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Upfront or delayed surgery in resectable hepatoblastoma: analysis from the children's hepatic tumors international collaboration database

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Summary

Background In the treatment of resectable hepatoblastoma (HB), it has not been established whether upfront surgery (UF) at diagnosis or neoadjuvant chemotherapy and delayed surgery (DL) is preferred. We compared patients with localized HB who underwent either UF, or DL after neoadjuvant chemotherapy in the Children's Hepatic tumors International Collaboration (CHIC) database of 1605 cases enrolled in eight multicenter hepatoblastoma trials between 1988 and 2010.

Methods Among the 512 resectable HB patients who had PRETEXT (PRETreament EXTent of disease) I or II unruptured tumors at diagnosis without extrahepatic invasion, distant metastases, or massive vascular invasion, 172 underwent UF and 340 underwent DL. The primary outcomes were event-free and overall survivals after start of treatment in these two groups. Survival analysis was performed using the Kaplan-Maier analysis with long-rank tests and multivariable Cox regression models.

Findings Complete resection rates were comparable (93.6% in UF and 89.7% in DL). The total cycles of chemotherapy of DL (median:6) were significantly more than those of UF (median:4) ($P < 0.01$). The 5-year event-free survival (EFS) was

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90.6% and 86.6% ($P = 0.89$) in the UF and DL cohorts, respectively. The surgical complications, recurrence rates, and late complications were not significantly different between the cohorts but the EFS rates of DL patients with a low alpha-fetoprotein (AFP) level (100–999 ng/mL) or older age at diagnosis (≥3 years old) were significantly worse than others.

Interpretation The outcomes, surgical resectability, and complications were not significantly different between the UF and DL groups. Eligible patients with a low AFP level (<1000 ng/mL) or older age (≥3 years old) showed better outcomes in the UF group and might be considered for initial resection.

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Keywords: Hepatoblastoma; Resectable; Up-front surgery; Outcome; Age at diagnosis; Alpha-fetoprotein

Research in context

Evidence before this study

The previous multicentral clinical trials for hepatoblastoma revealed that the cure of this tumor requires the suitable combination of complete tumor resection and chemotherapy. Traditionally, some trials advocate up-front surgery before adjuvant chemotherapy and others recommend neoadjuvant chemotherapy followed by delayed surgery. The latter group had the theoretical paradigm that neo-adjuvant chemotherapy would treat (micro)metastasis from day one, leading to less distant metastases during follow up. Participating in the current PHITT-trial, this strategy had to be left for some trial subgroups. To date it is unclear which approach, primary surgery vs primary chemotherapy, is more suitable in resectable cases at diagnosis because a randomized study addressing this question is difficult to be conducted, due to the rarity of this disease.

Added value of this study

The single database created by the Childhood Hepatic tumor International collaboration (CHIC) consists of the past eight clinical trials in Europe, North America and Japan, enabled to compare between the cases who underwent upfront surgery and those who underwent delayed surgery after neoadjuvant chemotherapy in 512 cases whose tumors were considered as resectable at diagnosis. No difference of the outcomes, surgical resectability, and complications were seen in these two groups, but the subgroups of elder cases (≥3 years old at diagnosis) and low alpha-fetoprotein (AFP) cases (100–1000 ng/mL) showed better outcome by up-front surgery.

Implications of all the available evidence

This result may promote up-front surgery for cases with resectable tumors at diagnosis to reduce the chemotherapy dose and/or its toxicity, which will be confirmed in global clinical PHITT-trial. A future analysis of the biological characteristics in elder cases and low AFP cases may identify useful markers of aggressive or chemo-resistant tumors.

