Supplementary Table 3. GRADE summary of findings for each key question

(1) GRADE summary of findings, KQ1

Outcomes	Impact	No. of participants (studies)	Certainty of the evidence (GRADE)
The impact of abdominal CT or liver MRI imaging on the detection rate of tumor lesions	Compared to multiphase contrast-enhanced abdominal CT, additional satellite lesions were detected on DW-MR, which upgraded their stage in 2 of 10 patients (20%).	10 (1 observational study)	⊕◯◯◯ Very low
The impact of abdominal CT or liver MRI imaging techniques on PRETEXT staging	In the 7 patients of 30 patients (7/30, 23.3%) with a malignant hepatic tumor (hepatoblastoma in most patients), the PRETEXT group changed with the addition of the hepatocyte phase of imaging of liver MRI.	30 (1 observational study)	⊕◯◯◯ Very low

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
KQ, key question; CT, computed tomography; MRI, magnetic resonance imaging; DW-MR, diffusion-weighted magnetic resonance; PRETEXT, PRE-Treatment EXTent of disease.

(2) GRADE summary of findings, KQ2

Outcomes	Impact	No. of participants (studies)	Certainty of the evidence (GRADE)
HR	In 12 studies reporting hazard ratios (HRs) for PRETEXT groups, an overall trend was observed in which HRs increased with higher PRETEXT group. Among these, 10 studies demonstrated a statistically significant increase in HR (P<0.05). Regarding PRETEXT annotation factors (V/P/E/F/R/C/N/M), they were reported in 6, 5, 2, 7, 4, 0, 0, and 13 studies, respectively. With the exception of one study reporting HRs for V and another reporting combined V/P findings, all other studies consistently showed that the presence of a positive annotation factor was associated with an increased HR compared with its absence.	4,524 (12 observational studies)	⊕◯◯◯ Very low
OS	In 11 studies reporting overall survival (OS) by PRETEXT group, 7 demonstrated a trend of decreasing OS with increasing PRETEXT group, of which 6 reached statistical significance (P<0.05). In 4 studies, reversal of OS among groups I–III was observed; however, when compared with groups I–III, group IV consistently showed decreased OS, with statistical significance confirmed in only 2 studies (P<0.05). A total of 7 studies presented OS outcomes according to PRETEXT annotation factors. Patients with V+, P+, F+, or M+ status exhibited lower OS in all studies compared with their negative counterparts. For E+ and R+ status, results varied across studies. Although statistical significance was inconsistent, 5 of 6 studies assessing M+ demonstrated significantly reduced OS (P<0.05).	1,305 (11 observational studies)	⊕◯◯◯ Very low
EFS	A total of 9 studies reported event-free survival (EFS) according to PRETEXT group. Seven studies demonstrated decreasing EFS with increasing PRETEXT group, while 2 studies reported lower EFS in group I compared with group II. Six studies confirmed statistical significance (P<0.05). Seven studies presented EFS outcomes based on PRETEXT annotation factors. Except for one study in which N– values were not reported, all studies demonstrated lower EFS in patients with positive annotation factors compared with those with negative factors.	1,180 (9 observational studies)	⊕◯◯◯ Very low

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
KQ, key question; PRETEXT, PRE-Treatment EXTent of disease; V, involvement of the hepatic veins or inferior vena cava; P, involvement of the main portal vein; E, extrahepatic disease extension including peritoneal seeding; F, presence of multiple intrahepatic tumors; R, evidence of tumor rupture; C, involvement of the caudate lobe; N, presence of regional lymph node metastasis; M, distant metastasis.

