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소아 간모세포종 환자에서 수술 전 항암치료 후 임상적, 영상의학적 소견의 예후적 가치 평가

Prognostic Value of POST-Treatment Extent of Tumor (POSTTEXT) System in Patients with Hepatoblastoma

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영문요약

Prognostic Value of POST-Treatment Extent of Tumor (POSTTEXT) System in Patients with Hepatoblastoma

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Objective: To assess prognostic values of the POST-Treatment Extent of Tumor (POSTTEXT) system and clinical factors after neoadjuvant chemotherapy in hepatoblastoma patients and evaluate benefits of posttreatment imaging and clinical factors concomitant with Children's Hepatic Tumors International Collaboration-Hepatoblastoma Stratification (CHIC-HS) system.

Materials and Methods: This single-center retrospective study analyzed hepatoblastoma cases from 2006 to 2022. Pediatric patients with histologically confirmed hepatoblastoma, receiving at least four cycles of neoadjuvant chemotherapy, with pre- and post-treatment imaging and complete medical records were included. Imaging analyses followed the 2017 PRE-Treatment EXTent of tumor (PRETEXT) staging system. Clinical data included age, sex, and serum alpha-fetoprotein (AFP) levels. Univariable and multivariable Cox regression analyses identified significant predictors of event-free survival (EFS). Time-dependent ROC curves assessed the predictive power of combining the CHIC-HS risk stratification with other posttreatment factors. Inter-reader agreement for staging and annotation factors were analyzed using weighted kappa.

Results: We reviewed 109 diagnosed hepatoblastoma patients, with 73 (mean age: 2.2 ± 2.7 years) meeting inclusion criteria. Kaplan-Meier analysis revealed a mean EFS of 13.0 years, with corresponding one-, three-, and five-year EFS rates of 88.9%, 80.3%, and 80.3%. Multivariable Cox proportional hazard analysis showed that significant prognostic factors for EFS included AFP levels after the fourth cycle of neoadjuvant chemotherapy (HR, 1.233; 95% CI, 1.806–1.400; P = 0.001), tumor size change ratio (HR, 0.654; 95% CI, 0.448–0.955; P = 0.03), and POSTTEXT annotation factor M (HR, 5.209; 95% CI, 1.639–16.553; P = 0.005). Incorporating AFP levels after the fourth cycle of neoadjuvant chemotherapy into the CHIC-HS significantly improved predictive power (P = 0.043). POSTTEXT system showed better inter-reader agreement than PRETEXT.

Conclusion: Significant predictors of EFS in pediatric hepatoblastoma include alpha-fetoprotein levels after the fourth cycle of neoadjuvant chemotherapy, tumor size change ratio, and metastasis (POSTTEXT M). Combining alpha-fetoprotein levels after the fourth cycle of neoadjuvant chemotherapy to the CHIC-HS significantly improved the predictive ability.

목차

표 및 그림 차례

서론

Hepatoblastoma, the most common primary hepatic malignancy in children, has an estimated annual incidence of approximately 1.5 cases per million [1]. Increases in hepatoblastoma over the past two decades are due to the improved survival rates of premature and low-birth-weight infants [2]. Treatment includes chemotherapy, surgical resection, and liver transplantation. These approaches have undergone advancements, improving survival outcomes [3]. The International Childhood Liver Tumors Strategy Group typically administers neoadjuvant chemotherapy to hepatoblastoma patients, followed by delayed surgery, with the advantage of reducing tumor size and down-staging in most cases [4].

Several studies have evaluated the prognosis of hepatoblastoma and guided clinical management. Prognostic factors include the PRE-Treatment EXTent of tumor (PRETEXT) system, the Children's Hepatic Tumors International Collaboration- Hepatoblastoma risk stratification (CHIC-HS), the measurement of alpha-fetoprotein (AFP) levels, and histological subtypes [5, 6]. Previous studies have reported that higher PRETEXT group classifications, as well as positive PRETEXT annotation factors P, F, and M, and either a low (<100 ng/mL) or a very high (>10^6 ng/mL) level of AFP at diagnosis, are associated with unfavorable outcomes in hepatoblastoma patients [5, 7]. The CHIC-HS has been introduced as a new risk stratification system for hepatoblastoma patients by collaborating with four major international liver groups [6]. It can be applied during initial diagnosis based on age, PRETEXT system, AFP level, and tumor resectability. Previous studies validated the prognostic effect of the CHIC-HS system in the Asian pediatric population, underscoring its significance as a predictor of event-free survival (EFS) [8, 9].

As neoadjuvant chemotherapy has been widely used in the treatment of hepatoblastoma, posttreatment evaluation of the disease is crucial for patient management. The PRETEXT group and PRETEXT annotation factors should be reassessed at each imaging time point. This is called the POST-Treatment EXTent of tumor (POSTTEXT) system. It evaluates the tumor extent response to neoadjuvant chemotherapy and provides information about posttreatment resectability. Due to the substantial size of the hepatoblastoma at the time of diagnosis, there is a considerable risk of misevaluation of the PRETEXT system [4]. Also, with remarkable advancements in neoadjuvant chemotherapy, previously deemed unresectable tumors have substantially reduced size, enabling complete resection [4]. In this regard, the accurate evaluation of the POSTTEXT system has gained paramount importance, surpassing reliance on the PRETEXT system alone.

