

ORIGINAL ARTICLE OPEN ACCESS

Treatment Adaptation to Surgical Timing in Pediatric Hepatoblastoma: A 19-Year Single-Center Experience With Resection and Liver Transplantation

Claudia Pellegrinelli¹  | Laura Cavalleri¹  | Michela Bravi²  | Paolo Marra^{3,4}  | Clarissa Valle³  | Lisa Licini⁵  | Domenico Pinelli⁶  | Massimo Provenzi¹  | Sandro Sironi^{3,4}  | Lorenzo D'Antiga^{2,4} 

¹Pediatric Oncology, Papa Giovanni XXIII Hospital, Bergamo, Italy | ²Pediatric Hepatology Gastroenterology and Transplantation, Papa Giovanni XXIII Hospital, Bergamo, Italy | ³Department of Radiology, Papa Giovanni XXIII Hospital, Bergamo, Italy | ⁴Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy | ⁵Unit of Pathology, Department of Oncology and Hematology, Papa Giovanni XXIII Hospital, Bergamo, Italy | ⁶Unit of General Surgery 3 and Transplantation, Papa Giovanni XXIII Hospital, Bergamo, Italy

Correspondence: Claudia Pellegrinelli (cpellegrinelli@asst-pg23.it)

Received: 17 June 2026 | **Revised:** 8 August 2026 | **Accepted:** 22 August 2026

Keywords: children | hepatoblastoma | liver tumors | survival | toxicity | transplantation

ABSTRACT

Background: The management of hepatoblastoma (HB) relies on chemotherapy combined with surgery, either liver resection (LR) or liver transplantation (LT), with reported overall survival (OS) of 80%, cardiac toxicity of 6%, nephrotoxicity of 21%, ototoxicity of 32%–46%. In clinical practice, deviations from protocol-defined chemotherapy are often required to achieve resectability or bridge to transplantation. We aimed to evaluate the impact of treatment adaptation to surgical timing on OS and toxicity in a selected group of patients referred to a transplantation center.

Methods: We retrospectively analyzed patients with HB treated according to SIOPEL protocols at our center between 2004 and 2022. We collected clinical data, focusing on deviations from protocol-specified therapy, timing of medical and surgical treatment, OS, treatment-related toxicities (left ventricular ejection fraction, LVEF < 50%, estimated glomerular filtration rate, eGFR < 90 mL/mL/m², increased hearing threshold of 20–40 dB at 4 kHz).

Results: Forty-two patients, median age at diagnosis 1.9 years (IQR 0.7–3.5), 16/42 (38.1%) with metastatic disease, 24/42 (57.1%) with vascular involvement were recorded. Additional chemotherapy beyond protocol indications, due to persistent pulmonary metastases, delayed organ availability, or disease progression was administered to 17/20 (85%) who underwent first-line LT and 10/22 (45%) who underwent LR ($p = 0.007$). Death occurred in 3/20 (15%) versus 7/22 (31.8%) ($p = 0.2$) respectively. After median follow-up of 4.5 years (IQR 1.2–6.2) OS is 32/42 (71.4%); cardiotoxicity developed in 1/42 (2.4%), nephrotoxicity in 8/42 (19%), ototoxicity in 9/42 (21.4%).

Conclusions: A large proportion of patients with HB require adaptation of protocol-specified therapy, especially LT candidates. This favors successful management and is not associated with increased toxicity compared to previous reports.

Abbreviations: AFP, alfa-fetoproteina; EFS, event free survival; eGFR, estimated glomerular filtration rate; HB, hepatoblastoma; HR, High-risk; IQR, interquartile range; LR, liver resection; LT, liver transplantation; LVEF, left ventricular ejection fraction; OS, overall survival; SR, standard-risk.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2026 The Author(s). *Pediatric Transplantation* published by Wiley Periodicals LLC.

1 | Introduction

Hepatoblastoma (HB) is the most common primary malignant liver tumor in the pediatric population [1–3], with an incidence of approximately 1.5–2.3 cases per million children per year. Historically, outcomes for HB were poor, but the implementation of multimodal therapy combining platinum-based chemotherapy with complete surgical excision has dramatically improved survival, with contemporary 5-year overall survival (OS) rates around 80% [4].

Complete tumor surgical removal, either by liver resection or liver transplantation (LT), remains the cornerstone of curative treatment [5]. Surgical resection following neoadjuvant chemotherapy has been demonstrated to be feasible in the majority of patients and is associated with favorable event-free survival (EFS) and OS [6]. Nevertheless, at diagnosis, a substantial proportion of tumors—particularly those classified at high stage or with vascular invasion—are unresectable. Neoadjuvant chemotherapy facilitates tumor shrinkage and downstaging, enabling liver resection in many cases that would otherwise require total hepatectomy and transplantation.

Consequently, during time, the aim of clinicians was to reduce long-term treatment-related toxicity. Scant data are available on long-term follow-up, but SIOPEL studies showed a cardiotoxicity prevalence of 6% in case of doxorubicin slow infusion [7], ototoxicity prevalence of 32% in high risk (HR) patients and 46.5% in standard risk (SR) ones, nephrotoxicity prevalence of 8%–25% [8–10]. In SIOPEL protocols, HR patients represent 43% of all pediatric HB [11].

