Neoadjuvant chemotherapy or upfront surgery in hepatoblastoma: A multicenter retrospective study

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Abstract

Background: We aimed to retrospectively investigate the role of neoadjuvant chemotherapy in low-risk patients with hepatoblastoma (HB) who underwent curative resection between February 2009 and December 2017. We also verified the feasibility of the risk stratification system to select the optimal patients for upfront resection. **Procedure:** We compared 5-year overall survival (OS) and event-free survival (EFS) between the upfront surgery (US) (n=26) and neoadjuvant chemotherapy (NC) (n=104) groups at three oncology centers in Beijing, China. To reduce the effect of covariate imbalances, propensity score matching (PSM) was used. We explored whether preoperative chemotherapy affected surgical outcomes and identified the risk factors for events and death, including resection margin status, PRETreatment EXTent of disease stages, age, sex, pathology classification, and α-fetoprotein levels. **Results:** The median follow-up period was 64 months (interquartile range 60–72). After PSM, 22 pairs of patients were identified and the patient characteristics were similar for all variables included in propensity score matching. In the US group, the 5-year EFS and OS rates were 81.8% and 86.3%, respectively. In the NC group, 5-year EFS and OS rates were 81.8% and 90.9%, respectively. No significant differences in EFS or OS were observed between the groups. Pathological classification was the only risk factor for death and disease progression, tumor recurrence, diagnosis of other malignant neoplasms, and death from any cause (p=0.007 and p=0.032, respectively). **Conclusion:** Upfront resection can achieve long-term disease control in low-risk patients with resectable HB, thus reducing the cumulative toxicity of platinum-based chemotherapy drugs.

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Abbreviations	
HB	Hepatoblastoma
OS	Overall survival
EFS	Event-free survival
PSM	Propensity score matching
SIOPEL	International Childhood Liver Tumors Strategy Group
NACT	Neoadjuvant chemotherapy
COG	Children's Oncology Group
JPLT	Japanese Study Group for Pediatric Liver Tumors
CHIC	Children's Hepatic Tumors International Collaboration
CIP	Capital Institute of Pediatrics
US	Upfront resection
AFP	α-fetoprotein
PRETEXT	PRETreatment EXTent of disease stages
PS	Propensity score
PSM	Propensity score matching
SMD	Standardized mean difference
PFH	Pure fetal histology
EMEF	Epithelial mixed embryonal/fetal
MEM	Mixed epithelial-mesenchymal
SCU	Small cell undifferentiated

Abstract

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patients with hepatoblastoma (HB) who underwent curative resection between February 2009 and December 2017. We also verified the feasibility of the risk stratification system to select the optimal patients for upfront resection.

Procedure: We compared 5-year overall survival (OS) and event-free survival (EFS) between the upfront surgery (US) (n=26) and neoadjuvant chemotherapy (NC) (n=104) groups at three oncology centers in Beijing, China. To reduce the effect of covariate imbalances, propensity score matching (PSM) was used. We explored whether preoperative chemotherapy affected surgical outcomes and identified the risk factors for events and death, including resection margin status, PRETreatment EXTent of disease stages, age, sex, pathology classification, and α-fetoprotein levels.

Results: The median follow-up period was 64 months (interquartile range 60–72). After PSM, 22 pairs of patients were identified and the patient characteristics were similar for all variables included in propensity score matching. In the US group, the 5-year EFS and OS rates were 81.8% and 86.3%, respectively. In the NC group, 5-year EFS and OS rates were 81.8% and 90.9%, respectively. No significant differences in EFS or OS were observed between the groups. Pathological classification was the only risk factor for death and disease progression, tumor recurrence, diagnosis of other malignant neoplasms, and death from any cause (p =0.007 and p =0.032, respectively).

Conclusion: Upfront resection can achieve long-term disease control in low-risk patients with resectable HB, thus reducing the cumulative toxicity of platinum-based chemotherapy drugs.

Introduction

Hepatoblastoma (HB) is a rare disease with an incidence of 1.6/million children. However, it is the most common malignant pediatric liver cancer, which usually develops in patients aged <3 years, and its incidence has increased by >5% annually[1,2]. With improvements in surgical techniques and the use of adjuvant chemotherapy, the 5-year survival rate of HB has increased from approximately 35% (50 years ago) to 80%–90% (currently) [3].