Our study aims to assess the prognostic value of the POSTTEXT system and clinical factors after neoadjuvant chemotherapy in hepatoblastoma patients and evaluates the benefits of posttreatment imaging and clinical factors after neoadjuvant chemotherapy in conjunction with the CHIC-HS system.

연구대상 및 연구방법

The Institutional Review Board approved this single-center retrospective study. The informed consent requirement was waived. This study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [10].

Patients

A retrospective database search was conducted at a tertiary referral center between March 2006 and March 2022 to identify eligible patients. The study period was from 2006 because liver transplantation was introduced for patients with hepatoblastoma at our center that year [3]. Inclusion criteria: (a) diagnosis of hepatoblastoma through histopathology; (b) age under 18 years; (c) patients who underwent neoadjuvant chemotherapy at least four times; (d) abdominal CT or MRI at the time of diagnosis and after the fourth cycle of neoadjuvant chemotherapy; and (e) accessible laboratory and follow-up electronic medical records. Exclusion criteria: (a) poor imaging quality hindering PRE- and POSTTEXT staging and (b) patients lost to follow-up. The fourth cycle of neoadjuvant chemotherapy was chosen because the median number of cycles was four [3]. Additionally, the SIOPEL group recommends four cycles of neoadjuvant chemotherapy for patients who undergo surgical resection [11].

PRE- and POSTTEXT Staging System

Two radiologists (H.M.Y., with nine years of experience in pediatric radiology, and H.N.J., with two years of experience in radiology) independently assessed the PRETEXT and POSTTEXT staging according to the updated 2017 PRETEXT staging system [12], based on CT or MRI images before treatment and after the fourth cycle of neoadjuvant chemotherapy. They were blinded to the clinical outcome. A PRE- and POSTTEXT staging training session was held with 25 cases that were not included in this study. The PRETEXT and POSTTEXT staging indicates the extent of the tumor based on the number of contiguous tumor-free hepatic sections, ranging from PRETEXT I (three consecutive sections free) to PRETEXT IV (no sections free). The annotation factors include vascular involvement (V, hepatic vein/inferior vena cava; P, portal vein), extrahepatic tumor extension (E), multifocality (F), tumor rupture (R), caudate lobe involvement (C), lymph node metastases (N), and distant metastases (M). With POSTTEXT R and M, it was considered positive if a newly developed rupture or metastasis satisfied the 2017 PRETEXT criteria. When the metastatic lesion decreased in size but remained measurable after the fourth cycle of neoadjuvant chemotherapy, it was also considered POSTTEXT M positive despite not meeting the 2017 PRETEXT criteria. According to the 2017 PRETEXT criteria, PRETEXT M positive is assigned when any of the following conditions are met: the presence of one non-calcified lung nodule (diameter $\geq$ 5 mm), the presence of two or more non-calcified lung nodules, each with a diameter $\geq$ 3 mm, or the presence of another pathologically proven metastatic disease [12]. If the metastatic lesions present at diagnosis were no longer visible post-treatment, POSTTEXT M was considered as negative. An aggregate factor, VPEFR, indicating the presence of at least one of the V, P, E, F, or R factors, was also assessed [6]. Any discrepancy between the two radiologists was resolved by consensus after reviewing all available clinical and imaging data (i.e., intraoperative findings, pathologic results, follow-up imaging, or PET/CT). In addition, the largest tumor diameter was measured on CT or MRI at the time of diagnosis and after the fourth cycle of neoadjuvant chemotherapy by one of two radiologists (H.N.J.).

Clinical Data Collection

Age, sex, and serum AFP levels were collected at diagnosis and after the fourth cycle of neoadjuvant chemotherapy. Patients were classified into very low to high-risk groups according to the CHIC-HS system. "Resectable at diagnosis," in the lexicon of the CHIC-HS system to differentiate very low to low risk, was retrospectively evaluated by a pediatric surgeon (J.M.N. with 10 years of experience in pediatric liver surgery). The total number and regimen of neoadjuvant chemotherapy and the surgical method were collected.

Statistical Analysis

The EFS was used as the primary outcome of this study, which is the time from enrollment until an event, including first relapse, disease progression, development of second malignancy, or death for any reason. The Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria were used to evaluate relapse and disease progression [13].

The Kaplan-Meier curves were generated to calculate EFS and overall survival (OS). The OS was defined as the period from diagnosis to death (treated as event) or the most recent follow-up (treated as censoring).

Univariable and multivariable Cox regression analyses were conducted to find significant predictors of EFS. Variables that showed a potential for statistical significance ($P < 0.05$) in the univariable model were included in the multivariable model. The POSTTEXT staging, rather than the PRETEXT staging, was primarily included in the multivariable analysis because there were concerns regarding multicollinearity, and the primary purpose of this study was to assess the prognostic value of the POSTTEXT system. However, the PRETEXT group was included in the multivariable analysis regardless of the *P*-value since it is a well-known risk factor associated with EFS [6]. The variables were selected through a backward elimination process. The level of risk associated with each variable was expressed as a hazard ratio (HR), along with a corresponding 95% confidence interval (CI). Additionally, time-dependent ROC curves for predicting 5-year EFS were evaluated to compare the predictive power of the CHIC-HS risk system alone and combination of CHIC-HS with other posttreatment factors having statistical significance. The best cut-off value for posttreatment AFP level was calculated with Uno's estimator of cumulative AUC [14].