Introduction

Hepatoblastoma (HB) is the most common malignant liver tumor occurring in children. Complete surgical resection is essential to achieve cure. Many previous multicenter trials[1–9] have advocated for up-front surgical resection (UF) at the time of diagnosis when feasible. Other trials, including all of the legacy Epithelial Liver Tumor Study Group (SIOPEL) trials, recommend neo-adjuvant chemotherapy and delayed surgery (DL) for all.[10] The SIOPEL group had the theoretical paradigm that neo-adjuvant chemotherapy would treat (micro) metastasis from day one, leading to less distant metastases during follow up. However, it has not been scientifically established that neoadjuvant chemotherapy is necessary in resectable disease. Leaders from the four cooperative trial groups (SIOPEL, Children's Oncology Group [COG], the German Society for Pediatric Oncology and Haematology [GPOH], and the Japanese Study Group for Pediatric Liver Tumors [JPLT]) joined forces to establish an international collaboration (Children's Hepatic tumors International Collaboration [CHIC] intended to collate data from 8 previously concluded consortia trials, and created a single database containing data from 1605 children using PRETEXT (PRETreatment EXTent of disease) groups and annotation factors.[11–13] Analysis of this database established the international risk stratification of HB which is being used for the current international trial, PHITT (Pediatric

Hepatic International Tumor Trial).[11] PRETEXT I tumors are located in one liver section with three contiguous liver sections tumor-free and PRETEXT II tumors are located in one or two liver sections leaving two contiguous liver sections tumor free. We used the CHIC database to determine whether UF in cases that are PRETEXT I or II, without major annotation factors, is effective or at least permissible as both stages can be treated either way.

Methods

All 1605 patients included in the CHIC collaborative database were treated in 1 of the following 8 prospective multicenter cooperative trials enrolled between 1988 and 2010[11,12]: SIOPEL-2[2]; SIOPEL-3[14,15]; COG-INT0098[1]; COG-P9645[16,17]; GPOH-HB89[16,17]; GPOH-HB99[18]; JPLT1[3]; and JPLT2.[4] As previously reported, analysis of each trial by outcome demonstrated no statistically significant differences.[11] The most powerful prognostic indicators were PRETEXT group (III and IV), a low alpha-fetoprotein (AFP) level (<100 ng/mL), PRETEXT annotation factors V (all hepatic veins or IVC involvement), P (both portal vein involvement), E (contiguous extrahepatic tumor), R (rupture), M (metastasis), and age.[13,14] Generally, the tumor is considered resectable if it is confined to one or two liver sections and does not involve large portal or hepatic veins. Therefore, in this study, we defined the eligible patients as resectable cases at diagnosis which were PRETEXT I or II, with V0 or V1, P0 or P1, E0, R0, and M0. Additionally, cases with very low AFP (<100 ng/mL) were also excluded. Among 519 patients with PRETEXT I or II without P2 or P3, V2 and M1, 512 were considered as eligible for this analysis; one patient whose parents declined treatment, 5 patients with unknown surgical dates and one patient with no follow-up data after surgery were excluded. Of the 512 patients, 172 were initially treated with UF at the time of diagnosis and 340 were treated with DL after neoadjuvant chemotherapy (Fig. 1). Among the UF and DL cohorts, 153 and 326 patients received adjuvant chemotherapy, respectively. The cycles and dosages of chemotherapy drugs in each trial are described in Appendix pages 6–11.

Procedures

The primary outcomes were 5-year event-free survival (EFS) and overall survival (OS). We defined EFS as the time from start time (surgery date in UF and chemotherapy start date in DL) to tumor recurrence, diagnosis of other tumors, death from any causes, or last follow-up evaluation without the occurrence of any of these events. OS was defined as patient survival from start zero time up. Secondary outcomes included a determination of whether UF or DL affected choice of surgical procedure, resectability, surgical complications, local recurrence,

