

Supplementary Materials: Prognostic Factors for Event-Free Survival in Pediatric Patients with Hepatoblastoma Based on The 2017 PRETEXT and CHIC-HS Systems

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Table S1. 2017 PRETEXT groups and annotation factors.

PRETEXT Groups	Definition
I	3 contiguous hepatic sections are free of tumor
II	2 contiguous hepatic sections are free of tumor
III	1 contiguous hepatic section is free of tumor
IV	Tumor affects all four hepatic sections (almost always multifocal or infiltrative)
Annotation Factors	Positive Definition
Hepatic venous/IVC involvement (V)	Any of the following criteria: Tumor obliterates or encases all three hepatic veins ^a or the intrahepatic IVC Tumor thrombus in any hepatic vein ^a or the intrahepatic IVC
Portal venous involvement (P)	Any of the following criteria: Tumor obliterates or encases either both portal veins ^b or the main portal vein Tumor thrombus in either or both the right and left portal veins ^b or the main portal vein
Extrahepatic tumor extension (E)	Any of the following criteria: Tumor crosses boundaries or tissue planes Tumor is surrounded by normal tissue more than 180° Peritoneal nodules: one nodule ≥ 10 mm or two or more nodules ≥ 5 mm
Multifocality (F)	Two or more separate hepatic tumors with normal liver tissue between the tumors
Tumor rupture (R)	Any findings of hemorrhage on imaging (Ultrasound, CT, MRI)
Caudate lobe (C)	Pathologically diagnosed after paracentesis/upfront resection Tumor involving the caudate lobe
Lymph node metastasis (N)	Considered when any of the following morphologic criteria is met (less sensitive for detection): Lymph node with short-axis diameter > 1 cm Portocaval lymph node with short-axis diameter > 1.5 cm Spherical lymph node shape with absent fatty hilum
Distant metastasis (M)	Any of the following criteria for pulmonary metastasis: Single non-calcified lung lesion with diameter ≥ 5 mm Two or more non-calcified lung lesions with each diameter ≥ 3 mm Any metastases diagnosed via pathology

IVC = inferior vena cava. ^a First-order hepatic vein: between its confluence with IVC and its most central branch. ^b First-order portal vein: between the bifurcation and the first major branch of the portal vein.

Table S2. Surgical treatment of patients with annotation factors V and P-positive.

Criteria for the assignment of V and P-positive	Total	Resection, N (%)	OLTx, N (%)
V (HV or IVC involvement)	31		
Tumor obliterates or encases all three HV	9	1 (11.1)	4 (44.4)
Tumor obliterates or encases IVC	21	7 (33.3)	5 (23.8)
Tumor thrombus in HV	3	2 (66.7)	1 (33.3)
Tumor thrombus in IVC	4	3 (75.0)	0
P (PV involvement)	15		
Tumor obliterates or encases both PV	6	2 (33.3)	2 (33.3)
Tumor obliterates or encases main PV	5	1 (20.0)	2 (40.0)
Thrombus within a first-order PV	7	0	1 (14.3)
Thrombus within main PV	1	0	1 (100)

OLTx, orthotopic liver transplantation; HV, hepatic vein; IVC, inferior vena cava; PV, portal vein.

Table 3. Performance measures of Cox proportional hazard models to predict EFS.

Model Type	Discrimination	
	C-statistic	Optimism-Corrected C-Statistic*
PRETEXT group	0.663 (0.535–0.791)	0.623 (0.495–0.751)
VPEFR†	0.639 (0.523–0.755)	0.636 (0.520–0.752)
F+M model	0.734 (0.612–0.854)	0.718 (0.598–0.837)

Data in parentheses are 95% confidence intervals; * Optimism-corrected C-statistic obtained from bootstrapping method; † One or more of V, P, E, F, or R present.