Inter-reader agreement between the radiologists was analyzed for PRETEXT and POSTTEXT staging using weighted kappa and annotation factors using kappa. Kappa values were interpreted as follows: 0–0.20 (slight agreement), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (substantial), and 0.81–1.00 (excellent) [15].

A *P*-value < 0.05 was considered statistically significant. The analysis used R software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and MedCalc version 22.007 (MedCalc Software, Ostend, Belgium).

연구결과

Baseline Patient Characteristics

Of the 109 patients diagnosed with hepatoblastoma during the study period, the following were excluded: 10 patients without follow-up clinical or imaging data, 15 patients who received less than four times of neoadjuvant chemotherapy, and 11 patients who did not undergo follow-up CT or MRI after four times of chemotherapy. A total of 73 patients were included (**Figure 1**). The baseline characteristics of the 73 patients are summarized in **Table 1**. The mean age of the patients was 2.2 ± 2.7 years, and 39 were male. The mean follow-up period was 3.5 years (range, 0.4–16.1 years). Before treatment, 61 patients (n = 61/65, 93.8%) had AFP levels of ≥1,000 ng/mL. However, after the fourth cycle of chemotherapy, the AFP levels decreased, and only 23 patients (n = 23/71, 32.4%) had AFP levels of ≥1,000 ng/mL. The size of the tumor was ≥10 cm in 55 patients (n = 55/73, 75.3%) before treatment, but only 11 patients (15.1%) had a tumor size of ≥10 cm after the fourth cycle of chemotherapy. There were no patients who developed new metastases or tumor ruptures during neoadjuvent chemotherapy. Among 23 patients who had metastasis at diagnosis (all metastases were in the lung), 4 patients had no imaging evidence of metastasis after the fourth cycle of chemotherapy, but the other 19 patients had decreased but measurable metastatic lesions after the fourth cycle.

The KM plots for EFS and OS are presented in **Figure 2**. The mean EFS was 13.0 years (95% CI, 11.4–14.6 years) and the mean OS was 14.5 years (95% CI, 13.2–15.8 years). The one-, three- and five-year EFS rates were 88.9%, 80.3%, and 80.3 %, respectively. The OS rates were 97.1%, 91.8%, and 89.3 % for one-year, three-year, and five-years, respectively.

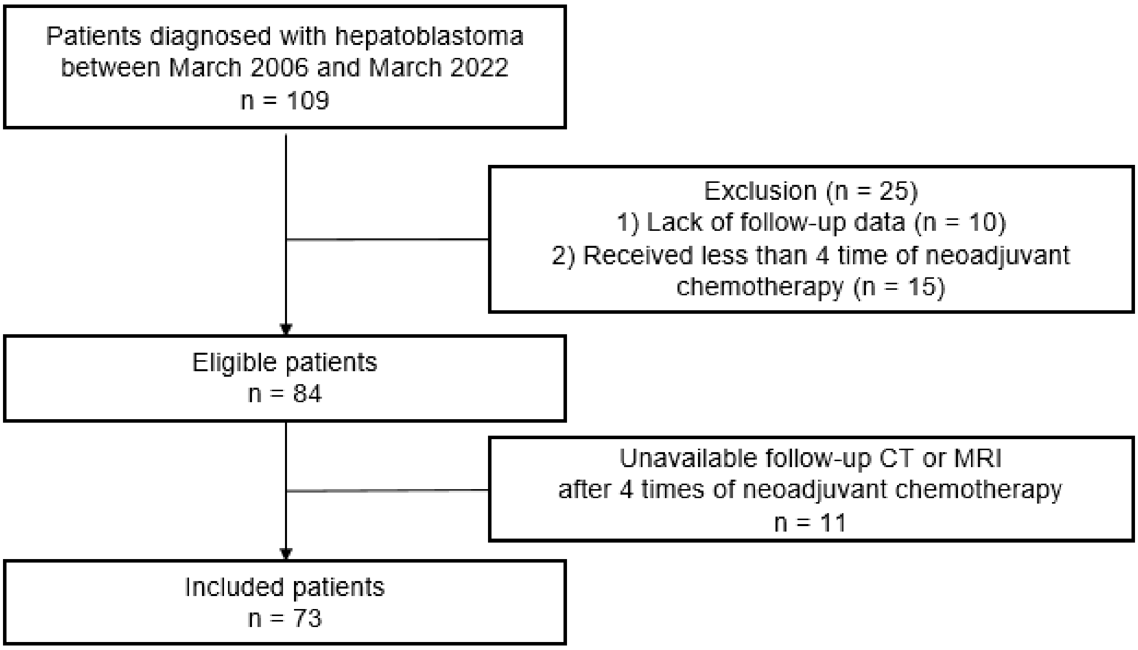

Figure 1. Flow diagram of the study

Table 1. Baseline patient characteristics

Characteristic	Category	Value (%)
Total number of patients		73
Age at initial diagnosis	≤2	50 (68.5)
	3~7	16 (21.9)
	≥8	7 (9.6)
Sex (male:female)		39:34
AFP at diagnosis	<1,000	4 (5.5)
	1,000~10^6	54 (74.0)
	>10^6	7 (9.6)
	missing	8 (11.0)
AFP after the fourth cycle of neoadjuvant chemotherapy (ng/mL)	<1,000	48 (65.8)
	1,000~10^6	23 (31.5)
	>10^6	0 (0)
	missing	2 (2.7)
PRETEXT group	I	3 (4.1)
	II	25 (34.2)