The role of LT has expanded over the past decades as an essential option for patients with tumors that remain unresectable despite intensive chemotherapy or in the context of multifocal disease. Although large registry analyses suggest that survival outcomes following LT are comparable to those achieved with liver resection in chemotherapy-treated patients, LT is typically reserved for cases in which liver resection cannot be safely achieved [5].

Despite advances in multimodal therapy, management of pediatric HB continues to face several challenges. These include determining the optimal timing of surgery relative to chemotherapy, balancing intensified preoperative therapy with the risks of treatment-related toxicity, and identifying which patients may benefit most from liver transplantation. Moreover, while international trials such as SIOPEL and collaborative studies like PHITT have established risk-adapted chemotherapy backbones, data regarding practical deviations from protocol—such as treatment intensification or additional cycles to facilitate definitive surgery—remain limited [12].

The primary aim of this study was to evaluate the impact of chemotherapy intensification and protocol deviations on surgical feasibility, treatment-related toxicity, and survival outcomes in children with hepatoblastoma treated at a single tertiary referral center.

2 | Materials and Methods

This was a retrospective, monocentric observational study conducted at the Pediatric Oncology and Liver Transplantations Units of ASST Papa Giovanni XXIII Hospital, Bergamo, Italy, a national referral center for pediatric liver tumors and liver transplantation. As a retrospective study conducted on anonymized records, the ethics committee evaluation was considered waived.

All consecutive pediatric patients diagnosed with hepatoblastoma or referred to our institution for treatment between January 2004 and December 2022 were eligible for inclusion. Inclusion criteria were as follows:

- Age inferior to 18 years at diagnosis
- Histologically or radiologically confirmed diagnosis of hepatoblastoma
- Treatment with curative intent
- Availability of complete clinical, treatment, and follow-up data

Patients with incomplete records were excluded. Patients were treated according to contemporary international protocols active at the time of diagnosis, including SIOPEL-3, SIOPEL-4, SIOPEL-6. Risk stratification was performed according to protocol definitions, incorporating PRETEXT staging, presence of metastases, serum alpha-fetoprotein (AFP) levels, and vascular involvement. Clinical data were retrieved from electronic medical records and institutional databases. The following variables were collected:

- Demographic data: age at diagnosis, sex, ethnicity, comorbidities.
- Disease characteristics: PRETEXT stage, presence and evolution of lung metastases, vascular involvement according to VPEFR (V = Vena Cava/Hepatic veins involvement; P = Portal Vein involvement; E = Extrahepatic extension; F = Multifocality; R = Tumor Rupture).
- Annotation factors, multifocality, AFP serum levels at diagnosis and during treatment.
- Treatment data: chemotherapy protocol, number and type of cycles administered, deviations from protocol-defined schedules, timing and type of definitive surgery (liver resection or liver transplantation), and use of rescue or bridging strategies.
- Surgical outcomes: completeness of tumor resection, surgical complications, and post-operative course.
- Toxicity: acute and long-term treatment-related toxicities, with particular focus on renal, auditory, and cardiac function.
- Follow-up data: disease status, relapse, survival, and last clinical evaluation.

Protocol deviation was defined as follows:

- Prolonged chemotherapy to allow achievement of resectability or bridge to liver transplantation;
- Postponed timing of surgery (either LR or LT) beyond 4 weeks after start of last chemotherapy cycle.

Toxicity was evaluated according to institutional follow-up protocols:

- Renal toxicity: assessed by serum creatinine by age and estimated glomerular filtration rate (eGFR inferior to 90 mL/min/1.73 m²) [13].
- Ototoxicity: evaluated by serial audiometric testing and classified according to standard pediatric ototoxicity grading systems (Chang scale if major of 20 and inferior to 40 dB at any frequencies below 4 kHz) [14].
- Cardiac toxicity: assessed by echocardiography, including left ventricular ejection fraction (LVEF) and signs of cardiomyopathy (LVEF < 50%).

Only persistent or long-term toxicities present at last follow-up were considered for the final analysis.

Continuous variables were expressed as median and interquartile range (IQR), while categorical variables were summarized as absolute numbers and percentages. Comparisons between groups (liver resection vs. liver transplantation; standard vs. intensified chemotherapy) were performed using the Mann–Whitney *U* test for continuous variables, the χ^2 test or Fisher's exact test for categorical variables, as appropriate.

Survival curves for EFS and OS were estimated using the Kaplan–Meier method and compared with the log-rank test. A *p* value < 0.05 was considered statistically significant. Data were analyzed using IBM SPSS Statistics, Version 29.0.2.0 (IBM Corp., 2023).

3 | Results

3.1 | Patients Demographic and Clinical Characteristics

Between January 2004 and December 2022, a total of 44 pediatric patients with hepatoblastoma were diagnosed or referred to our institution. Two patients were excluded because of incomplete clinical data, leaving 42 patients eligible for analysis.

The study population consisted of 29 males (69.1%) and 13 females (30.9%), with a median age at diagnosis of 1.9 years (IQR 0.7–3.5). Nineteen patients (45.2%) were initially diagnosed at other institutions and subsequently referred to our center for surgical management and continuation of chemotherapy. Overall, 22 patients (52.3%) underwent liver resection, while 20 patients (47.7%) underwent liver transplantation as first-line definitive surgery.

The median follow-up duration was 4.5 years (IQR 1.2–6.2). Most patients were of Caucasian ethnicity (92.8%), with a minority of South American (4.7%) and African (2.5%) origin.