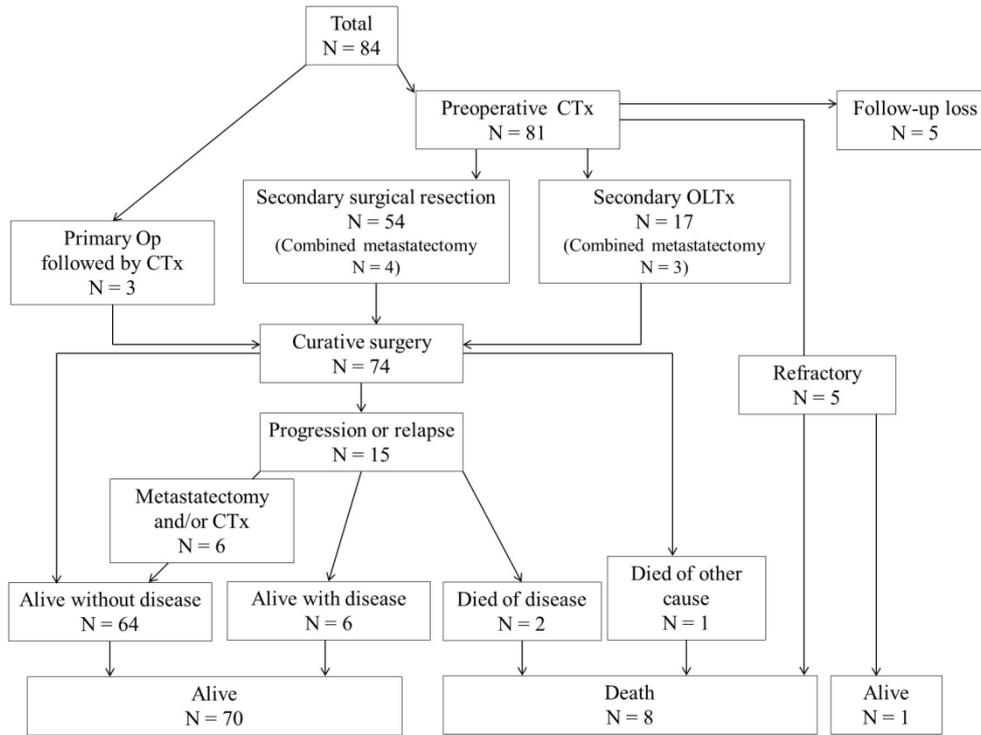


Figure S1. Clinical course of patients. CTx, chemotherapy; Op, operation; OLTx, orthotopic liver transplantation.