		III	27 (37.0)
		IV	18 (24.7)
POSTTEXT group		I	2 (2.7)
		II	31 (4.2)
		III	28 (38.4)
		IV	12 (16.4)
CHIC-HS[a] risk stratification		Very low	8 (11.0)
		Low	20 (27.4)
		Intermediate	14 (19.2)
		High	30 (41.1)
PRETEXT annotation factors			
	V	Yes	14 (19.2)
	P	Yes	10 (13.7)
	E	Yes	2 (2.7)
	F	Yes	28 (38.4)
	R	Yes	6 (8.2)
	C	Yes	16 (21.9)
	N	Yes	1 (1.4)
	M	Yes	23 (31.5)
	one or more V, P, E, F, or R	Yes	40 (54.8)
POSTTEXT annotation factors			
	V	Yes	7 (9.6)
	P	Yes	7 (9.6)
	E	Yes	0 (0)
	F	Yes	27 (37.0)
	R	Yes	0 (0)
	C	Yes	12 (16.4)
	N	Yes	0 (0)
	M[b]	Yes	19 (26.0)
	one or more V, P, E, F, or R	Yes	34 (46.6)
Tumor diameter at diagnosis (cm)		<10	18 (24.7)
		10~15	42 (57.5)
		>15	13 (17.8)
Tumor diameter after the fourth cycle of neoadjuvant chemotherapy (cm)		<10	62(84.9)
		10~15	8 (11.0)
		>15	3 (4.1)
Total number of neoadjuvant chemotherapy		4	27 (37.0)
		5~8	43 (58.9)
		>8	3 (4.1)
Neoadjuvant chemotherapy		Cisplatin/doxorubicin	1 (1.4)
		Cisplatin/5FU/vincristine	30 (41.1)
		Cisplatin/5FU/vincristine/doxorubicin	36 (49.3)
		others	5 (6.8)
		missing	1 (1.4)
Surgical method		Hepatectomy	60 (82.2)
		Liver transplantation	13 (17.8)

[a] One patient was unavailable for risk stratification based on CHIC-HS due to a lack of data on AFP levels.

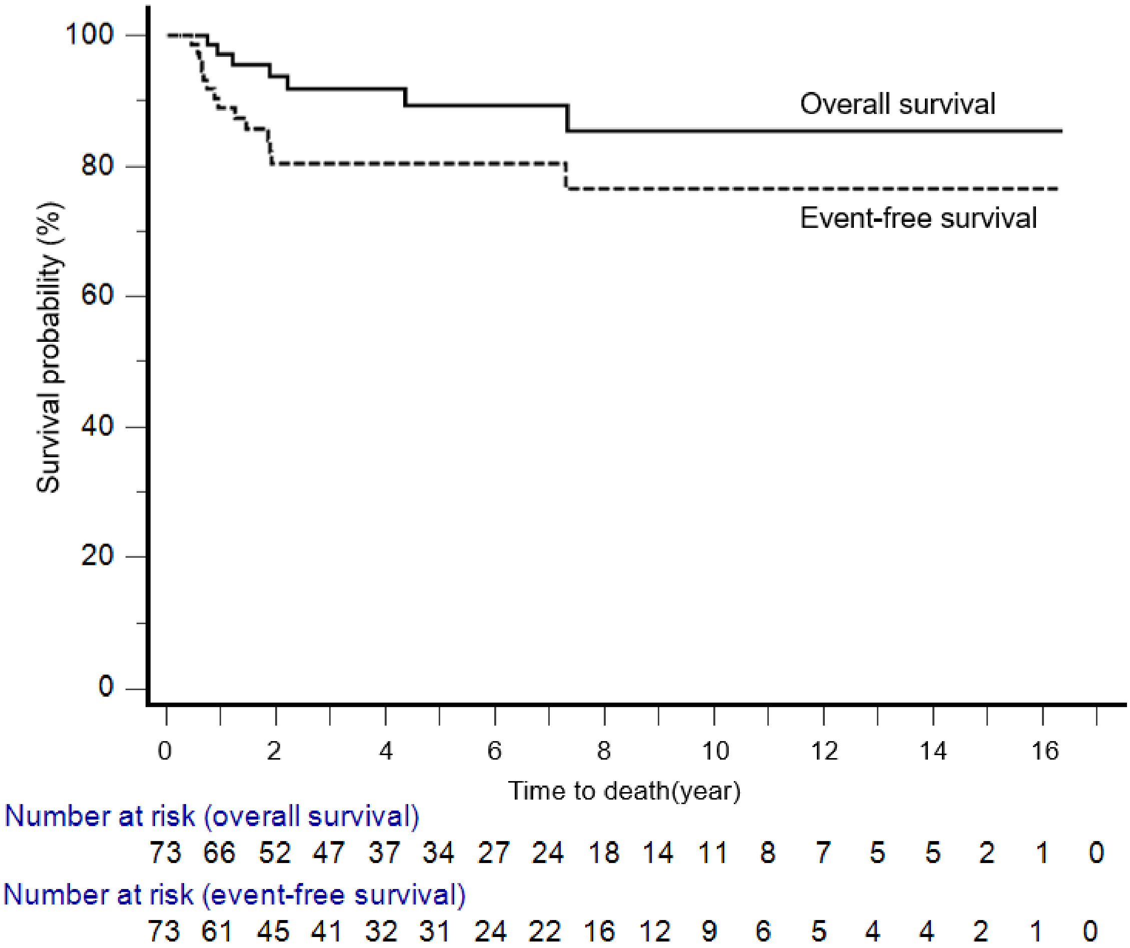

Figure 2. Event-free survival(EFS) and overall survival(OS) of the 73 patients analyzed.