At diagnosis, all patients presented with elevated serum alpha-fetoprotein (AFP) levels (> 100 ng/mL). The median AFP value was 53 000 ng/mL (IQR 27 033–270 000 ng/mL) for LR patients, 60 500 ng/mL (IQR 29 800–417 572 ng/mL) for LT ones.

According to PRETEXT staging, the majority of patients presented with advanced disease. PRETEXT IV tumors were observed in 59.5% of cases, followed by PRETEXT III in 21.4%, PRETEXT II in 11.9%, and PRETEXT I in 7.1%. At least one VPEFR annotation factor was present in 57.1% of patients.

Metastatic disease at diagnosis was documented in 38.1% of patients. Lung metastases were the most common presentation, either isolated or associated with lymph node involvement. A smaller proportion of patients presented with isolated nodal metastases.

Based on the SIOPEL criteria, 10 (23.8%) patients were classified SR HB, while 32 (67.2%) were classified as HR HB.

Post-chemotherapy staging was evaluated before surgery. Among patients undergoing LR, 11/22 patients had been classified as PRETEXT IV at diagnosis: 17/22 patients presented POST-TEXT II, 4/22 POST-TEXT III, and 1/22 POST-TEXT IV; following neoadjuvant chemotherapy, tumor response allowed surgical treatment with extended LR and additional wedge resections.

Among patients undergoing LT, 5/20 patients were classified as POST-TEXT III and 15/20 as POST-TEXT IV.

Baseline, clinical and detailed disease characteristics of the overall cohort are summarized in Table 1.

3.2 | Treatment Strategies and Protocol Deviations

All patients were treated according to contemporary international protocols active at the time of diagnosis, including SIOPEL-3, SIOPEL-4, SIOPEL-6. Treatment allocation reflected protocol-based risk stratification. Overall, more than half of the cohort received chemotherapy beyond protocol recommendations, either in terms of additional cycles or intensified regimens, with the primary goal of achieving complete surgical control of disease.

None of the patients included in the present cohort receive sodium thiosulfate.

Importantly, all patients received postoperative chemotherapy, regardless of completion of the full neoadjuvant schedule, in line with protocol recommendations and institutional practice.

Details of treatment protocols and deviations are summarized in Table 2.

TABLE 1 | Baseline demographic and clinical characteristics of the study population.

Demographic and clinical characteristics	Resection (<i>n</i> = 22)	Transplantation (<i>n</i> = 20)
Male sex, <i>n</i> (%)	15 (68.2)	14 (70.0)
Median age at diagnosis, years (IQR)	1.8 (0.8–3.5)	1.9 (0.7–3.8)
Median follow-up, years (IQR)	1.5 (0.9–5.8)	4.7 (2.2–9.8)
Ethnicity	22 (100.0)	20 (100.0)
Caucasian	21 (95.5)	18 (90.0)
African	0 (0.0)	1 (5.0)
South-American	1 (4.5)	1 (5.0)
Median α FP level, (ng/mL, IQR)	53 000 (27033–270 500)	60 500 (29800–417 572)
PRETEXT stage		
PRETEXT I, <i>n</i> (%)	1 (4.5)	0 (0.0)
PRETEXT II, <i>n</i> (%)	2 (9.1)	2 (10.0)
PRETEXT III, <i>n</i> (%)	5 (22.7)	4 (20.0)
PRETEXT IV, <i>n</i> (%)	13 (59.1)	14 (70.0)
VPEFR, <i>n</i> (%)	5 (46.7)	15 (75.0)
Metastasis at diagnosis, <i>n</i> (%)	6 (27.3)	10 (50.0)
Lung metastases	4 (66.7)	9 (90.0)
Lung and lymphnodes metastases	1 (16.6)	1 (10.0)
Lymphnodes metastases	1 (16.6)	0 (0.0)

Abbreviations: α FP, alfa-fetoprotein; IQR, interquartile range, PRETEXT, pre-treatment extent of disease, VPEFR, V = hepatic vein involvement/P = portal vein involvement/E = extrahepatic extension/F = multifocality/R = tumor rupture.

TABLE 2 | Treatment protocols and chemotherapy deviations.

Treatment characteristics	<i>N</i> (%)	Resection (<i>n</i> = 22)	Transplantation (<i>n</i> = 20)
Chemotherapy adaptation, <i>n</i> (%)	27 (64.3)	10 (45.5)	17 (85.0)
Primary definitive surgery, <i>n</i> (%)	40 (95.2)	22 (100.0)	18 (90.0)
Rescue transplantation after relapse, <i>n</i> (%)	2 (4.8)	—	2 (10.0)
Reasons for additional chemotherapy ^a			
Persistent lung metastases	6 (14.3)	3 (30.0)	3 (17.6)
Unresectable primary tumor	5 (30.9)	5 (50.0)	8 (47.1)
Disease progression	5 (11.9)	1 (10.0)	4 (23.5)
Bridge to surgery	3 (7.1)	1 (10.0)	2 (11.8)
Postoperative chemotherapy administered	42 (100.0)	22 (100.0)	20 (100.0)

^aPercentages calculated on patients receiving additional chemotherapy.

3.3 | Histological Characteristics

Histological subtype was available from diagnostic biopsy in 21/42 (50%) patients. Among these, 20 tumors showed epithelial HB features, while one patient showed mixed epithelial and mesenchymal ones.