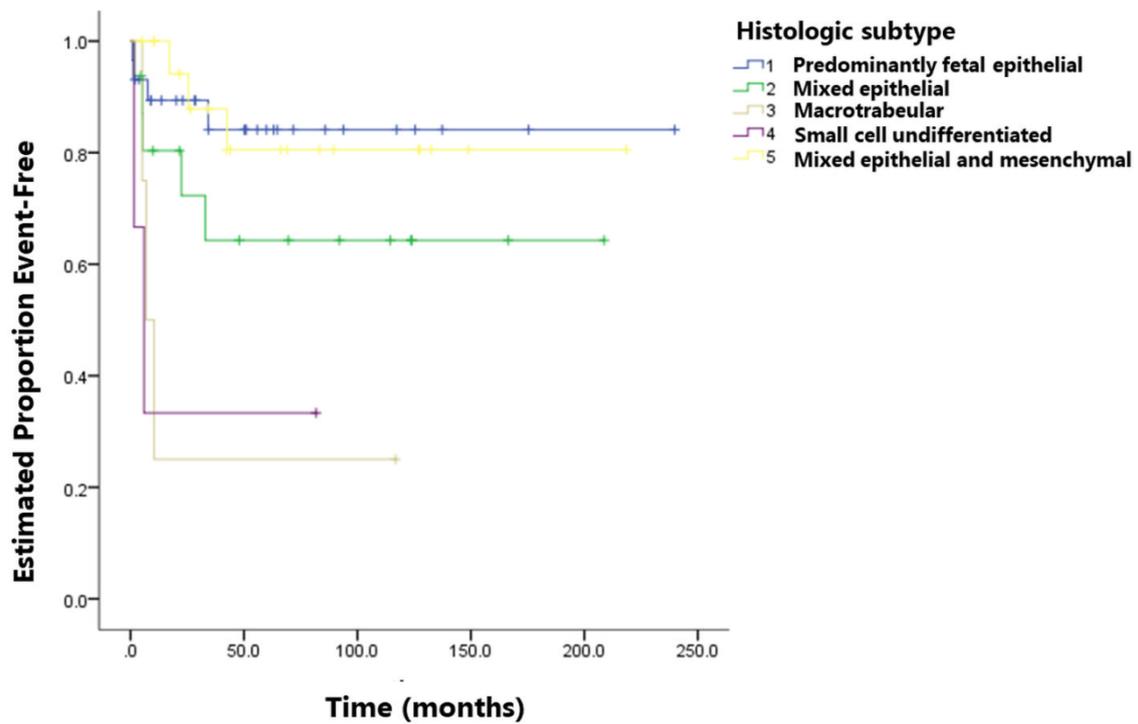


Figure S2. Effect of histologic subtypes on event-free survival. In the Kaplan–Meier curves of event-free survival according to the histologic subtype, the mean EFS was 203.9 months (95% CI of 171.1–236.6 months) for patients with predominantly fetal epithelial subtype, 139.4 months (95% CI of 90.1–188.7 months) for patients with mixed epithelial subtype, 34.9 months (95% CI of 0.0–81.2 months) for patients with macrotrabecular subtype, 29.8 months (95% CI of 0.0–71.5 months) for patients with small cell undifferentiated subtype, and 181.6 months (95% CI of 144.0–219.2 months) for patients with mixed epithelial and mesenchymal subtype, respectively. There were statistical significances in mean EFS between predominantly fetal epithelial subtype vs. macrotrabecular subtype ($p = 0.004$), and predominantly fetal epithelial subtype vs. small cell undifferentiated subtype ($p = 0.017$).