Prognostic Factors for Predicting Event-Free Survival

In the univariable Cox proportional hazards model, age at diagnosis; PRETEXT annotation factors F, N, and M; AFP level and tumor size after the fourth cycle of neoadjuvant chemotherapy; change ratio of AFP and tumor size; and POSTTEXT annotation factors M were associated with EFS (**Table 2**).

According to multivariable Cox proportional hazard analysis, AFP level after the fourth cycle of neoadjuvant chemotherapy (HR, 1.233; 95% CI, 1.806–1.400, per 10,000 ng/mL; *P* = 0.001); change ratio of tumor size at diagnosis and after the fourth cycle of neoadjuvant chemotherapy (HR, 0.654; 95% CI, 0.448–0.955, per 10%; *P* = 0.03); and POSTTEXT annotation factor M (HR, 5.209; 95% CI, 1.639–16.553; *P* = 0.005) were significant predictors of EFS (**Table 2**).

Table 2. Univariate and multivariable Cox proportional hazards model for prognostic factors for predicting event-free survival

		Univariable analysis			Multivariable analysis[e]		
		Unadjusted HR	95% CI	*P*-value	Adjusted HR	95% CI	*P*-value
	Sex	1.416	0.491–4.086	0.52			
At diagnosis	Age (year)	1.207	1.048–1.391	0.009			
	AFP (ng/mL, n=65)[b]	0.983	0.959–1.008	0.173			
	Tumor size (cm)	1.101	0.971–1.248	0.13			
	PRETEXT[d]						
	Group	1.716	0.901–3.267	0.101	Eliminated		
	V	1.568	0.492–5.002	0.447			
	P	2.66	0.725–9.765	0.14			
	E	Nonestimable[a]					
	F	4.686	1.464–15	0.009			
	R	0.942	0.123–7.234	0.954			
	VPEFR	3.506	0.976–12.59	0.055			
	C	1.401	0.439–4.469	0.569			
	N	71.5	4.472–1143	0.003			
	M	3.215	1.115–9.273	0.031			
After the fourth cycle of neoadjuvant chemotherapy	AFP[b] (ng/mL, n = 71)	1.207	1.086–1.341	0.0005	1.233	1.086–1.400	0.001
	AFP change (%)[c]	0.996	0.993–0.999	0.002			
	Tumor size (cm)	1.197	1.043–1.374	0.01	Eliminated		
	Size change (%)[c]	0.652	0.464–0.916	0.014	0.654	0.448–0.955	0.03

	POSTTEXT						
	Group	1.633	0.841–3.172	0.147			
	V	0.642	0.084–4.908	0.669			
	P	1.081	0.139–8.414	0.94			
	E	Nonestimable[a]					
	F	2.528	0.874–7.319	0.087			
	R	Nonestimable[a]					
	VPEFR	2.248	0.751–6.731	0.148			
	C	0.335	0.044–2.563	0.292			
	N	Nonestimable[a]					
	M	4.761	1.642–13.8	0.004	5.209	1.639–16.553	0.005

[a] HR was not estimable since patients with +event showed all PRETEXT E and POSTTEXT E, R, N negative.

[b] AFP was divided by 1,0000 in the regression model to obtain an understandable coefficient.

[c] Size and AFP change were divided by 10 in the regression model to obtain an understandable coefficient.

[d] PRETEXT was included in the multivariable analysis since PRETEXT is a well-known risk factor associated with EFS.

Time-dependent ROC analysis for 5-year Event-Free Survival

Table 3 shows the area under the curve (AUC) values for 5-year EFS obtained by incorporating various combinations of the significant parameters from the multivariable analysis, including POSTTEXT annotation factor M, AFP level, and the change ratio of tumor size after the fourth cycle of neoadjuvant chemotherapy into the well-known hepatoblastoma risk stratification system, CHIC-HS. The predictive power increased when the AFP level after the fourth cycle of neoadjuvant chemotherapy was added to the CHIC-HS (*P*=0.043). Although the additional combination of POSTTEXT annotation factor M to the former showed a significant increase in the AUC value (*P*=0.022), the AUC value remained constant at 0.84. **Figure 3** displays the added AUC values of two models, which combined AFP level after the fourth cycle of neoadjuvant chemotherapy and POSTTEXT M positive into the CHIC-HS system. The best cut-off value of the AFP level after the fourth cycle of neoadjuvant chemotherapy for predicting EFS was 1,000 (**Figure 4**).

