more courses of PLADO. Orthotopic liver transplantation was considered in patients with HB in all four liver sectors but completely confined to the liver, despite a positive response to adequate first-line chemotherapy. Results of orthotopic liver transplantation in SIOPEL-1 will be reported elsewhere. A total of 154 patients from 91 centers in 33 different countries entered onto the study, 128 of whom underwent resection of their primary liver tumor according to protocol guidelines.[7] Of these 128 patients, 15 patients had no central review of their preoperative PRETEXT. Thus, this comparative study focuses on the subset of the remaining 113 patients who all had a centrally reviewed preoperative PRETEXT and who all underwent surgery.

Accuracy and Interobserver Agreement of PRETEXT

To evaluate the accuracy of the PRETEXT system, results from the PRETEXT system taken after chemotherapy and before surgery were compared with results from the pathology report of the operative specimen using agreement beyond change (weighted κ). A weighted κ is a κ calculated with different weights that were given to the disagreements according to the magnitude of the discrepancy. For this purpose, the postoperative staging (gold standard) derived from the pathology report was retrospectively performed by doctors who were unaware of the PRETEXT results (J.M.S. and D.C.A.). The weighted κ was also calculated to evaluate the interobserver agreement by comparing PRETEXT staging results obtained from the local center with those from the central review.

Other Staging Systems

The CCSG/POG staging system and the conventional tumor-node-metastasis system for (adult) liver carcinomas were retrospectively applied to the patients after the pathology report was available. The staging was performed in a blinded fashion, with the PRETEXT staging (at diagnosis) of that tumor being unknown (J.M.S. and D.C.A.). The CCSG/POG system distinguishes the following four disease stages: stage I, complete surgical resection; stage II, microscopic residual disease; stage III, macroscopic residual disease; and stage IV, metastatic spread.[2,4] In the tumor-node-metastasis system, the T status comprises tumor size ($\leq$ or $>$ 2 cm), vascular invasion, lobe involvement, multifocality of tumor nodes, and extrahepatic growth; the N status records involvement of lymph nodes; and the M status records distant metastases.[12,15] The different tumor-node-metastasis system stages are listed in Table 1. We are aware that, in contrast to the PRETEXT staging system, the CCSG/POG staging system and tumor-node-metastasis system are postoperative staging systems that are validated on the surgical results before any other therapeutic intervention and that now they are being applied to patients who have been pretreated with chemotherapy.

Table 1. TNM System for Adult Liver Carcinomas[12,15]

Stage	Group	Description
I	T1N0M0	T1: solitary tumor, $\leq$ 2 cm, without vascular invasion N0: no regional lymph node metastasis M0: no distant metastasis
II	T2N0M0	T2: solitary tumor, $\leq$ 2 cm, with vascular invasion; or multiple tumors, $\leq$ 2 cm, limited to one lobe without vascular invasion; or solitary tumor, $>$ 2 cm, without vascular invasion
IIIA	T3N0M0	T3: solitary tumor, $>$ 2 cm, with vascular invasion; or multiple tumors, $\leq$ 2 cm, limited to one lobe with vascular invasion; or multiple tumors, $>$ 2 cm, limited to one lobe with or without vascular invasion
IIIB	T1N1M0 T2N1M0 T3N1M0	N1: regional lymph node metastasis
IVA	T4 each NM0	T4: multiple tumors in more then one lobe; or ingrowth of tumor(s) in portal or hepatic vein(s); or ingrowth in adjacent organs other than the gallbladder; or perforation of the visceral peritoneum
IVB	Any T any NM1	M1: distant metastasis

Abbreviation: TNM, tumor, node, metastasis.