The distribution of histological characteristics, after surgery, in patients undergoing LR and LT is reported in Table 3. Given the limited number of patients within each histological subgroup,

no statistical analysis of the correlation between histotype and outcome was performed.

3.4 | Surgical Management

Definitive surgical treatment consisted of either liver resection or liver transplantation. Patients were analyzed according to the initial surgical strategy. Therefore, patients who underwent LT after LR remained in the LR group for all analyses.

TABLE 3 | Histopathological characteristics after surgery.

Histological subtypes	All patients (n = 42)	Resection (n = 22)	Transplantation (n = 20)
Epithelial, n (%)	35 (83.3)	17 (77.3)	18 (90.0)
Fetal		3 (17.6)	5 (27.8)
Embryonal		—	—
Macrotrabecular		3 (17.6)	5 (27.8)
Hepatocarcinoma-like		6 (35.4)	4 (22.2)
Mixed		5 (29.4)	4 (22.2)
Mesenchymal, n (%)	—	—	—
Mixed epithelial and mesenchymal, n (%)	7 (16.7)	5 (22.7)	2 (10.0)

Among twenty-two patients undergoing liver resection, ten (45.5%) required additional preoperative chemotherapy beyond protocol recommendations. The most frequent reasons for intensification were: persistence of lung metastases (three out of ten), persistent unresectability of the liver lesion (five out of ten), disease progression during chemotherapy (one out of ten), or delayed surgical timing (one out of ten). Despite chemotherapy prolongation in many cases, 21 (95.5%) LR was performed within recommended timing windows and without unexpected perioperative complications. One patient underwent LR more than 4 weeks after the last pre-operative chemotherapy (after 31 days) cycle because of infectious complications.

Among 20 patients undergoing primary liver transplantation, 17 (85.0%) received intensified chemotherapy prior to transplantation. The most frequent reasons for intensification were: persistence of lung metastases (three of seventeen, 17.6%), persistent unresectability of the liver lesion (eight of seventeen, 47.1%), disease progression during chemotherapy (four of seventeen, 23.5%), or bridge to surgery (two of seventeen, 11.8%). Two patients underwent rescue liver transplantation, as second line surgery following hepatic recurrence after liver resection.

Despite chemotherapy prolongation in many cases, all transplant procedures were performed within recommended timing windows and without unexpected perioperative complications. A comprehensive overview of surgical strategies and outcomes is reported in Table 2.

3.5 | Toxicity

Treatment-related toxicity was evaluated at last follow-up among surviving patients. Overall, toxicity was manageable and did not appear to be substantially increased in patients receiving intensified chemotherapy.

Among patients alive at last follow-up ototoxicity was observed in nine (21.4%) patients, predominantly mild; moderate and severe ototoxicity were documented in two (22.2%). Nephrotoxicity was reported in eight (19.0%) patients, equally distributed between mild and moderate grades. Only one case showed clinically relevant long-term cardiac toxicity.

Importantly, the incidence of persistent renal or auditory toxicity did not differ substantially between resected and transplanted patients (p-value 0.823 for nephrotoxicity, 0.064 for ototoxicity, and 1 for cardiac toxicity).

No statistically significant differences in treatment-related organ toxicities were observed between patients receiving additional chemotherapy and those who did not.

Specifically, nephrotoxicity occurred in 5/27 patients (18.5%) in the group receiving additional chemotherapy and in 3/15 patients (20.0%) in the group without additional chemotherapy ($p = 0.743$).

Cardiotoxicity was a rare event, occurring in none of the patients in the additional chemotherapy group (0/27) and in 1/15 patients (6.7%) in the non-additional chemotherapy group ($p = 0.357$).

Ototoxicity was reported in 3/27 patients (11.1%) receiving additional chemotherapy and in 2/15 patients (13.3%) not receiving additional chemotherapy ($p = 0.488$).

Treatment-related toxicities are summarized in Table 4.

3.6 | Relapse Patterns

Disease relapse occurred in nine patients (21.4%). The lung was the most frequent site, involved in seven out of nine (77.8%). Relapse in the native liver occurred in two out of nine (22.2%), while combined relapses involving lung and liver (native or transplanted) were observed in two out of nine (22.2%).

Among patients who relapsed, six out of nine (66.7%) died within 1 year from diagnosis. Two transplanted patients (22.2%) experienced late deaths at 5 years, 3 months and 9 years, 6 months after first relapse, following multiple lines of salvage therapy, including metastasectomy, high-dose chemotherapy with autologous stem cell rescue, and liver retransplantation.

Two patients (22.2%) underwent rescue liver transplantation for liver relapse and died of extrahepatic disease recurrence within 1 year from transplant. In the first patient, hepatic resection was performed after a favorable response to chemotherapy, with

TABLE 4 | Outcome and middle-term treatment-related toxicities.