(3) GRADE summary of findings, KQ3

Outcomes	Impact	No. of participants (studies)	Certainty of the evidence (GRADE)
OS	In the CCG/POG trial by Ortega et al.,[39] 182 patients with hepatoblastoma were enrolled and randomly assigned to receive either cisplatin, vincristine, and fluorouracil (Regimen A) or cisplatin plus doxorubicin (Regimen B). The 5-yr OS rates were 69% (standard error=5%) in Regimen A and 72% (standard error=5%) in Regimen B, showing no significant difference between the 2 groups (P=0.88). In the SIOPEL 3 study by Perilongo et al.,[40] 126 patients with standard-risk hepatoblastoma were randomized to receive either cisplatin monotherapy (CDDP alone) or cisplatin plus doxorubicin (PLADO). The reported 3-yr OS was 95% in the cisplatin monotherapy group and 93% in the PLADO group, with no significant difference between the treatment arms.	308 (2 RCTs)	⊕⊕⊕○ Moderate
EFS	In the CCG/POG trial by Ortega et al.,[39] 182 patients with hepatoblastoma were randomized to receive either cisplatin, vincristine, and fluorouracil (Regimen A) or cisplatin plus doxorubicin (Regimen B). The 5-yr event-free survival (EFS) rates were 57% and 69% for Regimen A and Regimen B, respectively, showing no substantial difference in treatment outcomes. Among patients with stage IV disease, the 5-yr EFS was 25% in both groups, reflecting poor outcomes regardless of regimen. In the SIOPEL 3 study by Perilongo et al.,[40] 126 standard-risk patients aged ≤16 yr were treated with cisplatin monotherapy (CDDP alone) and 129 patients received cisplatin plus doxorubicin (PLADO). The 3-yr EFS rates were 83% in the cisplatin-alone group and 85% in the PLADO group, demonstrating comparable efficacy between the 2 regimens.	308 (2 RCTs)	⊕⊕⊕○ Moderate
Second malignant neoplasm	In the JPLT2 study, a total of 361 patients with hepatoblastoma were treated with a cisplatin-doxorubicin combination regimen (CITA), among whom 13 patients subsequently developed secondary malignancies.	361 (1 observational study)	⊕○○○ Very low
Hearing loss	In the SIOPEL3 trial reported by Perilongo et al.,[40] grade ≥3 hearing impairment was observed in 5 of 89 patients (5.6%) in the cisplatin monotherapy (CDDP) group and 7 of 79 patients (8.9%) in the cisplatin-doxorubicin (PLADO) group, with no significant difference between the 2 groups. In the JPLT2 study, hearing loss was documented in 61 of 361 patients (17%).	487 (1 RCT and 1 observational study)	⊕⊕○○ Low
Cardiac toxicity	In the JPLT2 study, cardiotoxicity was observed in 18 of 361 patients (5%).	361 (1 observational study)	⊕○○○ Very low

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
KQ, key question; OS, overall survival; CCG, Children's Cancer Group; POG, Pediatric Oncology Group; SIOPEL, International Childhood Liver Tumours Strategy Group; RCT, randomized controlled trial; JPLT, Japanese Study Group for Pediatric Liver Tumors.

(4) GRADE summary of findings, KQ4

Outcomes	Impact	No. of participants (studies)	Certainty of the evidence (GRADE)
OS	In patients who underwent upfront surgery, the 4-yr overall survival (OS) was 95% in the low-risk group and 100% in the very low-risk group in the COG AHEP0731 trial. Similarly, the JPLT1 and JPLT2 studies reported 5-yr OS rates of 100% for PRETEXT I and 93.8% for PRETEXT II. In patients who underwent delayed surgery, the SIOPEL3 trial demonstrated 3-yr OS rates of 95% in the cisplatin monotherapy group and 93% in the cisplatin-doxorubicin combination group.	417 (6 observational studies and 1 RCTs)	⊕○○○ Very low
EFS	In patients who underwent upfront surgery, the 4-yr event-free survival (EFS) was 92% in the low-risk group and 100% in the very low-risk group in the COG AHEP0731 trial, while the JPLT1 and JPLT2 studies reported 5-yr EFS rates of 88.9% for PRETEXT I and 73.5% for PRETEXT II. In patients who underwent delayed surgery, the SIOPEL3 trial demonstrated 3-yr EFS rates of 83% in the cisplatin monotherapy group and 85% in the cisplatin-doxorubicin combination group.	417 (6 observational studies and 1 RCTs)	⊕○○○ Very low
Surgical complications	In the COG AHEP0731 study, surgical complications were observed in 2 patients (4%) in the low-risk group, including bile leaks requiring re-exploration, while 1 patient in the very low-risk group sustained an intraoperative complication involving middle hepatic vein injury following upfront surgery. In the JPLT1 and JPLT2 studies, one patient who underwent an upfront nonanatomic right hepatectomy, performed based on institutional decision, died as a result of surgical complications.	417 (6 observational studies and 1 RCTs)	⊕○○○ Very low
Severe adverse events	In the COG AHEP0731 study, serious adverse events included febrile neutropenia in 7 patients (14%), infection and diarrhea in 4 (8%), neutropenia in 3 (6%), peripheral polyneuropathy in 2 (4%), and hearing impairment in 1 (2%). In the SIOPEL3 study, reported toxicities included ototoxicity of Brock grade ≥2 in 33 patients (13%), nephrotoxicity defined as glomerular filtration rate <80 mL/min/1.73 m² in 30 (12%), and cardiotoxicity with left ventricular fractional shortening <30% in 10 (4%).	417 (6 observational studies and 1 RCTs)	⊕○○○ Very low

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
KQ, key question; COG, Children's Oncology Group; PRETEXT, PRE-Treatment EXTent of disease; RCT, randomized controlled trial; JPLT, Japanese Study Group for Pediatric Liver Tumors; SIOPEL, International Childhood Liver Tumours Strategy Group.