Comparison and Survival Analysis

The predictive values of the three different staging systems were compared using the Akaike information criterion (AIC) obtained from each of the Cox proportional hazards models. The AIC (−2ln [maximum likelihood] + 2 [number of fitted parameters]) is a descriptive statistic only and not a formal hypothesis test. It provides a useful measure for comparing different models.[16] Subsequent overall survival curves of the different staging systems were obtained with the Kaplan-Meier method and compared within each system with the log-rank test.[17,18] Overall survival was defined as the time interval between the date of diagnosis and the date of death (from any cause) or the date of last follow-up. The level of significance was considered $P < .05$. Statistical procedures were performed with the SAS statistical package version 8.02 (SAS Institute, Cary, NC).

RESULTS

Centrally reviewed preoperative PRETEXT staging was available in all 113 patients. The patient characteristics are listed in Table 2. Median age at diagnosis was 17 months (range, 1 to 155 months), and median follow-up time was 5 years (range, 0 to 99 months). In 89 (79%) of 113 patients, a biopsy was performed. In the remaining 24 patients, the clinical diagnosis of HB was confirmed in the operative specimen. According to the protocol (suspicion on chest x-ray), 87 (77%) of 113 patients had a CT scan of the chest, and 20 patients (18%) had lung metastases at time of diagnosis. The frequency of the centrally reviewed preoperative PRETEXT stages were as follows: group I, 13 patients (12%); group II, 64 patients (57%); group III, 31 patients (27%), and group IV, five patients (4%).

Table 2. Patient Characteristics of 113 Patients With HB Who Entered the SIOPEL-1 Study, Underwent Surgical Resection, and Had a Centrally Reviewed Preoperative PRETEXT Staging

Characteristic	No. of Patients	%
Sex		
Male	70	62
Female	43	38
Age, months		
Median	17	
Range	0-155	
Serum α-fetoprotein, ng/ml		
Median	172,714	
Range	2-40 × 10^6	
Platelet count > 500 × 10^9/L	66	58
Solitary tumor	89	79
Pulmonary metastases, chest x-ray or lung CT scan	20	18
Follow-up time, months		
Median	60	
Range	0-99	
Lost to follow-up	3	—

Abbreviations: HB, hepatoblastoma; SIOPEL, Liver Tumor Study Group of the International Society of Pediatric Oncology; PRETEXT, pretreatment extent of disease; CT, computed tomography.

Accuracy of PRETEXT: Staging Before Surgery Versus Pathologic Specimen

In 91 patients (81%), exact tumor location in the liver could be traced from the pathology report (ie, the gold standard; Fig 2) and could, thus, be compared with the preoperative PRETEXT staging system after central review. In 22 patients, the pathology report was not available. Fifty-one percent of the patients (46 of 91 patients) were staged correctly (ie, tumor found in the sectors predicted by the PRETEXT staging system). In 37% of the patients (34 of 91 patients), the PRETEXT staging was too high (overstaged), compared with the exact tumor localization, whereas in 12% of patients (11 of 91 patients), staging was too low (understaged). A positive resection margin was found in four of these 11 patients, and the other seven children underwent a complete surgical resection. Of the four patients with positive resection margins, none developed a local recurrence, which demonstrated the tumor negative status of the unresected liver segments in all patients.

The cross tabulation of the preoperative (centrally reviewed) and postoperative PRETEXT staging according to the pathology report (ie, the gold standard) is shown in Table 3. The weighted κ value was 0.44 (95% CI, 0.26 to 0.62).

Interobserver Agreement: Original Versus Centrally Staged Preoperative PRETEXT

In 97 patients (86%), original PRETEXT preoperative staging could be compared with the centrally obtained staging. In 16 patients, one or both PRETEXT stagings were missing (Fig 2). There was an interobserver agreement in 79% of the patients (77 of 97 patients; Table 4). The weighted κ, which was calculated by comparing the original and central PRETEXT staging preoperatively of the 97 patients, was 0.76 (95% CI, 0.64 to 0.88); on the basis of this 95% CI, we have a 95% certainty that the κ lies between 0.64 and 0.88 (ie, good agreement). For the 77 patients (68%) in whom the pathologic data were also available, the weighted κ was 0.71 (95% CI, 0.56 to 0.86).