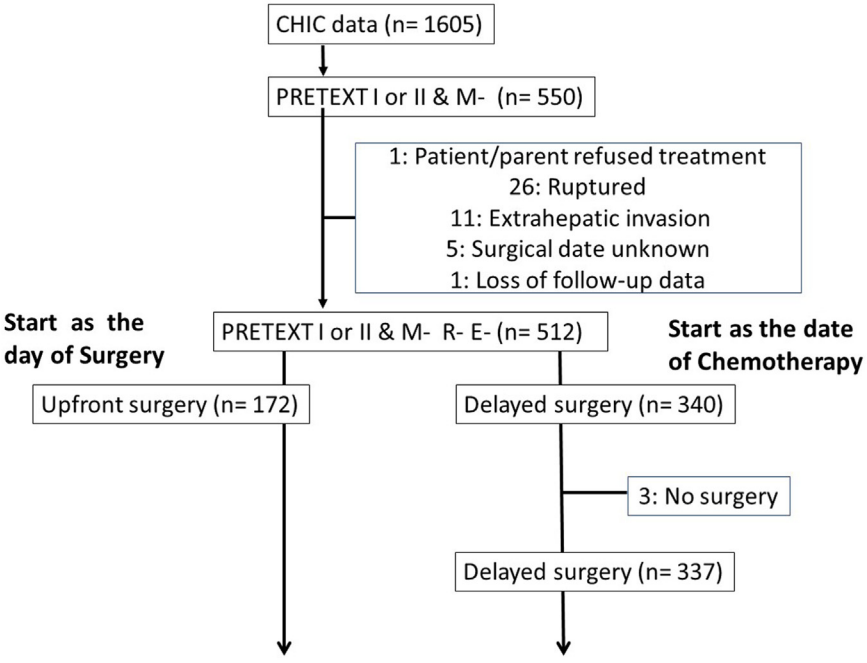

***Fig. 1:* Profile for patients enrolled in the low-risk hepatoblastoma study.** Five hundred fifty HB patients without distant metastases were selected from a total of 1605 patients in the CHIC database (2004–2013) as PRETEXT I or II. Thirty-six patients were excluded for the following reasons: declined treatment, 1; ruptured cases, 26; extrahepatic invasion, 11; and unknown surgical dates, 4. A final cohort of 512 patients, including 172 who underwent initial up-front surgery (UF cohort) and 340 patients who received preoperative chemotherapy (DL cohort) were enrolled in this study. Among 340 patients in the DL cohort, 3 had disease progression and did not undergo DL.

distant metastasis, and late complications. We analyzed risk factors for EFS and OS, such as resection margin status, PRETEXT group, age at diagnosis, gender, AFP level at diagnosis, and histology, which were identified in the previous CHIC data analysis.[11,19–21] We classified resectability into microscopically negative margins, macroscopically complete resection with positive microscopic margins (microscopically positive), and macroscopically positive resection.

Age at diagnosis was divided into the following four groups, as described by the report for age as a prognostic factor for HB patient outcome: <1 year; 1–2 years, 3–4 years; and ≥5 years.[19] Serum levels (ng/mL) of AFP at diagnosis were divided into the following 5 groups: 101–999; 1000–9999; 10,000–99,999; 100,000–999,999; and ≥1,000,000. We excluded those patients whose AFP level was ≤ 100 ng/mL as prior analysis has shown them to be high-risk, and sometimes rhabdoid patients.[21] Surgical procedures were classified into the following three groups; right or left hemihepatectomy; right or left extended hemihepatectomy; and others including sectionectomy and non-anatomic resection according to Brisbane terminology.[22] Histology was established based on consensus review of microscopic slides by expert pathologists.[13]

Since cisplatin, one of the most effective agents against HB, has been commonly used in the protocols. Platinum-induced hearing loss has occurred at a high rate.[4,23] And chemotherapeutic agents used in HB treatment are known to be associated wit the increase of the development of second malignant neoplasms (SMNs).[24] Therefore, as late complications, ototoxicity requiring hearing aids and SMNs were analyzed in the CHIC database.