The primary treatment modality for HB is complete surgical resection; however, 60%–70% patients are inoperable during diagnosis because of a high tumor bulk volume or major blood vessel invasion[4]. Systemic cisplatin-based chemotherapy is effective for reducing tumor volume in patients with HB and can convert most unresectable tumors into resectable tumors. Therefore, the International Childhood Liver Tumors Strategy Group (SIOPEL) prefers the use of neoadjuvant chemotherapy (NACT) and delayed resection to facilitate tumor resection [4]. However, the Children's Oncology Group (COG) trial AHEP0731 and Japanese Study Group for Pediatric Liver Tumors (JPLT) study indicated that upfront resection in selected HB cases achieved excellent outcomes [5,6]. Unnecessary NACT may result in potential exposure to chemotherapy and treatment-related toxicity, and an increased number of chemotherapy cycles are associated with chemotherapy resistance[7-9]. However, the value of upfront resection has not been established, and there is no clear consensus regarding which patients with HB benefit the most from this form of treatment.

Due to the lack of a uniform staging system, it is difficult to interpret and compare the results reported by different research groups, and it creates difficulties in terms of optimal patient selection. Four major cooperative trial groups (SIOPEL, COG, the German Society for Pediatric Oncology and Hematology, and JPLT) formed the Children's Hepatic Tumors International Collaboration (CHIC) to define a common hepatoblastoma stratification (CHIC-HS), which makes the heterogenous results of prior research more comparable [10].

In this retrospective, multicenter study, we compared event-free survival (EFS) and overall survival (OS) in CHIC-HS low-risk patients with HB who underwent surgical resection and NACT and verified the feasibility of the risk stratification systems used to select the optimal treatment for patients with HB.

Methods

The study was performed in accordance with the Strengthening the Reporting of Observational Studies

in Epidemiology guidelines. This study complied with the tenets of the Declaration of Helsinki and the Capital Institute of Pediatrics' (CIP) ethics committee approved this study (SHERLL2022047). Due to the retrospective nature of the study, the need for informed consent was waived.

Patient selection

The medical records of patients with HB who underwent curative resection with or without NACT at CIP (Beijing, China) and two other centers between February 2009 and December 2017 were collected. We classified patients into upfront surgery (US) and NACT (NC) groups, based on whether they had received NACT or not. The CHIC-HS system assigned patients to four risk groups based on age, serum α-fetoprotein (AFP) levels, and PRETreatment EXTent of disease stages (PRETEXT) stage and its annotation factors [11]. Eligible patients were stratified into a very low- or low-risk group (Table 1), were <8 years old, and had a histopathologic diagnosis of HB. The tumors were estimated to be resectable at the time of diagnosis, patients had complete clinical and follow-up data, and liver and kidney function were normal. Patients with other tumors or serious medical diseases, who refused surgery, and who refused postoperative chemotherapy were excluded.

Outcomes

The primary outcomes were 5-year OS and EFS. We defined EFS as the time from surgery to tumor recurrence, diagnosis of other tumors, death from any cause, or last follow-up without the occurrence of any of these events.

The secondary objectives were to 1) explore whether preoperative chemotherapy affected surgical outcomes and 2) identify risk factors for events and death, e.g., resection margin status, PRETEXT stages, age, sex, pathology classification, and AFP level at diagnosis. R0 resection was defined as a microscopically negative margin, and R1 resection as macroscopically complete resection with positive microscopic margins.

Statistical analysis

The non-parametric Mann–Whitney U test was used to compare non-normal data between groups. All tests were two-sided, and ap -value of <0.05 was considered statistically significant.

To reduce the confounding effects of imbalances in the study covariates, propensity score matching (PSM) was performed. The propensity score (PS) was estimated using a logistic regression model, in which the treatment modality was regressed onto sex, age at surgery, AFP levels at diagnosis, and PRETEXT stage as potential covariates. The US group was PS-matched to the NC group in a 1:1 ratio, using maximum distance (caliper) of 0.15 between matched participants based on their propensity score. The balance in covariates between the groups before and after PSM was evaluated using standardized mean differences (SMDs). SMD <0.2 was deemed to be the ideal balance.

The Kaplan–Meier method was performed to estimate OS and EFS, and a log-rank test was conducted to compare these results among the patient groups.

The relationships between resection margin status, PRETEXT stages, age, sex, pathology classification, AFP levels, and outcome events (events and deaths) were analyzed using logistic regression, since we only studied the effects of variables on death and events, but not on the length of survival. Statistical significance was set at two-sided p -value <0.05.

3. Results

3.1. Baseline characteristics of the patient sample

Between February 1, 2009, and February 1, 2017, 130 patients were included, with 99 patients in the very low-risk group and 31 patients in the low-risk group, according to the CHIC-HS criteria. Totally, there were 26 and 104 patients included in the US and NC groups, respectively. All patients received adjuvant chemotherapy postoperatively.