Prognosis According to the Different Staging Systems

Survival analysis according to the different staging systems could be performed in 110 patients (97%). Follow-up data were missing for three patients. Tumor-node-metastasis system–based staging could only be performed in 98 patients (87%) because of missing data. The results according to the different staging systems are listed in Table 5. The 5-year overall survival rates according to the different preoperative PRETEXT groups after central review were 100% for group I, 95% for group II, 93% for group III, and 40% for group IV (Fig 3A). This system revealed a decreasing trend in overall survival related to the different subgroups that seemed to be highly significant ($P = .0006$).

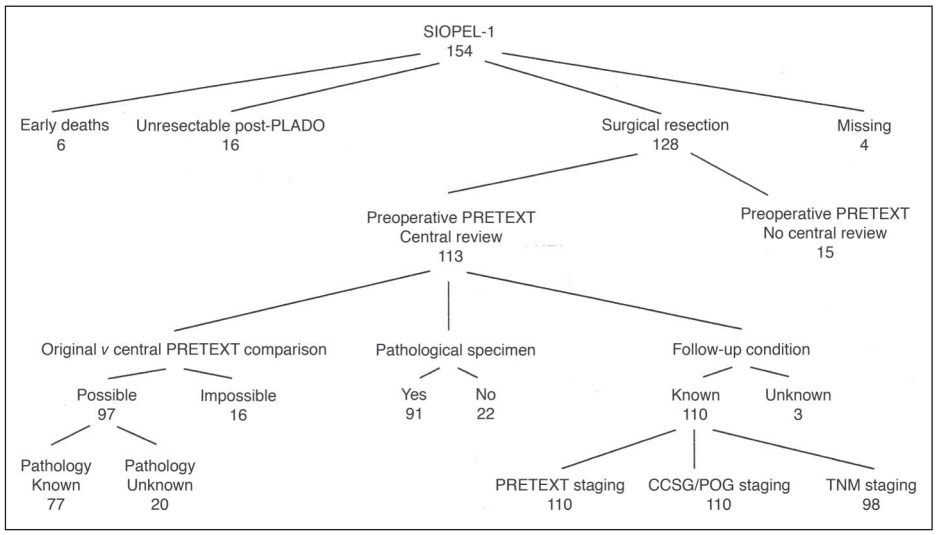

Fig 2. Flow diagram of the 154 patients who were younger than 16 years with hepatoblastoma (HB) and who were registered onto the Liver Tumor Study Group of the International Society of Pediatric Oncology (SIOP) SIOPEL-1 study between January 1990 and February 1994. PLADO, cisplatin and doxorubicin; PRETEXT, pretreatment extent of disease; CCSG/POG, Children's Cancer Study Group/Pediatric Oncology Group; TNM, tumor-node-metastasis.

The 5-year overall survival according to the CCSG/POG-based staging system is presented in Figure 3B. Patients with metastases (stage IV), who had complete surgical resection of their primary tumor (a select group of patients who underwent the exact SIOPEL-1 protocol and who were, therefore, included in this analysis), had the same survival rate (95%) as those patients with complete resection without metastases (stage I; 94%), microscopic residual disease (stage II; 88%), or macroscopic residual disease (stage III; 83%). These differences were not significant ($P = .516$). Note that there was a difference between the absolute figures of CCSG/POG-based staging and true CCSG/POG staging; in the original group of 154 patients, 31 patients who entered onto the trial with lung metastases (CCSG/POG stage IV) showed a 5-year event-free survival rate of 57% and 5-year overall survival rate of 28% (OS), respectively.[19] Finally, the 98 patients who were staged according to the tumor-node-metastasis–based staging system (Fig 3C) showed a 5-year overall survival rate of 95% for stage II patients (stage I did not occur), 57% for stage III patients, and 93% for stage IV patients. Patients with a stage IV tumor who underwent the exact SIOPEL-1 protocol and, therefore, included in this analysis were a select group of patients. The tumor-node-metastasis–based staging system

Table 3. The Preoperative (centrally reviewed) and Postoperative PRETEXT Staging of 91 Patients Who Entered the SIOPEL-1 Study