Outcome and treatment related-toxicities	All patients (n = 42)	Resection (n = 22)	Transplantation (n = 20)
Overall survival, n (%)	32 (76.2)	15 (68.1)	17 (85.0)
Relapse, n (%)	9 (21.4)	6 (27.3)	3 (15.0)
Site of relapse			
Lung	7 (77.8)	4 (66.7)	3 (100.0)
Naïve liver	2 (22.2)	2 (33.3)	—
Lung and liver	—	—	—
Lymphnodes	1 (11.1)	—	1 (33.3)
Toxicity profile, n (%)	18 (42.8)	7 (31.8)	11 (55.0)
Ototoxicity	9 (21.4)	2 (100.0)	7 (100.0)
Mild	7 (77.8)	2 (100.0)	5 (71.4)
Moderate	1 (11.1)	—	1 (14.3)
Severe	1 (11.1)	—	1 (14.3)
Nephrotoxicity	8 (19.0)	4 (100.0)	4 (100.0)
Mild	5 (62.5)	3 (75.0)	2 (50.0)
Moderate	3 (37.5)	1 (25.0)	2 (50.0)
Severe	—	—	—
Cardiac Toxicity	1 (2.4)	1 (100.0)	—
Mild	—	—	—
Moderate	—	—	—
Severe	1 (100.0)	1 (100.0)	—

downstaging from PRETEXT IV to POSTTEXT II. In the second patient, initially classified as PRETEXT IV, chemotherapy resulted in POSTTEXT IV.

In both cases, recurrence occurred in areas corresponding to previous tumor localization. In one patient, histological examination showed microscopic tumor involvement at the resection margin.

3.7 | Survival Outcomes

At a median time of 4.5 years of follow up (range) there were three deaths (15%) in patients transplanted as first line and in seven (31.8%) treated with liver resection. Kaplan-Meier analysis curve showed that Event-free survival (EFS) (Figure 1) and overall survival (OS) (Figure 2) were comparable between patients undergoing liver resection and those undergoing liver transplantation ($p=0.832$, log rank 0.045).

Among the two patients who underwent rescue LT because of intra-hepatic relapse, both died following a second disease relapse after LT: 1/2 developed post-transplant lymph node metastasis, whereas the other experienced lung metastases.

Among the three patients who underwent primary liver transplantation and subsequently died, all deaths were attributable to post-transplant lung metastatic disease.

In particular, 1/3 developed lung metastases even if they were not present at diagnosis; histopathological examination demonstrated a predominantly epithelial fetal HB.

The remaining two patients had lung metastases at diagnosis, which showed complete radiological response before LT. In both cases, histopathological examination revealed predominant fetal-type HB.

Among seven patients who died after liver resection, 3/7 received additional chemotherapy because of persistent lung metastases, 1/7 because of progression of the disease during treatment, and 2/7 because of intrahepatic relapse during treatment. Only one of the patients who received additional preoperative chemotherapy to reach resectability eventually died.

No statistically significant survival difference was observed between patients treated with standard chemotherapy and those receiving modulated regimens ($p=0.570$, Chi-square 0.323).

Survival outcomes are detailed in Table 4.

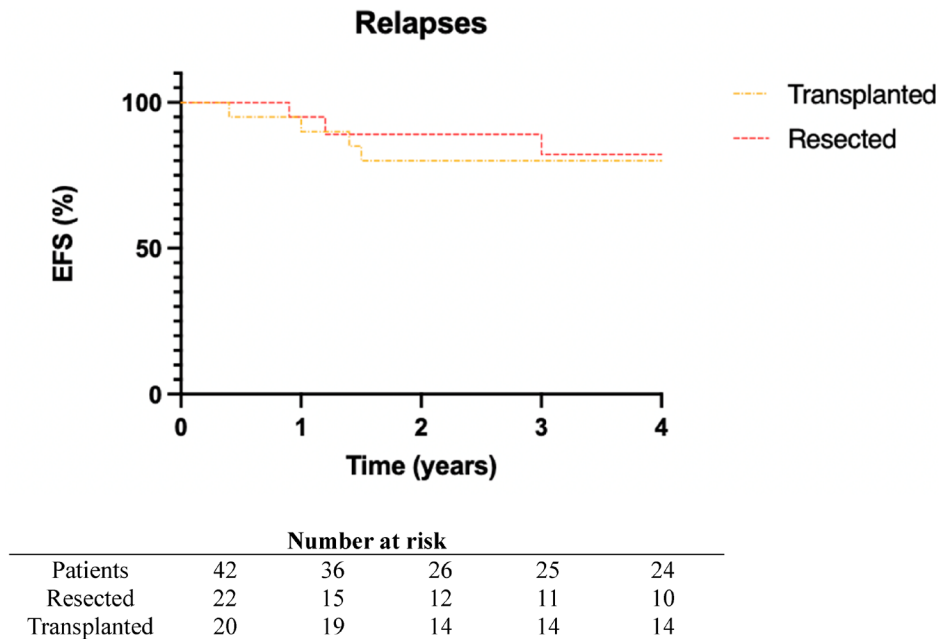


FIGURE 1 | Time to relapse in pediatric patients affected by hepatoblastoma: 4-years event-free survival (EFS) is comparable between liver resection (LR) patients (81.9%) and liver transplantation (LT) ones (75%).