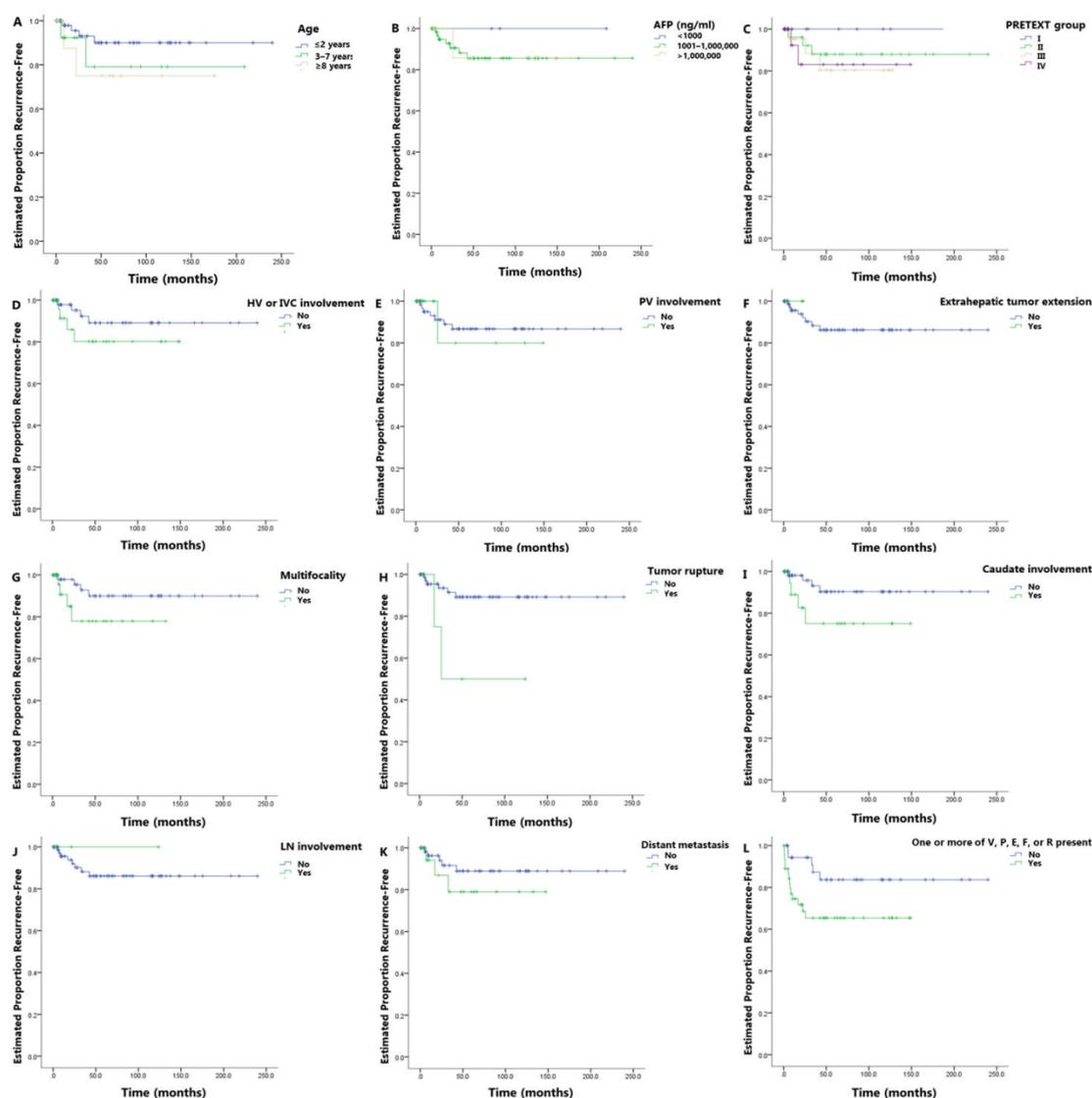


Figure S3. Kaplan-Meier (KM) curves of recurrence-free survival (RFS). Figure 3A. KM curves according to age at initial presentation. The mean RFS was 218.3 months (95% CI, 198.2–238.4 months) for patients ≤ 2 years, 169.9 months (95% CI of 120.5–219.2 months) for patients aged 3–7 years, and 135.5 months for patients ≥ 8 years (95% CI of 87.5–183.6 months), respectively. There was no significant difference in mean RFS among three groups ($p = 0.376$). Figure 3B. KM curves according to serum alpha-fetoprotein (AFP) levels at initial presentation. The mean RFS of patients with AFP < 1000 ng/mL was not estimated because no event was observed in this group. The mean RFS was 208.4 months (95% CI, 186.6–230.1 months) for patients with AFP of 1001–1000000 ng/mL, and 146.3 months (95% CI, 109.8–182.8 months) for patients with AFP more than 1000000 ng/mL, respectively. There was no significant difference in mean RFS between two groups ($p = 0.938$). Figure 3C. KM curves according to PRETEXT group. The mean RFS was 213.4 months (95% CI, 185.4–241.5 months) for patients with group II, 108.1 months (95% CI, 88.0–128.2 months) for patients with group III, and 125.9 months (95% CI, 96.8–155.1 months) for patients with group IV, respectively. The mean RFS of PRETEXT group I was not estimated because no event had been observed in this group. There was no significant difference in mean RFS among four groups ($p = 0.657$). Figure 3D. KM curves according to HV or IVC involvement (V). The mean RFS was 216.7 months (95% CI, 195.2–238.2 months) for patients with negative V, and 122.5 months (95% CI, 99.1–145.9 months) for patients with positive V, respectively. There was no significant difference in mean EFS between two groups ($p = 0.271$). Figure 3E. KM curves according to PV involvement (P). The mean RFS was 210.7 months (95% CI, 190.5–230.9 months) for patients with negative P, and 124.2 months (95% CI, 81.0–167.5 months)

