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

Hee Mang Yoon, Jisun Hwang, Kyung Won Kim, Jung-Man Namgoong, Dae Yeon Kim, Kyung-Nam Koh, Hyery Kim, and Young Ah Cho

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 or the intrahepatic IVC |
| Tumor thrombus in any hepatic vein or the intrahepatic IVC |
| Any of the following criteria: |
| Portal venous involvement (P) | Any of the following criteria: |
| Tumor obliterates or encases either both portal veins or the main portal vein |
| Tumor thrombus in either or both the right and left portal veins or the main portal vein |
| Extrahepatic tumor extension (E) | Any of the following criteria: |
| Tumor crosses boundaries or tissue planes |
| Portal venous involvement (P) | Any of the following criteria: |
| Tumor involves the caudate lobe |
| Multifocality (F) | Any of the following criteria for multifocality: |
| Two or more separate hepatic tumors with normal liver tissue between the tumors |
| Pathologically diagnosed after paracentesis/upfront resection |
| Caudate lobe (C) | Tumor involving the caudate lobe |
| Lymph node metastasis (N) | 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 distant metastasis: |
| Single non-calcified lung lesion with diameter ≥ 5 mm |
| Two or more non-calcified lung lesions with each diameter ≥ 3 mm |

IVC = inferior vena cava. * First-order hepatic vein: between its confluence with IVC and its most central branch. ‡ 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 < 1000ng/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 1001–1000000ng/mL, and 146.3 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 < 1000ng/mL and 100–1000000ng/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 100–1000000ng/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
The mean RFS was 210.9 months (95% CI, 191.8–230.0 months) for patients with negative R. 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 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 < 1000ng/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 1001–100000ng/mL, and 146.3 months (95% CI, 109.8–182.8 months) for patients with AFP more than 100000ng/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, 12.5–103.9 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).