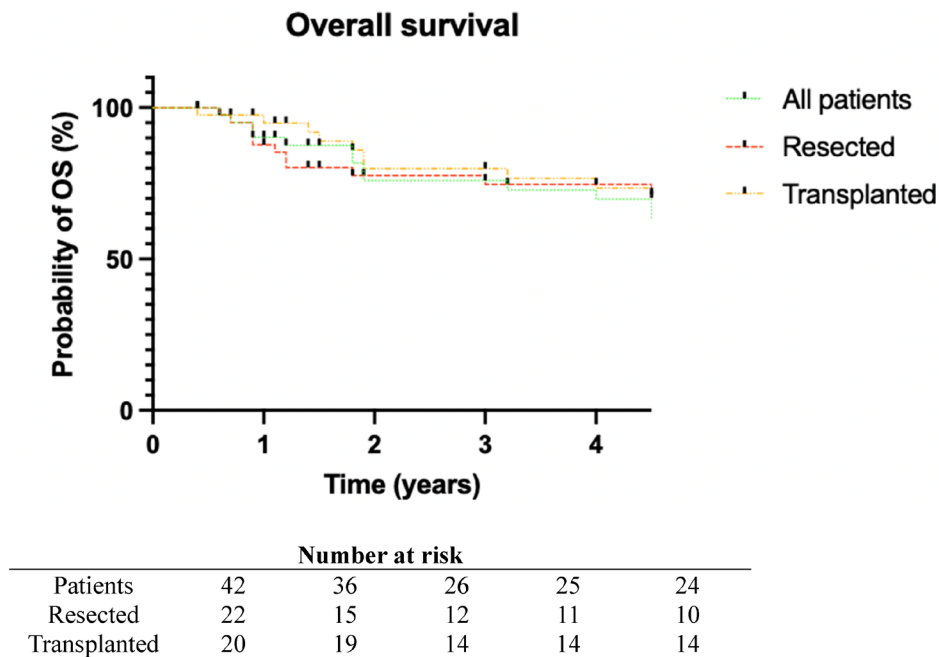


FIGURE 2 | Overall survival in pediatric patients affected by hepatoblastoma who underwent either liver resection (LR) or liver transplantation (LT) is comparable between LR and LT patients, respectively 68.1% versus 85%.

4 | Discussion

In this retrospective single-center study spanning almost two decades, we analyzed real-world treatment strategies and outcomes in a cohort of pediatric patients with hepatoblastoma managed in a tertiary referral center with integrated oncologic, surgical, and transplant expertise. Our findings confirm that, despite well-established international treatment protocols, individualized treatment adaptations—particularly chemotherapy

intensification and flexible surgical timing—are frequently required to achieve definitive disease control. Our cohort size corresponds to approximately 2.33 cases per year, representing about one quarter of the expected annual number of new HB diagnoses in Italy [4]. Compared with previously published single-center studies, this represents the second largest monocentric cohort described in the literature [6, 15]. To date, no published studies have reported real-world deviations from protocol-recommended therapy in patients with hepatoblastoma.

The demographic features of our cohort are consistent with previously published epidemiological data, confirming a marked male predominance and a median age at diagnosis below 2 years [16–18].

However, compared with the literature, fewer PRETEXT II and more PRETEXT IV tumors were observed [19]. The high proportion of patients presenting with advanced PRETEXT stages and metastatic disease reflects the referral nature of our institution as one of the national pediatric transplant centers. More than half of our patients presented with PRETEXT IV disease, and over one-third had metastatic involvement at diagnosis. These data are slightly higher than those reported in population-based studies but comparable to series from specialized centers managing complex and high-risk cases [6]. This relative selection of severe cases allowed us to strengthen our message on the need to tailor the treatment for high risk hepatoblastoma. The frequent presence of VPEFR annotation factors further underlines the surgical complexity of this population and supports the need for early referral to experienced hepatobiliary units. Remarkably, metastatic status did not significantly affect overall survival, consistent with published evidence [20–22].

One of the key findings of our study is the high frequency of deviations from protocol-defined chemotherapy schedules. More than half of the patients received additional or intensified chemotherapy, most commonly to address persistent metastatic disease or unresectable primary tumors.

While international protocols such as SIOPEL-3, SIOPEL-4, and SIOPEL-6 provide structured treatment frameworks, the new PHITT protocol highlights the need for clinical judgment in different scenarios. Remarkably, in the new PHITT protocol, treatment tailoring has the major advantage of reducing the exposure to chemotherapy in low risk cases, allowing it to proceed to surgery at an early stage of the treatment schedule [23]. Recently Hiyama showed that in low risk patients treated according to the PHITT protocol, EFS and OS in upfront surgery and delayed surgery are comparable [24].

In this study we focus on treatment tailoring in HR cases with complex scenarios, for which published data specifically addressing the safety and outcomes of chemotherapy addition or intensification remain limited.

The prevalence of HR HB in our cohort significantly exceeds the distribution reported in current literature [11, 19]. This discrepancy likely reflects a selection bias, as our institution serves as a tertiary referral center for the management of complex cases, including advanced surgical interventions.

Notably, despite the predominance of HR patients, our overall survival is comparable, and the intermediate-term toxicity profile is consistent with established literature data [7–10].

Our experience suggests that such deviations, when driven by surgical objectives and closely monitored, can be safely implemented without compromising long-term organ function.

Importantly, additional or intensified chemotherapy in our cohort did not translate into a higher incidence of clinically relevant

long-term renal, auditory, or cardiac toxicity compared with historical series both for resected and transplanted patients [7–9]. This observation aligns with emerging evidence that cumulative toxicity is influenced not only by total drug exposure but also by supportive care, dosing intervals, and patient selection.