for patients with positive P, respectively. There was no significant difference in mean RFS between two groups ($p = 0.950$). Figure 3F. KM curves according to extrahepatic tumor extension (E). The mean RFS was 209.8 months (95% CI, 190.3–229.2 months) for patients with negative E. The mean EFS of patients with positive E was not estimated because no event had been observed in this group. There was no significant difference in mean EFS between two groups ($p = 0.703$). Figure 3G. KM curves according to multifocality (F). The mean RFS was 218.5 months (95% CI, 198.7–238.4 months) for patients with negative F, and 106.5 months (95% CI, 83.7–129.4 months) for patients with positive F, respectively. There was no significant difference in mean RFS between two groups ($p = 0.141$). Figure 3H. KM curves according to tumor rupture (R). The mean RFS was 216.3 months (95% CI, 198.3–234.2 months) for patients with negative R, and 72.7 months (95% CI, 22.3–123.1 months) for patients with positive R, respectively. There was significant difference in mean RFS between two groups ($p = 0.020$). Figure 3I. KM curves according to caudate involvement (C). The mean RFS was 219.3 months (95% CI, 200.0–238.5 months) for patients with negative C, and 115.6 months (95% CI, 87.0–144.2 months) for patients with positive C, respectively. There was no significant difference in mean EFS between two groups ($p = 0.085$). Figure 3J. KM curves according to lymph node involvement (N). The mean RFS was 209.5 months (95% CI, 189.9–229.1 months) for patients with negative N. The mean RFS of patients with positive N was not estimated because no event had been observed in this group. There was no significant difference in mean EFS between two groups ($p = 0.634$). Figure 3K. KM curves according to distant metastasis (M). The mean RFS was 215.8 months (95% CI, 195.7–235.8 months) for patients with negative M, and 120.6 months (95% CI, 93.5–147.7 months) for patients with positive M, respectively. There was no significant difference in mean RFS between two groups ($p = 0.313$). Figure 3L. KM curves of recurrence-free survival (RFS) according to presence of one or more of VPEFR. The mean RFS was 217.8 months (95% CI, 194.1–241.5 months) for patients with negative VPEFR, and 126.0 months (95% CI, 107.6–144.5 months) for patients with positive VPEFR, respectively. There was no significant difference in mean RFS between two groups ($p = 0.366$).