Preoperative PRETEXT: Central Review	Postoperative PRETEXT: Pathology Report				
	Group I	Group II	Group III	Group IV	Total
Group I					
No.	7	3	0	0	10
%	—	—	—	—	11
Group II					
No.	12	30	8	0	50
%	—	—	—	—	55
Group III					
No.	3	18	7	0	28
%	—	—	—	—	31
Group IV					
No.	0	0	1	2	3
%	—	—	—	—	3
Total					
No.	22	51	16	2	91
%	24	56	18	2	100

NOTE. The pathology report was not available in 22 patients. The weighted κ value is 0.44 (95% CI, 0.26 to 0.62).
Abbreviations: PRETEXT, pretreatment extent of disease; SIOPEL, Liver Tumor Study Group of the International Society of Pediatric Oncology.

Table 4. The Preoperative Original (ie, the staging according to the local center) and Centrally Reviewed PRETEXT Staging of 97 Patients Who Entered the SIOPEL-1 Study

Preoperative PRETEXT: Central Review	Preoperative PRETEXT: Original Staging				
	Group I	Group II	Group III	Group IV	Total
Group I					
No.	6	6	0	0	12
%	—	—	—	—	12
Group II					
No.	2	47	7	0	56
%	—	—	—	—	58
Group III					
No.	1	3	20	1	25
%	—	—	—	—	26
Group IV					
No.	0	0	0	4	4
%	—	—	—	—	4
Total					
No.	9	56	27	5	97
%	9	58	28	5	100

NOTE. In 16 patients, data was missing. The weighted κ value was 0.76 (95% CI, 0.64 to 0.88).
Abbreviations: PRETEXT, pretreatment extent of disease; SIOPEL, Liver Tumor Study Group of the International Society of Pediatric Oncology.

Table 5. PRETEXT Grouping, CCSG/POG Staging, and TNM Staging of the 110 Patients With HB Who Were Treated With Surgical Resection in the SIOPEL-1 Study and Were Centrally Reviewed*

Group	No. of Patients	%	No. of Patients Who Died
Preoperative PRETEXT			
Group I	13	12	0
Group II	63	57	3
Group III	29	26	2
Group IV	5	5	3
Total	110	100	—
CCSG/POG staging			
Stage I	77	70	5
Stage II	8	7	1
Stage III	6	6	1
Stage IV	19	17	1
Total	110	100	—
TNM staging			
Stage I	0	0	
Stage II	63	57	3
Stage III	7	6	3
Stage IV	28	26	2
Missing	12	11	—
Total	110	100	—

Abbreviations: PRETEXT, pretreatment extent of disease; CCSG/POG, Children's Cancer Study Group/Pediatric Oncology Group; TNM, tumor, node, metastasis; HB, hepatoblastoma.
*See also Figure 2.

seemed to be highly significant in relation to overall survival as well ($P = .0021$).

Cox Proportional Hazard Ratios

For each of the three staging systems, a Cox proportional model was obtained, which entered the staging levels as independent variables considering the highest level as reference category. AIC was used for comparison of the three models. The best statistical fit was obtained with the PRETEXT staging system, which revealed the lowest AIC score (67.4), followed by the tumor-node-metastasis–based staging system (67.9) and the CCSG/POG-based staging system (75.3). The higher AIC score of the CCSG/POG-based staging system indicates the weakest statistical fit.

DISCUSSION

In the last decade large international, study protocols for the treatment of children with HB have been developed in the United States, Germany, and Japan and by the SIOPEL group.[3-5,20-22] Currently, overall survival rates lie in the range of 75% to 80%, and event-free survival rates range from 57% to 69%.[5,7,9,22] In this respect, the various protocols or treatment strategies do not show large differences in outcome. The different study groups used several staging systems, of which, all were reported to be significant in respect to prognostic relevance. The drawback to the use of