Complete surgical removal of the tumor remains the cornerstone of hepatoblastoma curative plan. In our cohort, liver resection was feasible in slightly more than half of the patients, while liver transplantation was required in the remaining cases, primarily due to extensive PRETEXT IV disease or vascular involvement. Notably, almost half of the patients who ultimately underwent liver resection required chemotherapy intensification to achieve resectability, thereby avoiding transplantation. This finding reinforces the concept that aggressive neoadjuvant strategies, when applied in experienced centers, may expand the indications for liver resection even in advanced disease. Conversely, liver transplantation proved to be an effective first-line option for patients with unresectable disease, in line with previously reported survival outcomes comparable to those achieved with liver resection [4, 6].

At last follow-up, 85% of transplanted patients and 68.2% of resected patients were alive and disease-free. Mortality did not significantly differ between groups. However, our data also confirm the poor prognosis associated with rescue transplantation after relapse, particularly in the presence of extrahepatic disease, as consistently reported in the literature [25].

These findings emphasize the importance not only of appropriate patient selection and timing of transplantation, but also the need to refer patients to a center specialized also in pediatric hepatobiliary surgery.

Relapse occurred in approximately one-fifth of patients, with the lung representing the most frequent site of recurrence. This pattern is well described in hepatoblastoma [20, 26] and reflects both the biology of the disease and the challenges of achieving durable control of metastatic sites.

Despite the availability of aggressive salvage strategies—including metastasectomy, high-dose chemotherapy, and stem cell rescue [21, 27]—outcomes after relapse remained poor, with most patients dying within 1 year of recurrence [28]. This underscores the critical importance of achieving complete disease control upfront and supports ongoing efforts to refine risk stratification and early surgical decision-making.

With regard to end-of-treatment organ toxicity, no statistically significant differences were observed between treatment groups.

The retrospective and monocentric nature of this study represents an inherent limitation, as does the relatively small sample size. However, given the rarity of hepatoblastoma, single-center experiences from high-volume referral institutions, performing both LR and LT, provide valuable insights into complex clinical decision-making that may not be fully captured in multicenter trials.

Our findings highlight several clinically relevant points. First, strict adherence to protocol-defined chemotherapy schedules

may not always be feasible or optimal in real-world practice. Second, treatment intensification driven by surgical goals can be effective and safe in specialized centers. Third, early centralization of patients with advanced hepatoblastoma is essential to allow multidisciplinary evaluation and access to complex surgical and transplant strategies. These observations are particularly relevant in the context of the PHITT protocol, which aims to harmonize international treatment approaches while allowing flexibility based on tumor biology and surgical feasibility. Future prospective studies should incorporate real-world data to better define acceptable ranges of treatment adaptation and to identify patients most likely to benefit from intensified preoperative strategies.

Larger studies, including long-term follow-up and accounting for the potential impact of post-transplant immunosuppressive therapy, are warranted to better define late toxicity and long-term outcomes in this patient population.

Acknowledgments

The authors gratefully acknowledge all healthcare professionals of Papa Giovanni XXIII Hospital for their commitment to patient care and their contribution to the clinical activities that made this study possible. The authors also thank the referring centers for their continued collaboration and for the trust placed in our institution through the referral of patients. Most importantly, we express our sincere gratitude to the patients and their families for their trust, cooperation, and participation. Open access publishing facilitated by Aziende Socio Sanitarie Territoriali Papa Giovanni XXIII, as part of the Wiley – SBBL agreement.

Funding

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. J. Feng, G. Polychronidis, U. Heger, G. Frongia, A. Mehrabi, and K. Hoffmann, "Incidence Trends and Survival Prediction of Hepatoblastoma in Children: A Population-Based Study," *Cancer Communications* 39, no. 1 (2019): 62.
2. R. L. Meyers, "Tumors of the Liver in Children," *Surgical Oncology* 16, no. 3 (2007): 195–203.
3. J. B. Litten and G. E. Tomlinson, "Liver Tumors in Children," *Oncologist* 13, no. 7 (2008): 812–820.
4. I. Cozzi, E. Santelli, E. Lapucci, et al., "Incidenza di tumori nella popolazione infantile e adolescenziale (0-19 anni) della Regione Lazio, anni 2009-2015 [Incidence of Cancer Among Children and Adolescents (0-19 Years) in Lazio Region (Central Italy), 2009-2015]," *Epidemiologia e Prevenzione* 46, no. 1–2 (2022): 47–58.
5. G. Perilongo, E. Shafford, R. Maibach, et al., "Risk-Adapted Treatment for Childhood Hepatoblastoma. Final Report of the Second Study