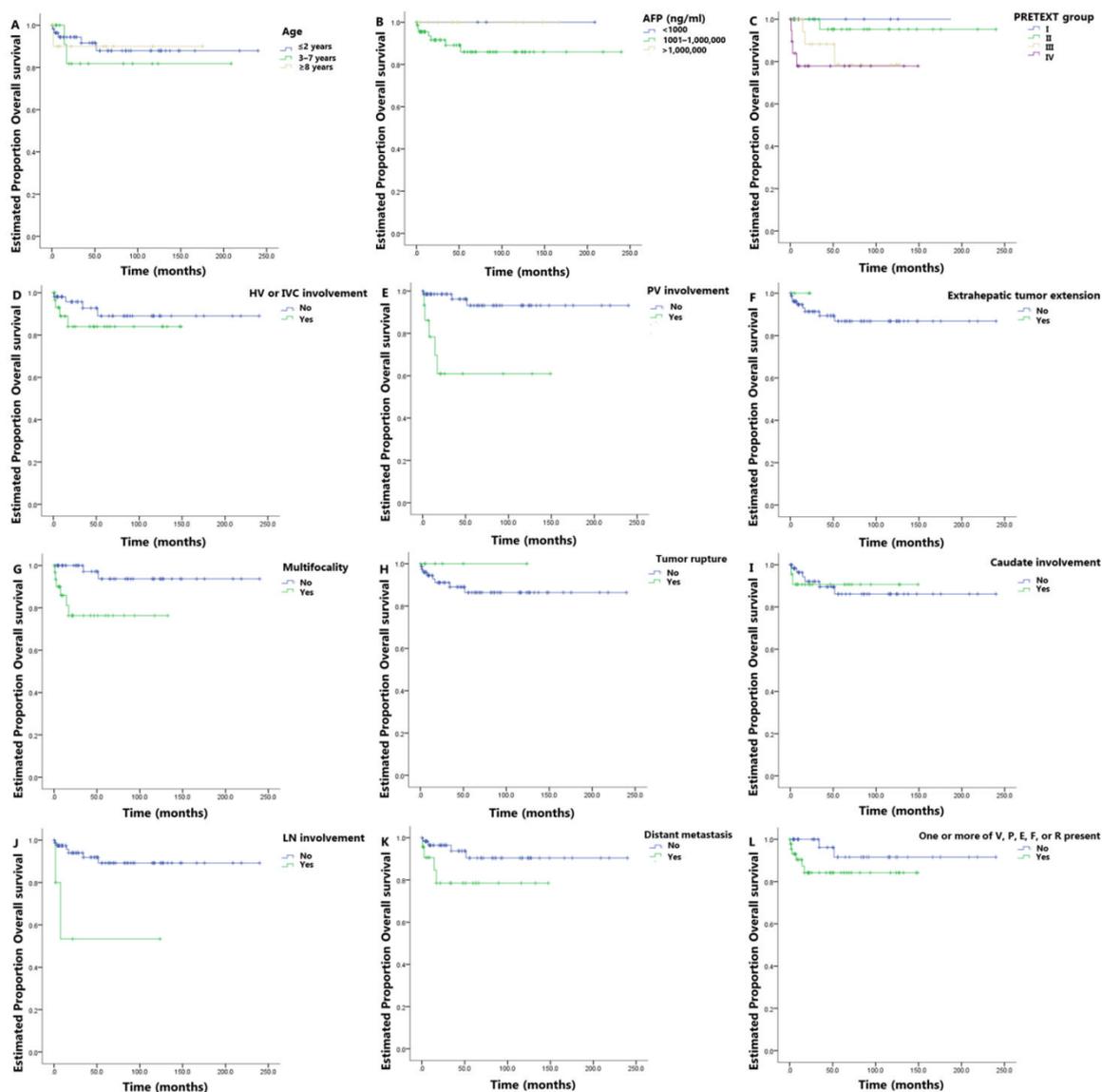


Figure S4. Kaplan-Meier (KM) Curves of Overall Survival (OS). Figure 4A. KM curves according to age at initial presentation. The mean OS was 213.9 months (95% CI of 192.1–235.8 months) for patients ≤ 2 years, 173.6 months (95% CI of 129.6–217.6 months) for patients aged 3–8 years, and 158.1 months for patients ≥ 8 years (95% CI of 125.8–190.4 months), respectively. There was no significant difference in mean OS among three groups ($p = 0.835$). Figure 4B. KM curves according to serum alpha-fetoprotein (AFP) levels at initial presentation. The mean OS of patients with AFP < 1000 ng/mL and 1001–1000000 ng/mL was not estimated because no event was observed in these groups. The mean OS was 209.3 months (95% CI, 187.7–230.9 months) for patients with AFP of 1001–1000000 ng/mL. There was no significant difference in mean RFS between two groups ($p = 0.476$). Figure 4C. KM curves according to PRETEXT group. The mean RFS was 230.0 months (95% CI, 211.3–248.7 months) for patients with group II, 107.0 months (95% CI, 86.0–128.0 months) for patients with group III, and 116.7 months (95% CI, 88.7–144.7 months) for patients with group IV, respectively. The mean RFS of PRETEXT group I was not estimated because no event had been observed in this group. There was no significant difference in mean RFS among four groups ($p = 0.077$). Figure 4D. KM curves according to HV or IVC involvement (V). The mean OS was 216.7 months (95% CI, 195.2–238.2 months) for patients with negative V, and 126.4 months (95% CI, 105.9–146.8 months) for patients with positive V, respectively. There was no significant difference in mean EFS between two groups ($p = 0.295$). Figure 4E. KM curves according to PV involvement (P). The mean OS was 225.8 months (95% CI, 210.2–241.4 months) for patients with negative P, and 94.3 months (95% CI, 56.4–132.2 months) for patients with positive P, respectively. There was a significant difference in mean OS between two groups ($p < 0.001$). Figure 4F. KM curves according to

extrahepatic tumor extension (E). The mean RFS was 210.9 months (95% CI, 191.8–230.0 months) for patients with negative E. The mean OS of patients with positive E was not estimated because no event had been observed in this group. There was no significant difference in mean EFS between two groups ($p = 0.621$). Figure 4G. KM curves according to multifocality (F). The mean OS was 227.4 months (95% CI, 210.7–244.1 months) for patients with negative F, and 103.1 months (95% CI, 82.2–124.0 months) for patients with positive F, respectively. There was a significant difference in mean OS between two groups ($p = 0.006$). Figure 4H. KM curves according to tumor rupture (R). The mean OS was 209.9 months (95% CI, 190.3–229.6 months) for patients with negative R. The mean OS of patients with positive R was not estimated because no event had been observed in this group. There was no significant difference in mean EFS between two groups ($p = 0.468$). Figure 4I. KM curves according to caudate involvement (C). The mean OS was 210.0 months (95% CI, 187.3–232.6 months) for patients with negative C, and 135.2 months (95% CI, 117.1–153.3 months) for patients with positive C, respectively. There was no significant difference in mean OS between two groups ($p = 0.992$). Figure 4J. KM curves according to lymph node involvement (N). The mean OS was 216.6 months (95% CI, 198.6–234.5 months) for patients with negative N, and 68.3 months (95% CI, 10.8–125.8 months) for patients with positive N. There was a significant difference in mean OS between two groups ($p = 0.003$). Figure 4K. KM curves according to distant metastasis (M). The mean OS was 219.6 months (95% CI, 200.4–238.9 months) for patients with negative M, and 117.7 months (95% CI, 91.8–143.7 months) for patients with positive M, respectively. There was no significant difference in mean RFS between two groups ($p = 0.084$). Figure 4L. KM curves according to presence of one or more of VPEFR. The mean OS was 223.3 months (95% CI, 201.3–245.3 months) for patients with negative VPEFR, and 126.6 months (95% CI, 110.1–143.1 months) for patients with positive VPEFR, respectively. There was no significant difference in mean RFS between two groups ($p = 0.137$).