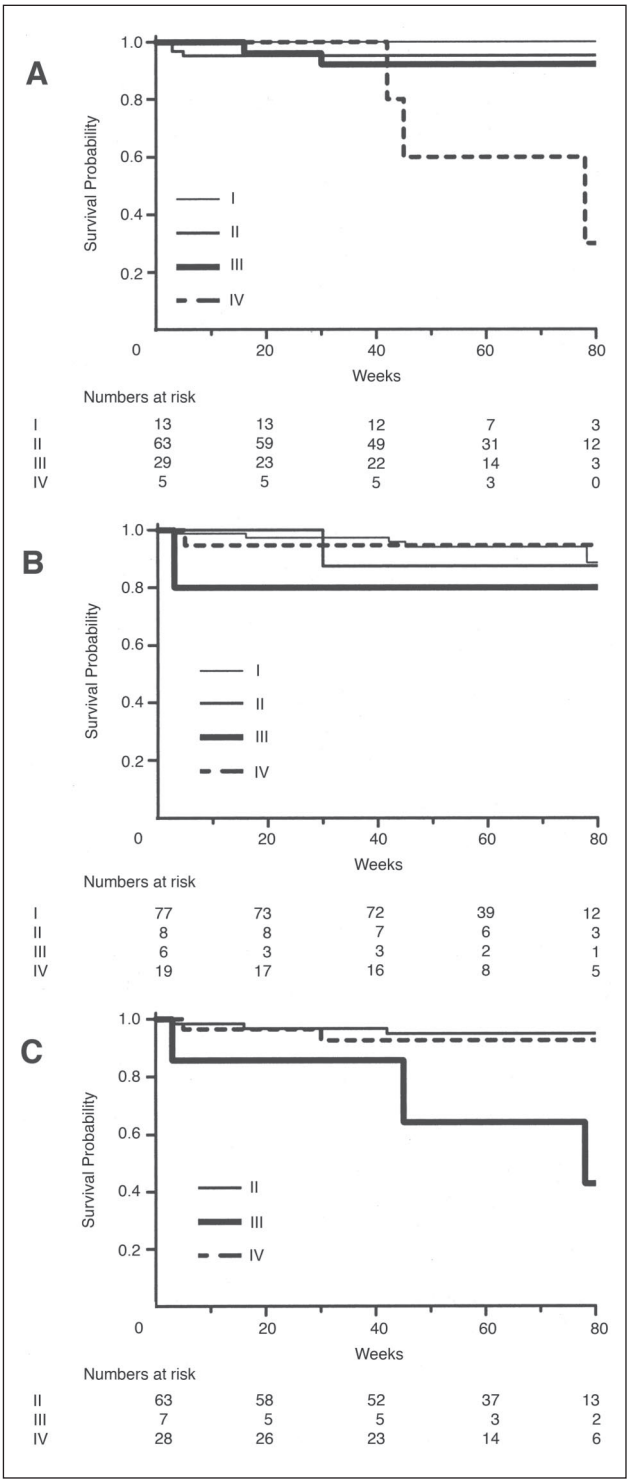

Fig 3. (A) The 5-year overall survival according to the different preoperative pretreatment extent of disease (PRETEXT) groups after central review ($P = .0006$, log-rank test). (B) The 5-year overall survival according to the system used by the Children's Cancer Study Group/Pediatric Oncology Group (CCSG/POG; $P = .516$, log-rank test). (C) The 5-year overall survival according to the tumor-node-metastasis (TNM) system for (adult) liver carcinomas ($P = .0021$, log-rank test).

different staging systems is that patients and, thus, study results are difficult to compare. Almost all groups use postoperative staging. The CCSG/POG study groups and the German group used the same postoperative system, which the German group compared with the prognostic relevance of the adult liver carcinoma tumor-node-metastasis system of the International Union Against Cancer,[13,23] and a Japanese study group proposed the postoperative Japanese tumor-node-metastasis system.[24] The German group advised the use of the tumor-node-metastasis system for comparison of the treatment results in HB but stated that a disadvantage of the tumor-node-metastasis staging systems is that they are based on postoperative pathologic findings and, therefore, can only be applied to patients who underwent surgery. Therefore, the advantages of the preoperative imaging–based staging system developed by the SIOPEL-1 study group are that it can be applied to all patients, it can be used to monitor the effect of preoperative chemotherapy, and it can assess the resectability of the tumor and the required type of resection before surgery.