The baseline demographic and clinical characteristics before and after PSM are shown in Table 2. Before PSM, there were no significant differences in sex and serum AFP levels between the NC and US groups (p =0.21 and p =0.437, respectively), but SMD was 0.264 for sex and 0.189 for serum AFP levels. The mean age of the patients was higher in the US group than in the NC group, although the difference was not significant (702±533 vs. 561±525, mean±standard deviation,p =0.098, SMD=0.269). In contrast, the distribution of PRETEXT stages differed significantly between the groups (p =0.001, SMD=0.849). After PSM, all SMD values were <0.2. In the NC and US groups, the mean age was 528.0±324.8 days and 603.7±522.1 days, respectively (p =0.851), with 50% male participants in each group (p =1). The distribution of PRETEXT stage and serum AFP levels was similar between the groups (p =0.655 and p =0.806, respectively). Overall, patient characteristics were similar for all variables included in PS matching.

3.2. Association between NACT, surgical outcomes, and pathological findings

Postoperative pathological results are shown in Table 3. A positive surgical margin was observed in three (13.6%) and six (27.3%) patients in the US and NC groups, respectively. There was no significant difference between the groups (p =0.268). There were significant differences in pathological classification between the groups (p =0.031). The pathological classification in the NC and US groups was pure fetal histology (PFH) in five (22.7%) and two (9.1%) patients, epithelial mixed embryonal/fetal (EMEF) in nine (40.9%) and 16 (72.7%) patients, mixed epithelial-mesenchymal (MEM) in eight (36.4%) and two (9.1%) patients, and small cell undifferentiated (SCU) in zero (0%) and two (9.1%) patients, respectively. The number of EMEF cases was significantly higher in the NC group than in the US group.

3.3. Patient outcomes

The median follow-up period was 64 months (95% confidence interval [CI]: 58.2–65.5): US group, 62.18 months (interquartile range [IQR]: 60–69) and NC group, 68.82 months (IQR: 60–75.75). In the US group, the 5-year EFS and OS were 81.8% (95% CI: 60.9–93.3) and 86.3% (95% CI: 65.8–96), respectively. Events occurred in four (16.7%) patients, all of whom experienced an event <14 months after surgery (Table S1). One patient with EMEF pathology died during chemotherapy from sepsis, two SCU patients and one patient with EMEF pathology experienced recurrence, and the lesion in one patient with SCU recurred as a hepatic sarcoma. Three patients underwent a second surgery after relapse, and the tumors were resected. The patient with EMEF pathology survived, and the two SCU patients died due to progression of lung metastases.

In the NC group, the 5-year EFS and OS were 81.8% (95% CI: 60.9–93.3) and 90.9% (95% CI: 71.0–98.7), respectively. Events occurred in four (16.7%) patients, all of whom experienced an event <9 months after surgery (Table S1). One patient with EMEF pathology died due to multiple organ failure, and three patients with MEM pathology developed recurrence and underwent a second surgery; one patient died of hepatic metastases, and two patients had long-term survival after surgery. No significant difference was observed between the groups in terms of EFS and OS (p =0.964 and$p$ =0.655, respectively) (Fig. 1). Our analysis of the putative risk factors of interest showed that resection margin status, PRETEXT stages, age, sex, and AFP levels were not associated with death or events, but that pathological classification was significantly associated (p =0.007 and p=0.032, respectively). However, no events occurred in patients with PFH pathology, and they survived until the last follow-up, whereas all SCU patients died, and the sample size was thus underpowered to calculate odds ratios and conduct further analyses.

4. Discussion

In this retrospective multicenter study of 130 patients with HB in the CHIC-HS, the very low- and low-risk groups underwent surgery with curative intent and were followed up for >5 years. We investigated the effect of NACT on the 5-year OS and EFS. According to our results, there was no survival benefit to using NACT before surgery in terms of EFS and OS. Pathological classification was a risk factor for adverse events and mortality; three (30%) patients with MEM pathology experienced tumor recurrence and one (10%) patient died. One (4%) patient with EMEF pathology had tumor recurrence and remains alive to date, while two (8%) patients with EMEF pathology died from other factors. All SCU patients died of progressive disease after relapse, and no adverse events or deaths were observed in patients with PFH pathology. Moreover,

pathological alterations were observed after NACT.