Supplementary Figure Legend for Figure 2. Kaplan-Meier (KM) Curves of Event-Free Survival (EFS).

Figure 2A. KM curves according to age at initial presentation. The mean EFS was 197.3 months (95% CI, 172.0–222.6 months) for patients ≤ 2 years, 131.9 months (95% CI of 78.4–185.5 months) for patients aged 3–7 years, and 102.0 months for patients ≥ 8 years (95% CI of 53.3–150.8 months), respectively. There was no significant difference in mean EFS among three groups ($p = 0.078$).

Figure 2B. KM curves according to serum alpha-fetoprotein (AFP) levels at initial presentation. The mean EFS of patients with AFP < 1000 ng/mL was not estimated because no event was observed in this group. The mean EFS was 175.9 months (95% CI, 149.8–202.0 months) for patients with AFP of 1001–1000000 ng/mL, and 146.3 months (95% CI, 109.8–182.8 months) for patients with AFP more than 1000000 ng/mL, respectively. There was no significant difference in mean EFS between two groups ($p = 0.389$).

Figure 2C. KM curves according to PRETEXT group. The mean EFS was 190.7 months (95% CI, 155.9–222.5 months) for patients with group II, 93.7 months (95% CI, 70.7–116.6 months) for patients with group III, and 92.7 months (95% CI, 60.0–125.5 months) for patients with group IV, respectively. The mean EFS of PRETEXT group I was not estimated because no event had been observed in this group. There was no significant difference in mean EFS among four groups ($p = 0.106$).

Figure 2D. KM curves according to HV or IVC involvement (V). The mean EFS was 194.6 months (95% CI, 167.9–221.2 months) for patients with negative V, and 97.6 months (95% CI, 72.0–123.3 months) for patients with positive V, respectively. There was no significant difference in mean EFS between two groups ($p = 0.079$).

Figure 2E. KM curves according to PV involvement (P). The mean EFS was 191.0 months (95% CI, 167.4–214.7 months) for patients with negative P, and 79.9 months (95% CI, 38.5–121.3 months) for patients with positive P, respectively. There was a significant difference in mean EFS between two groups ($p = 0.030$).

Figure 2F. KM curves according to extrahepatic tumor extension (E). The mean EFS was 179.3 months (95% CI, 155.8–202.8 months) for patients with negative E. The mean EFS of patients with positive E was not estimated because no event had been observed in this group. There was no significant difference in mean EFS between two groups ($p = 0.456$).

Figure 2G. KM curves according to multifocality (F). The mean EFS was 204.9 months (95% CI, 181.1–228.7 months) for patients with negative F, and 78.1 months (95% CI, 54.4–101.7 months) for patients with positive F, respectively. There was a significant difference in mean EFS between two groups ($p = 0.002$).

Figure 2H. KM curves according to tumor rupture (R). The mean EFS was 186.6 months (95% CI, 163.5–209.7 months) for patients with negative R, and 59.2 months (95% CI, 12.5–105.9 months) for patients with positive R, respectively. There was no significant difference in mean EFS between two groups ($p = 0.089$).

Figure 2I. KM curves according to caudate involvement (C). The mean EFS was 184.9 months (95% CI, 158.6–211.1 months) for patients with negative C, and 105.2 months (95% CI, 75.7–134.6 months) for patients with positive C, respectively. There was no significant difference in mean EFS between two groups ($p = 0.492$).

Figure 2J. KM curves according to lymph node involvement (N). The mean EFS was 183.8 months (95% CI, 160.5–207.1 months) for patients with negative N, and 67.9 months (95% CI, 9.9–125.8 months) for patients with positive N, respectively. There was no significant difference in mean EFS between two groups ($p = 0.133$).

Figure 2K. KM curves according to distant metastasis (M). The mean EFS was 199.7 months (95% CI, 175.8–223.7 months) for patients with negative M, and 83.2 months (95% CI, 53.8–112.7 months) for patients with positive M, respectively. There was a significant difference in mean EFS between two groups ($p = 0.003$).

Figure 2L. KM curves according to presence of one or more of VPEFR. The mean EFS was 204.8 months (95% CI, 176.6–233.0 months) for patients with negative VPEFR, and 100.6 months (95% CI, 79.7–121.4 months) for patients with positive VPEFR, respectively. There was a significant difference in mean EFS between two groups ($p = 0.035$).



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