Table 3. Time-dependent ROC analysis for 5-year event-free survival

Combination	AUC 5-year	*P*-value
CHIC-HS	0.70	-
CHIC-HS + POSTTEXT-M	0.75	0.090
CHIC-HS + AFP level after chemotherapy	0.84	0.043
CHIC-HS + size change after chemotherapy	0.74	0.599
CHIC-HS + POSTTEXT-M + AFP level after chemotherapy	0.84	0.022
CHIC-HS + POSTTEXT-M + size change after chemotherapy	0.78	0.177
CHIC-HS + AFP level after chemotherapy + size change after chemotherapy	0.77	0.542
CHIC-HS + POSTTEXT-M + AFP level after chemotherapy + size change after chemotherapy	0.85	0.058

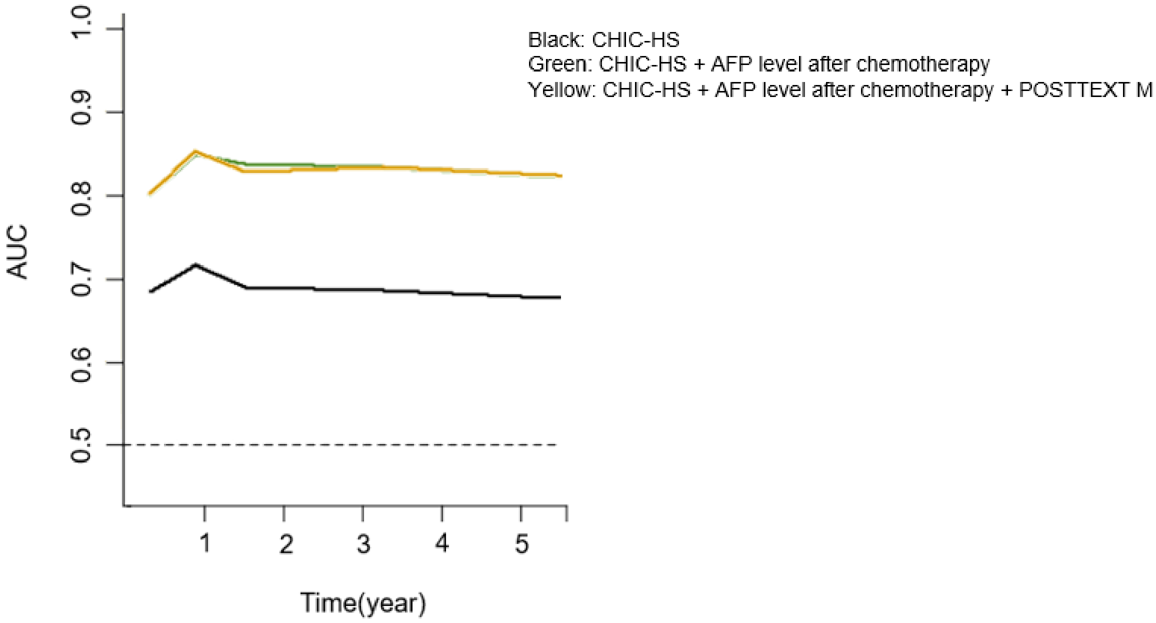

Figure 3. Time dependent ROC curves for significant combinations in addition to the CHIC-HS.

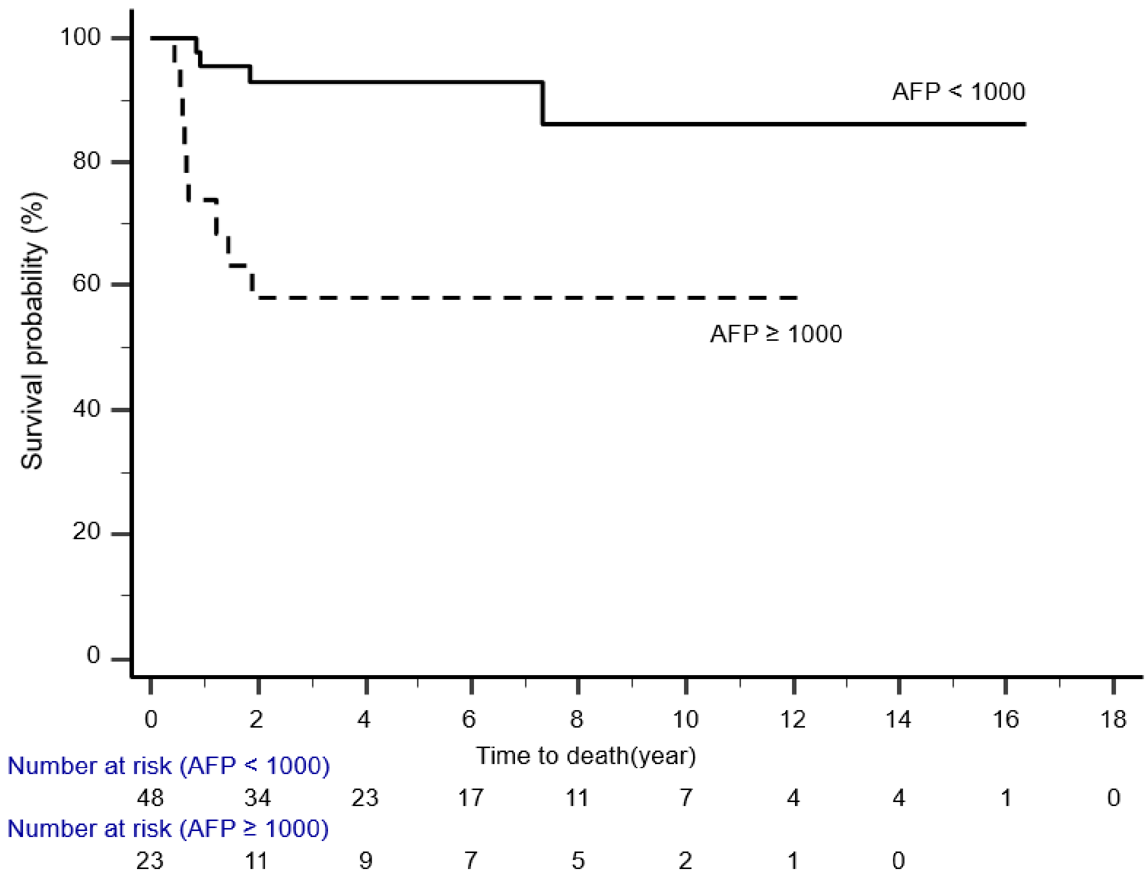

Figure 4. Event-free survival (EFS) according to AFP level.