To assess the accuracy of the PRETEXT system, the preoperative PRETEXT staging was compared with the pathology report of the postoperative resection specimen (ie, the gold standard). Therefore this could only be applied to patients who underwent surgery, which is a selected subgroup of all HB patients. Our data showed that only 46 (51%) of 91 tumors were correctly staged, with a tendency to overstage the tumor (37%). For example, tumors were staged as group IV (ingrowth), whereas, in fact, they should have been staged as group III (compression). This phenomenon may be explained by the difficulty, if not impossibility, of distinguishing parenchymal compression of a tumor-free liver sector from tumor ingrowth into that sector. The weighted κ value of 0.44 supports this assumption because it means that the accuracy of PRETEXT is moderate. Hopefully, future improvement of imaging quality and obligatory central review may improve this discrepancy, maybe even by using other imaging techniques, like magnetic resonance imaging. However, this assumption has to be studied prospectively.

However, the interobserver agreement of staging tumors according to the PRETEXT system is good as shown by the weighted κ value of 0.76. This means that the system is reproducible, and one might assume that the system can easily be applied by different clinicians and that a relative uniformity of tumor staging exists. Although, one has to keep in mind that 63% of all patients (97 of 154 patients) who were eligible on the SIOPEL-1 study had their local PRETEXT staging compared with central staging, and 50% of all patients (77 of 154 patients) who were eligible on the SIOPEL-1 study were available to compare pathology with pretreatment staging (see flow chart in Fig 2).

Similarly, only 64% (98 of 154 patients) to 71% of the patients (110 of 154 patients) were available for comparing the three different staging systems in use for HB (Fig 2). Still, our data show that the predictive value in relation to survival of the PRETEXT system is at least as good as the well-known tumor-node-metastasis–based system. Both systems had a highly significant predictive value in relation to survival in the SIOPEL-1 study. In contrast, in this select group of patients, the CCSG/POG-based system seemed to be not significantly related to survival, probably because most patients had stage I disease. This finding was also confirmed by the statistical fit of the three staging systems in the Cox proportional hazards models, which showed a superiority for the PRETEXT system.

In conclusion, the results of the present data show that the accuracy of the PRETEXT system is moderate when the pre- and postoperative stages are being compared, probably as a result of the difficulty to distinguish parenchymal compression from true parenchymal ingrowth of the tumor; there was a tendency to overstage the patients; and the PRETEXT system demonstrated a good interobserver agreement, which means that this staging system is reproducible. The predictive value for survival of PRETEXT and of the tumor-node-metastasis–based system was highly significant in contrast to the predictive value of the CCSG/POG-based system. However, the PRETEXT system has an advantage because it offers the opportunity to monitor the effect of the neoadjuvant therapy used before surgery. Further research is necessary to evaluate the predictive value of PRETEXT in patients who do not receive surgical resection to evaluate the predictive value of this PRETEXT system and its use in monitoring the effects of preoperative chemotherapy, not only in patients who receive surgical resection, but in all patients. We recommend that all patients with HB included in the trials from the different study groups be staged both by their own preferred staging system as well as according to the PRETEXT system. This offers the opportunity to monitor preoperative treatment and to compare the results from the various trials in a more accurate way.