https://doi.org/10.3345/cep.2026.02691

(5) GRADE summary of findings, KQ5

Outcomes	Impact	No. of participants (studies)	Certainty of the evidence (GRADE)
OS	In a single-institution retrospective study (Hu et al.[51]) including 75 patients with pulmonary metastases, the 3-year overall survival (OS) was 73.3% in those who underwent pulmonary metastasectomy compared with 56.1% in those who did not, with no statistically significant difference (*P*=0.099). A multicenter prospective study (JPLT-2; Hishiki et al.[49]) analyzed 33 patients with residual pulmonary metastases after chemotherapy and reported 3-year OS rates of 63.6% in the surgical group versus 41.8% in the nonsurgical group, which was not statistically significant (*P*=0.8402). Similarly, a multicenter prospective trial (AHEP0731; O'Neill et al.[50]) that included 29 patients with pulmonary metastases found no significant difference in 3-year OS between those who underwent metastasectomy and those who did not (*P*=0.67).	137 (3 observational studies)	⊕○○○ Very low
EFS	In a multicenter prospective study (JPLT-2; Hishiki et al.[49]), among 33 patients with residual pulmonary metastases after chemotherapy, the 3-year event-free survival (EFS) was 45% in those who underwent pulmonary metastasectomy and 21.8% in those who did not, with no statistically significant difference (*P*=0.4096). In another multicenter prospective trial (AHEP0731; O'Neill et al.[50]) involving 29 patients with pulmonary metastases, no significant difference in 3-year EFS was observed between patients who underwent metastasectomy and those who did not (*P*=0.11).	62 (2 observational studies)	⊕○○○ Very low
Surgical complications	In the multicenter prospective trial AHEP0731 (O'Neill et al.[50]) pulmonary metastasectomy was performed in 10 patients, and no surgery-related complications were reported.	10 (1 observational study)	⊕○○○ Very low

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
KQ, key question; JPLT, Japanese Study Group for Pediatric Liver Tumors.

(6) GRADE summary of findings, KQ6

Outcomes	Impact	No. of participants (studies)	Certainty of the evidence (GRADE)
Incidence of hearing impairment	In the SIOPEL 6 trial, the incidence of any hearing loss was significantly lower in the STS group compared with the non-STS group (33% [18 of 55] vs. 63% [29 of 46], *P*=0.002). Similarly, in the COG ACCL0431 trial, hearing loss occurred in 29% of patients (14 of 49) in the STS group versus 56% (31 of 55) in the non-STS group (*P*=0.0002). In SIOPEL 6, the relative risk of hearing loss with cisplatin plus STS was 0.52 (95% CI, 0.33–0.81), indicating a 48% risk reduction. The overall likelihood of hearing impairment was also significantly lower with STS administration (odds ratio, 0.31; 95% CI, 0.13–0.73; *P*=0.0036).	234 (2 RCTs)	⊕○○○ Very low
OS	In the SIOPEL 6 trial, the 3-yr overall survival (OS) was 98% (95% CI, 88–100) in the STS group versus 92% (95% CI, 81–97) in the non-STS group. In contrast, the COG ACCL0431 trial reported a 3-year OS of 70% (95% CI, 56–80) in the STS group compared with 87% (95% CI, 76–93) in the non-STS group (*P*=0.07).	234 (2 RCTs)	⊕○○○ Very low
EFS	In the SIOPEL 6 trial, the 3-yr event-free survival (EFS) was 82% (95% CI, 69–90) in the STS group and 79% (95% CI, 65–88) in the non-STS group. In the COG ACCL0431 trial, the corresponding 3-year EFS was 54% (95% CI, 40–66) versus 64% (95% CI, 50–74), showing no statistically significant difference (*P*=0.36).	234 (2 RCTs)	⊕○○○ Very low
Severe adverse events (CTCAE grade≥3)	In the SIOPEL 6 trial, 8 serious adverse reactions were reported as possibly associated with STS, including 2 cases of infection, 2 of neutropenia, one of anemia, 2 of tumor progression, and one of nausea and vomiting. In contrast, in the COG ACCL0431 trial, 194 serious adverse events were documented in 26 participants who had received STS; however, none were considered probably or definitely related to STS. The most frequently reported serious adverse event was decreased neutrophil count, with 26 episodes occurring in 14 participants.		⊕○○○ Very low

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
KQ, key question; COG, Children's Oncology Group; STS, Sodium Thiosulfate; CI, confidence interval; SIOPEL, International Childhood Liver Tumours Strategy Group; RCT, randomized controlled trial; CTCAE, Common Terminology Criteria for Adverse Events.

https://doi.org/10.3345/cep.2026.02691

(7) GRADE summary of findings, KQ7

Outcomes	Impact	No. of participants (studies)	Certainty of the evidence (GRADE)
OS, PFS, and EFS of WDF histology	An overall survival advantage was observed in patients with pure (or predominantly) fetal tumors, and this trend approached statistical significance	59 (2 observational studies)	⊕◯◯◯ Very low
OS, PFS, and EFS of SCU histology	Small cell undifferentiated elements were statistically significant predictors of increased risk of death. The category of pure small cell undifferentiated HB is no longer accepted, because tumors showing loss of SMARCB1 (INI1) nuclear staining should be classified as malignant rhabdoid tumors.	178 (1 observational study)	⊕⊕◯◯ Low

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
KQ, key question; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; WDF, well-differentiated fetal; SCU, small cell undifferentiated.

https://doi.org/10.3345/cep.2026.02691