Statistical analysis

To minimalize the immortal time bias,[25] the day of surgery was defined as time-zero in the UF cases and the first day for neoadjuvant chemotherapy as time-zero in the DL cases. Groups were compared using a chi-square test for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables. The continuous variables analyzed such as age at diagnosis and AFP levels were obviously non-normally distributed in their histograms. The Shapiro–Wilk test of these variables showed $P < 0.001$. Therefore, Wilcoxon-Mann-Whitney test was used for these non-normally distributed variables. Survival analyses were performed using unadjusted Kaplan–Meier analysis with log-rank tests and multivariable Cox proportional hazards regression. Into this Cox analysis, we put the factors that had been most predictive of outcome by univariable analysis in CHIC database.[11,12] These factors were AFP, age at diagnosis, PRETEXT, and the annotation factor F (multifocality). The followings were added and then adjusted for in the multivariable Cox proportional hazards model: eight study trials in four groups, surgical timing (UF or DL), gender, surgical type, and histology.

Ethical statement

Ethical approval was obtained prior to enrollment of participants with informed consent in each clinical trial at all four groups. This study protocol was approved by the ethics committee of Hiroshima University (approval number: Hi-219).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Raw data were accessible only to the trial group statisticians (EH, TH, KY, MK, and RM) and the database managers (JP, and JL). EH, TH, KY, MK, RM, AR, PC, RLM, and DCA, had final responsibility for the decision to submit for publication

Results

A final cohort of 512 patients, including 172 UF cohort and the remaining 340 DL cohort were analyzed (Fig. 1). The UF and DL cohorts were comparable with respect to age at diagnosis, gender, vascular invasion, multifocality, and serum AFP levels (Appendix page 1). The UF cohort had a significantly higher number of PRETEXT I patients than the DL cohort ($P < 0.01$). The median duration of follow-up was also comparable between the groups.

Neoadjuvant chemotherapy in the DL cohort

The neoadjuvant chemotherapy cycles in the DL cohorts ranged in number between 1 and 12 (median: 4) and depended primarily upon the protocol regimen (Table 1). These clinical trial regimens consisted of eight separate trials (Appendix page 6–11): SIOPEL-2,[2] SIOPEL-3,[14,15] COG-INT0098,[1] COG-P9645,[16,17] GPOH-HB89,[18,26] GPOH-HB99,[18] JPLT-1,[3] and JPLT-2.[4] These regimens mainly consisted of cisplatin and anthracyclines and were in some cases augmented by carboplatin, doxorubicin, pirarubicin, 5-fluorouracil, vincristine, and/or etoposide per individual trial and treatment arm. During/after neoadjuvant chemotherapy, 3 patients could not undergo surgery due to progression of disease. Therefore, 337 patients underwent DL for definitive tumor resection.

Surgical procedure and resectability

The surgical procedures are shown in Table 1. Right or left hemi-hepatectomies were 84 of 117 UF cases (71.7%) and 195 of 312 DL cases (62.5%). An extended hemihepatectomy, which was performed in 4 UF patients (3.4%) and 42 DL patients (13.5%), was more often in the DL cohort in the comparison with hemihepatectomy ($P = 0.0025$). Complete resection was performed in 147 of 157 UF (93.6%) and 287 of 320 DL cases (89.7%); there was no significant difference ($P = 0.168$). The recurrence rates were marginally higher in the margin-positive UF cases (Tables 1 and 2). Type

of surgical procedure was not significantly correlated with recurrence in either cohort (Table 2).

Surgical complications

Surgical complications, including bleeding, infection, and biliary leakage, occurred in 6 (6.12%) of 98 patients in the UF cohort and 43 (13.4%) of 313 patients in the DL cohort ($P = 0.042$). Among them, 1 patient each in both cohorts has surgical-related deaths. All 6 UF patients with surgical complications underwent a hemihepatectomy. Among the 43 DL patients, 9 underwent an extended hemihepatectomy, 26 underwent a hemihepatectomy, and 8 underwent other procedures.