- of the International Society of Paediatric Oncology—SIOPEL 2," *European Journal of Cancer* 40, no. 3 (2004): 411–421.
6. F. Guérin, F. Gauthier, H. Martelli, et al., "Outcome of Central Hepatectomy for Hepatoblastomas," *Journal of Pediatric Surgery* 45, no. 3 (2010): 555–563.
7. J. Shapira, M. Gotfried, M. Lishner, and M. Ravid, "Reduced Cardiotoxicity of Doxorubicin by a 6-Hour Infusion Regimen. A Prospective Randomized Evaluation," *Cancer* 65, no. 4 (1990): 870–873.
8. R. Peña Zavala, M. Marzouki, M. Beaunoyer, and F. Alvarez, "Glomerular Filtration Rate in Liver Transplant for Unresectable Hepatoblastoma," *Pediatric Transplantation* 24, no. 6 (2020): e13746.
9. R. L. Mulder, S. L. Knijnenburg, R. B. Geskus, et al., "Glomerular Function Time Trends in Long-Term Survivors of Childhood Cancer: A Longitudinal Study," *Cancer Epidemiology, Biomarkers & Prevention* 22, no. 10 (2013): 1736–1746.
10. T. G. Bonnesen, J. F. Winther, P. H. Asdahl, et al., "Long-Term Risk of Renal and Urinary Tract Diseases in Childhood Cancer Survivors: A Population-Based Cohort Study," *European Journal of Cancer* 64 (2016): 52–61.
11. J. Zsiros, L. Brugieres, P. Brock, et al., "Dose-Dense Cisplatin-Based Chemotherapy and Surgery for Children With High-Risk Hepatoblastoma (SIOPEL-4): A Prospective, Single-Arm, Feasibility Study," *Lancet Oncology* 14, no. 9 (2013): 834–842.
12. P. Czauderna and H. Garnier, "Hepatoblastoma: Current Understanding, Recent Advances, and Controversies," *F1000Res* 7 (2018): 53.
13. G. J. Schwartz, A. Muñoz, M. F. Schneider, et al., "New Equations to Estimate GFR in Children With CKD," *Journal of the American Society of Nephrology* 20, no. 3 (2009): 629–637.
14. K. W. Chang and N. Chinosornvatana, "Practical Grading System for Evaluating Cisplatin Ototoxicity in Children," *Journal of Clinical Oncology* 28 (2010): 1788–1795.
15. K. Hirohara, H. Tomita, N. Shimojima, et al., "Surgery for Hepatoblastoma in Children With Trisomy 18: A Monocentric Study," *Pediatric Surgery International* 40, no. 1 (2024): 223.
16. P. Dasgupta, C. Henshaw, D. R. Youlden, et al., "Global Trends in Incidence Rates of Childhood Liver Cancers: A Systematic Review and Meta-Analysis," *Paediatric and Perinatal Epidemiology* 34, no. 5 (2020): 609–617.
17. L. M. Turcotte and L. G. Spector, "What Do We Know About the Etiology of Hepatoblastoma?," *Hepatoma Oncology* 1, no. 1 (2014): 7–10.
18. S. de Fine Licht, L. S. Schmidt, N. H. Rod, et al., "Hepatoblastoma in the Nordic Countries," *International Journal of Cancer* 131, no. 4 (2012): E555–E561.
19. R. L. Meyers, J. R. Rowland, M. Krailo, Z. Chen, H. M. Katzenstein, and M. H. Malogolowkin, "Predictive Power of Pretreatment Prognostic Factors in Children With Hepatoblastoma: A Report From the Children's Oncology Group," *Pediatric Blood & Cancer* 53, no. 6 (2009): 1016–1022.
20. D. Wanaguru, A. Shun, N. Price, and J. Karpelowsky, "Outcomes of Pulmonary Metastases in Hepatoblastoma—Is the Prognosis Always Poor?," *Journal of Pediatric Surgery* 48, no. 12 (2013): 2474–2478.
21. J. Fuchs, G. Seitz, R. Handgretinger, J. Schäfer, and S. W. Warmann, "Surgical Treatment of Lung Metastases in Patients With Embryonal Pediatric Solid Tumors: An Update," *Seminars in Pediatric Surgery* 21, no. 1 (2012): 79–87.
22. R. L. Meyers, H. M. Katzenstein, M. Krailo, E. D. McGahren, 3rd, and M. H. Malogolowkin, "Surgical Resection of Pulmonary Metastatic Lesions in Children With Hepatoblastoma," *Journal of Pediatric Surgery* 42, no. 12 (2007): 2050–2056.
23. V. Moroz, B. Morland, G. Tiao, E. Hiyama, P. Kearns, and K. Wheatley, "The Paediatric Hepatic International Tumour Trial (PHITT): Clinical Trial Design in Rare Disease," *Trials* 16, no. Suppl 2 (2015): P224.

24. E. Hiyama, T. Hishiki, K. Yoshimura, et al., "Upfront or Delayed Surgery in Resectable Hepatoblastoma: Analysis From the Children's Hepatic Tumors International Collaboration Database," *EClinicalMedicine* 76 (2024): 102811.
25. H. Ismail, D. Broniszczak, P. Kaliciński, et al., "Changing Treatment and Outcome of Children With Hepatoblastoma: Analysis of a Single Center Experience Over the Last 20 Years," *Journal of Pediatric Surgery* 47, no. 7 (2012): 1331–1339.
26. G. Perilongo, J. Brown, E. Shafford, et al., "Hepatoblastoma Presenting With Lung Metastases: Treatment Results of the First Cooperative, Prospective Study of the International Society of Paediatric Oncology on Childhood Liver Tumors," *Cancer* 89, no. 8 (2000): 1845–1853.
27. B. K. Kim, J. Y. Choi, K. T. Hong, H. J. Park, and H. J. Kang, "Successful Treatment of Refractory or Relapsed Hepatoblastoma With Autologous Hematopoietic Stem Cell Transplantation in Children," *Journal of Pediatric Hematology/Oncology* 46, no. 5 (2024): e265–e271.
28. R. Maxwell, B. Häberle, R. Kappler, et al., "Hepatoblastoma Relapse—Findings From the German HB99 Trial and the German Liver Tumor Registry," *Cancers* 16, no. 4 (2024): 696.