Because of the rarity of HB and the fact that only 30% of patients had resectable tumors at the time of diagnosis, it was difficult to perform a prospective study, and few studies have addressed which patients benefit the most from upfront surgery. Currently, surgeons mainly judge whether the tumor is resectable based on subjective evaluation and experience. For PRETEXT stage III patients, most surgeons usually choose to receive NACT to make surgery easier, even when tumors are resectable at the time of diagnosis. Therefore, very few patients with PRETEXT stage III HB were included in this study. The SIOPEL group reported that patients with resectable tumors using NACT before surgery had less surgical complications and better outcomes. Therefore, they recommended that all patients receive NACT before surgery [4], resulting in further reduction in the number of patients undergoing upfront surgery. Establishing objective patient selection criteria for US is paramount, and the COG argues for decreasing the total cumulative administered dose of cisplatin to protect patients from hearing loss[6,12]. The JPLT-2 study showed PRETEXT stage I patients and some PRETEXT stage II patients without positive annotation factors who underwent US and had good outcomes (5-year EFS and OS: 74.2% and 89.9%, respectively) [5]. The COG study achieved similar outcomes; the 5-year EFS and OS of patients with PFH pathology were 100% [12], and in PRETEXT stage I or II patients without PFH and SCU pathology, the 5-year EFS and OS were 88% and 91%, respectively [6]. However, there was no comparison between the two approaches in these studies, and differences in the inclusion criteria made it difficult to compare these results.

To standardize surgical decision-making, an objective and comparable evaluation method was used to determine the optimal patients for upfront surgery. We used the risk-stratified staging developed by the CHIC to explore whether patients with HB in the very low-risk and low-risk groups benefited from upfront surgery. In this study we verify whether the CHIC-HS can be used to screen patients with HB for tumors that can be resected at the time of diagnosis. According to our data, both patient groups had a relatively favorable prognosis, and there was no significant difference in the 5-year OS and EFS between the groups. This suggests that US can achieve long-term disease control in these patients, which can decrease cisplatin chemoresistance and reduce the total chemotherapy dose.

NC has some effects on surgical operations, which can lead to tumor shrinkage and downstaging and the tumor shrinking further away from the blood vessels [13]. This approach can reduce the risk of intraoperative bleeding and other complications, making surgery easier to perform. However, after the tumor shrinks, the tissues around the tumor often show an abnormal shape when relieving compression from the tumor. Pathological examination showed that these tissues are usually liver parenchyma, and some surgeons choose to retain this part of the tissue to obtain a larger residual liver volume. Our results showed that this did not affect the surgical outcome. There was no statistical difference in the rate of R1 resection between the groups, and R1 resection had no effect on the 5-year OS and EFS (Table 3), which are consistent with the findings of previous studies[14,15].

Notably, we found that, among the pathologic changes induced by NACT, some EMEF tumors presented mature mesenchymal tissues (Table S1). This finding is consistent with those reported by Stephen et al.[16], and "maturation" of malignant clones or the result of selective ablation of immature clones were thought to predict a better prognosis [17]. However, a recent study showed that patients with MEM pathology were more likely to experience recurrence and metastasis because they had low sensitivity to chemotherapy, but no prechemotherapy pathology was available in that study [18]. Consequently, it was difficult to compare these two studies. In our research, the rate of recurrence and metastasis in patients with MEM and SCU pathology was higher than that in other patients, but no conclusion could be drawn due to the small sample size. The prognostic effect of pathological classification changes due to NC and effect of pathological classification on prognosis in different risk groups merit further investigation.

The study limitations include its retrospective nature and small sample size, that NACT regimens and the number of cycles of NACT varied across institutions, and our failure to evaluate tumor response to chemotherapy and acute and long-term toxicities of platinum-based chemotherapy, especially ototoxicity.

In the future, it will be necessary to explore whether more patients with HB can benefit from upfront resection, similar to our study, and the impact of preoperative chemotherapy in altering pathologic type upon prognosis. Experiments need to be designed to evaluate the chemotherapy resistance of tumors and the degree of hearing loss in patients. Owing to the rarity of HB, further studies with a larger sample size and multicentric samples are needed.

In conclusion, our findings suggested that upfront resection can achieve long-term disease control in patients with HB and resectable tumors at diagnosis in the CHIC-HS very low- and low-risk groups. This treatment approach can reduce the cumulative toxicity of platinum-based chemotherapy drugs, including in PRETEXT stage III patients. SCU patients had poorly differentiated tumors and a poor prognosis; treatment of these patients is controversial, and the optimal therapies need further investigation. This HB risk stratification system provides an objective criterion to evaluate whether patients are suitable for upfront resection. Our findings may help future clinical studies to explore whether more patients with HB can benefit from upfront resection.