Adjuvant chemotherapy in the UF cohort

Nineteen patients in the UF cohort did not receive chemotherapy postoperatively; 16 patients whose tumors were the pure fetal type, a special subtype of epithelial HB, were alive with disease-free but 2 of the other 3 cases died with recurrent tumors. All remaining patients received adjuvant chemotherapy. The median number of chemotherapy cycles 4 (0–12) administered to these patients mainly depended on the protocols and were comparable to the number of adjuvant chemotherapy cycles administered to the DL cohort. These regimens also mainly consisted of cisplatin and anthracyclines. Adjuvant chemotherapy was started 0–64 days (median, 15 days) after surgical resection. In the patients with local recurrences or distant metastases, chemotherapy was started 0–31 days (median, 14 days) after resection, which was comparable to the event-free cases.

Adjuvant chemotherapy in the DL cohort

Among 337 patients who underwent DL, 9 patients did not receive adjuvant chemotherapy. One of these 9 cases was a surgical death. In the remaining 328 DL patients, 1–10 (median: 2) adjuvant chemotherapy cycles were administered. These regimens mainly consisted of cisplatin and anthracyclines, similar to those of the UF cohort. Therefore, the total numbers of chemotherapy cycles in the DL cohort were 1–12 (median: 6), which were significantly larger than the UF cohort ($P < 0.01$).

Recurrence

Recurrence occurred in 13 (7.6%) of 171 UF cases and 42 (11.3%) of 339 DL cases excluding 2 surgical death and 1 recurrence unknown case. Local recurrence and liver metastases occurred in 9 (5.3%) and 11 UF cases (6.4%) and in 24 (7.1%) and 23 DL cases (6.8%), respectively. Seven UF cases and 10 DL cases had combined liver and lung metastases (4.1% and 2.9%, respectively); 7 of the 13 UF recurrent cases and 19 of the 42 DL recurrent cases died from the tumor. Recurrence rates were similar in both groups. Three (30%) of 10 margin-positive UF cases showed local recurrence, which seemed higher than margin positive DL cases,

	Total	Upfront surgery	Delayed surgery	χ2 P value
Preoperative chemotherapy (cycles)				
0	172	172	–	
1	16		16	
2	75		75	
3	13		13	
4	167		167	
5	23		23	
6≤	24		23	
Unknown	23		23	
Surgical type				
Right/left hemihepatectomy	280	84	195	0.0025[c]
Extended hemihepatectomy	46	4	42	
Others	103	29	75	
Unknown	84	55	25	
Surgery not done			3	
Surgical extent				
Complete resection	435	147	287	0.158
Marginal positive	43	10	33	
Microscopic-positive	39	8	31	
Macroscopic-positive	4	2	2	
Unknown	32	15	17	
Surgery not done	3	–	3	
Surgical complication				
No	362	92	270	0.042[b]
Yes	49	6	43	
Surgical death	2	1	1	
Unknown	98	74	24	
Surgery not done	3		3	
Cycle of postoperative chemotherapy				
0	28	19	9	
1	53	2	51	
2	185	15	170	
3	15	0	15	
4	107	48	59	
5	9	1	8	
6≤	64	61	3	
Unknown	48	26	22	
Surgery not done	3	–	3	
Recurrence[a]				
No	455	158	297	0.100
Yes	55	13	42	
Liver		9	24	
Lung		11	23	
Other sites		2	12	
Unknown			1	
Age				
0–2	37/435	10/143	27/292	0.429
<1	13/188	5/63	8/125	0.695
1–2	24/247	5/80	19/167	0.208
3≤	18/75	3/28	15/47	0.038[b]
3–4	8/44	1/16	7/28	0.109
5≤	10/31	2/12	8/19	0.14

(Table 1 continues on next page)

	Total	Upfront surgery	Delayed surgery	χ2 P value
(Continued from previous page)				
AFP				
100–999	15/60	1/18	14/42	0.023[b]
1000–9999	2/68	0/21	2/47	0.337
10,000–99,999	13/117	4/31	9/86	0.717
100,000–999,999	17/148	5/34	12/114	0.502
≥1,000,000	3/32	0/2	3/30	0.656
Unknown	5/85	3/65	2/20	–
Outcome				
Alive	480	164	316	0.289
Dead	32	8	24	
Dead of tumor progression		7	20[b]	
Surgical death		1	1	
Chemotherapy death			1	
Others			2	

[a]Excluding 2 surgical death cases. [b]$P < 0.05$. [c]$P < 0.01$.