Appendix

We would like to emphasize that this study could only be conducted with the participation of the following centers: Argentina: Buenos Aires, Italian Hospital of Buenos Aires; Australia: Adelaide, Adelaide Children's Hospital; Brisbane, Royal Children's Hospital; Melbourne, Royal Children's Hospital; Paramatta, The New Children's Hospital; Westmead, Westmead Hospital; Belgium: Brussels, Cliniques Universitaires Saint-Luc; Brussels, Hôpital Universitaire des Enfants; Gent, University Hospital/Kliniek voor Kinderziekten; Leuven, University Hospital Gasthuisburg; Montegnee, Clinique de Montegnee; Brazil: Sao Paulo, AC Camargo Hospital; Sao Paulo, Amico Hospital; Sao Paulo, Centro Infantil; Sao Paulo, Hospital Servidor Publico Estadual; Sao Paulo, Santa Casa; Croatia: Zagreb, Children's Clinic Salata; Czechoslovakia: Banska Bystrica, Pediatric Oncological Centre/Regional Hospital; Prague, Clinic of Children Oncolgy; Denmark: Copenhagen, University Hospital; Odense, Odense University

Hospital; Egypt: Alexandria, University of Alexandria; Finland: Helsinki, Children's Hospital; France: Lille, Centre Oscar Lambret; Lyon, Centre Leon Berard; Nancy, Hôpital d'Enfants; Paris, Institut Curie; Germany: Tubingen, University of Tubingen/Eberhard Karls Universitat; Greece: Athens, Children's Hospital; Thessaloniki, Ippokation Hospital; Hungary: Budapest, Semmelweis University Medical School; Miskolc, Miskolc Medical School; Ireland: Dublin, Our Lady's Hospital for Sick Children; Israel: Haifa, Rambam Medical Centre; Italy: Bari, Policlinico Universita Bari; Genova, Giannina Gaslini Children's Hospital; Padova, Chirurgica Pediatrica; Torino, Ospedale Regina Margherita; Japan: Saporro, Sapporo National Hospital; Malaysia: Kelantan, Hospital Universiti Sains Malaysia; Netherlands: Amsterdam, Emma Children's Hospital AMC; Amsterdam, Vrije Universiteit Medical Center; Leiden, University Hospital of Leiden; Nijmegen, University Hospital Nijmegen; New Zealand: Auckland, Starship Children's Hospital; Wellington South, Wellington School of Medicine; Northern Ireland: Belfast, Royal Hospital for Sick Children; Norway: Bergen, University Hospital; Oslo, Rikshospitalet; Poland: Szczecin, Pomeranian Medical Academy; Warsaw, Research Institute of Mother and Child; Wroclaw, Medical Academy; Portugal: Porto, Hospital St Antonio; Slovenia: Ljubljana, University Pediatric Hospital; South Africa: Cape Town, Red Cross Children's Hospital; Johannesburg, Baragwanath Hospital; Pretoria, Medunsa, Kalatonge Hospital; Tygerberg, Tygerberg; Spain: Barcelona, Hospital Infantil Valle Hebron; Bilbao, Hospital Infantil de Cruces; Malaga, Hospital Materno-Infantil; Valencia, Hopital "La Fe"; Sweden: Goteborg, University of Goteborg; Lund, University Hospital; Stockholm, Karolinska Hospital; Switzerland: Bern, Universitäts-Kinderklinik; Lausanne, University Hospital (CHUV); Zurich, Children's University Clinic; Taiwan Republic of China: Taipei, National Taiwan University Hospital; Turkey: Ankara, Hacattepe University; United Kingdom: Aberdeen, Royal Aberdeen Children's Hospital; Birmingham, The Children's Hospital; Bristol, Royal Hospital for Sick Children; Edinburgh, Royal Hospital for Sick Children; Glasgow, Royal Hospital for Sick Children; Leeds, St James' University Hospital; Leicester, Leicester Royal Infirmary; Liverpool, Royal Liverpool Children's Hospital; London, Hospital for Sick Children; London, King's College Hospital; London, Middlesex Hospital; London, Royal Marsden Hospital; London, St Bartholomew's Hospital; Manchester, Royal Manchester Children's Hospital; Newcastle, Royal Victoria Infirmary; Nottingham, Queen's Medical Centre; Oxford, John Radcliff Hospital; Sheffield, Children's Hospital; Southampton, Southampton General Hospital; and Uruguay: Montevideo, Hospital Pereira Rossell.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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