Inter-reader Agreement

Table 4 shows the inter-reader agreement between the two radiologists for the PRETEXT and POSTTEXT groups and annotation factors. Overall, the POSTTEXT system showed better inter-reader agreement than the PRETEXT system. PRETEXT V and R showed fair and moderate agreement, respectively. All POSTTEXT systems, including POSTTEXT M, showed substantial to near-perfect agreement.

Table 4. Inter-reader agreement of PRETEXT and POSTTEXT staging systems

	PRETEXT	**POSTTEXT**
Stage	0.79 (0.79–0.79)	0.93 (0.93–0.93)
Annotation factor		
V	0.38 (0.15–0.6)	0.92 (0.75–1.00)
P	0.8 (0.61–0.99)	0.80 (0.58–1.00)
E	-0.014 (-0.03-0.005)	Not estimable[b]
F	0.91 (0.81–1.00)	0.94 (0.86–1.00)
R	0.51 (0.13–0.88)	Not estimable[c]
VPEFR	0.67 (0.5–0.84)	0.92 (0.83–1.00)
C	0.62 (0.42–0.82)	0.79 (0.58–0.99)
N	Not estimable[a]	Not estimable[c]
M	0.93 (0.84-1)	0.92 (0.821)

[a] Kappa calculation was not available since reader 1 interpreted N as 0 in all patients.

[b] Kappa calculation was not available since both readers interpreted E as 0 in all patients.

[c] Kappa calculation was not available since reader 2 interpreted N and R as 0 in all patients.

고찰

This retrospective study demonstrated the significance of various imaging features included in the POSTTEXT system and posttreatment clinical factors as predictors of EFS in patients with hepatoblastoma. Specifically, the AFP level and, tumor size change after the fourth cycle of neoadjuvant chemotherapy, and the POSTTEXT annotation factor M emerged as significant predictors. Integrating these factors into the CHIC-HS system, a well-known risk stratification system of hepatoblastoma, significantly enhanced the predictive power. Notably, including AFP level after the fourth cycle of neoadjuvant chemotherapy contributed to a clinically significant improvement in prognosis prediction.

Prior studies have consistently identified AFP levels as a crucial prognostic factor in hepatoblastoma [16, 17]. The prognosis for pediatric hepatoblastoma patients with an AFP level <100 ng/mL or >1,000 ng/mL at the initial diagnosis was found to be worse than patients with AFP levels between 100 and 1,000 ng/mL [17]. Moreover, a more significant reduction in AFP levels after neoadjuvant chemotherapy was associated with improved prognosis [16]. A significant correlation was observed between the reduction in serum AFP levels after neoadjuvant chemotherapy and a smaller tumor size following the same treatment [16]. Our study aligns with these findings, thereby emphasizing the importance of precise measurement of the AFP levels and changes in tumor size after the fourth cycle of neoadjuvant chemotherapy as predictors of EFS.

In a previous study analyzing prognostic factors in hepatoblastoma patients, size reduction of less than 25% after chemotherapy, post-chemotherapy metastasis on CT (POSTTEXT M positive), and POSTTEXT-Portal vein involvement (POSTTEXT P positive) were associated with poor outcomes [18]. Similar results were observed in our study except for the association of POSTTTEXT P positive. This discrepancy may be attributed to the unavailability of liver transplantation in the institution where the previous research was conducted. For patients with a positive POSTTEXT M, it indicated the presence of a residual tumor even after chemotherapy, probably associated with persistent higher levels of AFP after treatment, potentially leading to poorer outcomes in our study.

Among various POSTTEXT annotation factors, only POSTTEXT M showed prognostic value. Other factors did not show a prognostic effect. Annotation factors V, P, F, and C are associated with intrahepatic tumor spread and resectability. When such annotation factors are positive, surgical removal may be challenging. Still, with advancements in surgical techniques and liver transplantation feasibility, even in cases with positive findings, a favorable prognosis can be anticipated. Annotation factors E, R, and N are associated with intra-abdominal tumor spread and may also present challenges for complete tumor resection. In our study, these positive factors in patients were relatively rare before treatment, and all those factors turned negative after neoadjuvant chemotherapy. It is important to note that these factors were relatively rare and did not significantly impact the feasibility of liver transplantation in previous studies [12, 19]. This observation implies that hepatoblastoma patients with an advanced local stage, even after neoadjuvant chemotherapy, can be managed successfully with minimal impact on survival.

The CHIC-HS system, which integrates factors such as the presence of metastasis, age group, serum AFP level, aggregated PRETEXT VPEFR factor status, and resectability, serves as a risk stratification tool for patients with hepatoblastoma at the initial diagnosis time point [8, 9]. In our study, incorporating AFP levels after the fourth cycle of neoadjuvant chemotherapy into the CHIC-HS system substantially enhanced its predictive power for 5-year EFS. A higher AFP level after neoadjuvant chemotherapy indicates the presence of a residual tumor [20], which might not be detectable through standard CT or MRI scans. This observation could explain why the additional inclusion of AFP levels after neoadjuvant chemotherapy to the CHIC-HS system significantly enhanced the prognosis prediction. Nonetheless, these findings warrant further validation in future studies.