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Conflict of Interest Statement

The authors of the above-mentioned paper have no affiliations or associations with any organization/entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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TABLE 1. Children's hepatic tumors international collaboration—hepatoblastoma stratification

Risk group	Criteria
Very low-risk	PRETEXT I Resectable at diagnosis and VPEFRM(-) PRETEXT II Resectable at diagnosis, VPEFRM(-), <8 years and AFP >100 ng/ml
Low-risk	PRETEXT I Unresectable at diagnosis and VPEFRM(-) PRETEXT II Unresectable at diagnosis, VPEFRM(-), <8 years and AFP >100 ng/ml PRETEXT III VPEFRM(-), <8 years and AFP >1000 ng/ml

Risk group	Criteria
Intermediate-risk	PRETEXT I VPEFR(+), M(-) and <8 years PRETEXT II <8 years, AFP >100 ng/ml, VPEFR(+) and M(-) PRETEXT III <8 years, AFP 101-1000 ng/ml or AFP >1000 ng/ml and VPEFR (+), M(-) PRETEXT IV M(-), <3 years and AFP >100 ng/ml
High-risk	M(+) PRETEXT I VPEFR(+), and [?]8 years PRETEXT II <8 years, and AFP [?]100 ng/ml [?]8 years PRETEXT III <8 years and AFP [?]100 ng/ml [?]8 years PRETEXT IV <3 years and AFP [?]100 ng/ml [?]3 years

AFP, α-fetoprotein; PRETEXT, PRETreatment EXTent of disease; VPEFRM, PRETEXT annotation factors: V, involvement of vena cava; P, involvement of portal vein; E, contiguous extrahepatic intra-abdominal tumor extension—contiguous involvement of adjacent organs; F, multifocal liver tumor; R, tumor rupture at diagnosis; M, metastasis[11]

TABLE 2. Patient characteristics before and after propensity score matching

	Before matching (n = 130)	Before matching (n = 130)	Before matching (n = 130)	Before matching (n = 130)	Before matching (n = 130)	Before matching (n = 130)		After matching (n = 44)	After matching (n = 44)	After matching (n = 44)	After matching (n = 44)	After matching (n = 44)
	Upfront surgery (N = 26)	Upfront surgery (N = 26)		Neoadjuvant chemotherapy (N = 104)	Neoadjuvant chemotherapy (N = 104)	p	SMD	Upfront surgery (N = 22)	Upfront surgery (N = 22)		Neoadjuvant chemotherapy (N = 22)	Neoadjuvant chemotherapy (N = 22)
	N	%		N	%			N	%		N	%
Sex	13	13		66	38	0.21	0.264	11	11		11	11
Male	50	50		63.5	36.5			50	50		50	50
Female												
Age at surgery (d), Mean (standard deviation)	561 (525)			702 (533)		0.098	0.269	603.7 (522.1)			528.0 (324.8)	
PRETEXT stage	5	22	4	5	85	0.001	0.849	1	20	1	1	19 2
I	19.2	84.6		4.8	81.7			4.5	90.9		4.5	86.4
II	15.4			14					4.5			9.1
III				13.5								

	Before matching (n = 130)	Before matching (n = 130)	Before matching (n = 130)	Before matching (n = 130)	Before matching (n = 130)	Before matching (n = 130)		After matching (n = 44)	After matching (n = 44)	After matching (n = 44)	After matching (n = 44)	Afte matc ing (n =
AFP [?]100 101–1000 1001–10000 >10000	1 2 6 17	3.8 7.7 23.1 65.4		0 7 22 75	0 6.7 21.2 72.1	0.437	0.189	1 1 6 14	4.5 4.5 27.3 63.6		0 2 7 13	0 9.1 31.8 59.1

AFP, α -fetoprotein; SMD, standardized mean difference

TABLE 3. Comparison of surgical outcomes and pathological findings

	Upfront surgery (N = 22)	Neoadjuvant chemotherapy (N = 22)	*p*
Resection margin status R0 resection R1 resection	19 (86.4%) 3 (13.6%)	16 (72.7%) 6 (27.3%)	0.268
Pathological findings PFH EMEF MEM SCU	2 (9.1%) 16 (72.7%) 2 (9.1%) 2 (9.1%)	5 (22.7%) 9 (40.9%) 8 (36.4%) 0 (0%)	0.031
Postoperative chemotherapy regimen C5V (2–4) PLADO (2–4)	13 (59.1%) 9 (40.9%)	14 (63.6%) 8 (36.4%)	0.77

PFH, pure fetal histology; EMEF, epithelial mixed embryonal/fetal; MEM, mixed epithelial-mesenchymal; SCU, small cell undifferentiated; C5V: vincristine+5-fluorouracil+cisplatin; PLADO: cisplatin+doxorubicin

Legend

Figure 1. Kaplan–Meier curves for event-free and overall survival; A Event-free survival; B Overall survival

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