We analyzed inter-reader agreement between two radiologists for PRETEXT and POSTTEXT groups and annotation factors. The overall level of agreement was higher within the POSTTEXT system than the PRETEXT system. Among the PRETEXT factors, we observed good agreement in the order of M, F, and P, known as significant prognostic factors in previous studies [7, 21] . The aggregation factor VPEFR, crucial within the context of the CHIC-HS system, exhibited relatively poor agreement. This underscores the importance of careful evaluation and precise definition of each factor in clinical practice. POSTTEXT factor M emerged as the sole significant prognostic factor among the POSTTEXT group and annotation factors. This factor exhibited substantial inter-reader agreement, suggesting its feasibility for clinical application.

There are several limitations in this study. First, a potential bias may exist due to its retrospective nature and the reliance on data from a single tertiary hospital cohort. However, given the paucity of hepatoblastoma cases, this study design was inevitable. We tried to include most hepatoblastoma patients from a tertiary referral center over 16 years, but the number of patients remained relatively small (n = 73). Further studies should be conducted on a larger cohort to obtain a more comprehensive investigation of the prognostic factors identified in our study. Second, the study spanned an extended period, resulting in relatively shorter follow-up periods for patients in the later period. However, since most events and deaths generally occur within three years of diagnosis, a more extended follow-up period may not significantly alter the results.

결론

In conclusion, the AFP level, the change ratio of tumor size and presence of metastasis (POSTTEXT M) after the fourth cycle of neoadjuvant chemotherapy emerged as significant predictors of EFS in children with hepatoblastomas. Including AFP level after the fourth cycle of neoadjuvant chemotherapy improved the predictive ability when combined with the CHIC-HS. This suggests that post-treatment evaluation might be focused on the presence of distant metastasis, tumor size change and AFP levels rather than thorough scrutiny of the extent of hepatoblastoma itself on CT or MRI. Our results imply the potential for a new risk stratification model combining posttreatment factors in hepatoblastoma patients undergoing neoadjuvant chemotherapy before surgical resection. However, this model requires further external validation on a larger cohort in future studies.

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국문요약

연구제목: 소아 간모세포종 환자에서 수술 전 항암치료 후 임상적, 영상의학적 소견의 예후적 가치 평가

목적: 간모세포종 환자에서 수술 전 항암요법 이후 POSTTEXT 병기설정 시스템과 임상적 요인의 예후 가치를 평가하고, 이들을 CHIC-HS 위험 측정법에 적용시에 예후 예측에 추가적 이점을 제공하는지 평가하고자 하였다.

대상 및 방법: 본 단일 센터 후향적 연구는 2006 년부터 2022 년까지 간모세포종을 진단받은 환자들을 대상으로 하였다. 조직학적으로 진단된 소아 간모세포종 환자, 적어도 네 번의 수술 전 항암요법을 시행 받은 환자, 치료 전후 영상 자료 및 의무 기록이 있는 환자들이 포함되었다. 영상 분석은 2017 년 PRETEXT 분류 시스템을 따랐으며, 임상 자료에는 연령, 성별 및 혈청 AFP 수준이 포함되었다. 일변량 및 다변량 콕스 회귀 분석을 수행하여 사건 발생까지의 생존(Event-free survival; EFS)의 예측 요인을 확인하였다. 시간에 따른 ROC 곡선을 사용하여(Time-dependent ROC curve) CHIC-HS 위험 측정법에 항암 치료 후 영상 및 임상 요인들을 결합하였을 때의 예후 예측 능력을 평가하였다. 가중 카파(Weighted kappa)를 사용하여 평가자들 사이의 PRETEXT 및 POSTTEXT 요인 일치도를 분석하였다.

결과: 처음 진단받은 간모세포종 환자 109 명을 검토하여 제외 조건을 고려한 뒤 73 명의 환자(평균 연령: 2.2 ± 2.7 세)가 포함되었다. Kaplan-Meier 분석 결과 EFS 평균 기간은 13.0 년이었으며, 1 년, 3 년 및 5 년 EFS 비율은 각각 88.9%, 80.3%, 80.3%였다. 다변량 콕스 회귀 분석에서 EFS 에 대한 중요한 예측 요인으로는 4 차 항암요법 후 AFP 수준 (HR, 1.233; 95% CI, 1.806-1.400; p = 0.001), 종양 크기 변화 비율 (HR, 0.654; 95% CI, 0.448-0.955; p = 0.03), 그리고 POSTTEXT 요소 M (HR, 5.209; 95% CI, 1.639-16.553; p = 0.005)이 있었다. 4 차 항암요법 이후 AFP 수준을 CHIC-HS 에 통합하면 예후 예측 능력이 유의하게 향상되었다(p=0.043). POSTTEXT 시스템은 PRETEXT 시스템보다 더 나은 평가자 간 일치도를 보였다.

결론: 소아 간모세포종 환자에서 EFS 의 중요한 예측 요인은 4 차 항암요법 이후 AFP 수준, 종양 크기 변화 비율 및 전이 병변 (POSTTEXT M) 이었다. CHIC-HS 에 4 차 항암요법 이후 AFP 수준을 함께 고려 시 예후 예측 능력이 유의하게 향상되었다.