Table 1: **Treatment process of patients with PRETEXT I or II hepatoblastoma without distant metastases, rupture, or extrahepatic invasion.[b]**

but not significantly ($P = 0.127$) (Table 2). In the DL cohort, the recurrence rates in cases older than 3 years of age at diagnosis were significantly higher than the younger cases ($\chi2 = 20.0$, $P < 0.0001$) and those of the case whose AFP at diagnosis less than 1000 ng/mL were also significantly higher in other cases ($\chi2 = 19.165$, $P < 0.0001$). In the cases older than 3 years of age at diagnosis, the recurrence rate of DL cases was relatively higher than that of UF cases ($\chi2 = 4.32$, $P = 0.038$). In the cases whose AFP at diagnosis less than 1000 ng/mL, the recurrence rate of DL cases was relatively higher than that of UF cases ($\chi2 = 5.18$, $P = 0.023$).

Survival rates in the UF and DL cohorts

The 5-year EFS for the UF and DL cohorts were 90% and 86.6% and the 5-year OS were 95.3% and 92.5%, respectively, which were almost comparable in both groups (Fig. 2). These are no significant differences in both EFS and OS between the UF and DL groups. In DL cohort, the EFS rates of the patients whose age at diagnosis was old (≥3 years old) was worse than the other DL cohort ($P < 0.01$, Fig. 3 B & D, Appendix page 2). The EFS rates of these DL patients older than 3 years of age at diagnosis were also significantly less than those of the comparable UF cases ($P = 0.030$, Fig. 4 A), however these patients had salvageable disease (as demonstrated in Fig. 2 and Appendix page 2). The EFS of the DL cohort patients with a low AFP (100–999 ng/mL) at diagnosis were significantly worse than the other DL cohort patients ($P < 0.01$, Fig. 3C &D, Appendix page 2). The EFS rate of these low-AFP DL patients were also less than that of the comparable UF cases, but not significantly ($P = 0.150$, Fig. 4B). The OS of the UF and DL cohort patients were nearly equivalent in the patients with an AFP level ≥1000 ng/mL (Appendix page 2). In order to assess the prognostic significance of age at diagnosis in DL surgery, EFSs were compared between

	Total	Recurred [Dead]	Liver [Dead]	Lung [Dead]	Other [Dead]
Upfront surgery	171[a]				
Rt/Lt hemi-hepatectomy	83	5 (6.0%) [3 (3.6%)]	2 (2.4%) [2 (2.4%)]	5 (6.0%) [3 (3.6%)]	1 (1.2%) [2 (2.4%)]
Extended hemihepatectomy	4	0	0	0	0
Others	29	1 (3.4%) [0]	0	1 (3.4%) [0]	0
Unknown	55	4 (7.3%) [2 (3.6%)]	4 (7.3%) [2 (3.6%)]	3 (5.5%) [2 (3.6%)]	1 (1.8%) [1 (1.8%)]
Margin-negative	146	9 (6.2%) [5 (2.7%)]	5 (3.4%) [4 (2.7%)]	9 (6.2%) [4 (2.7%)]	2 (1.4%) [2 (2.7%)]
Margin-positive	10	3 (30.0%) [2 (2.7%)]	3 (30.0%) [2 (2.7%)]	2 (20.0%) [2 (2.7%)]	0
Microscopic-positive	8	2 [1]	2 [1]	1 [1]	0
Macroscopic-positive	2	1 [1]	1 [1]	1 [1]	0
Margin-Unknown	15	1 (6.2%) [0]	1 (6.2%) [0]	0	0
Delayed surgery	335[b]				
Rt/Lt hemi-hepatectomy	192	21 (10.9%) [11 (5.7%)]	10 (5.2%) [4 (2.1%)]	14 (7.3%) [8 (4.2%)]	7 (3.6%) [6 (3.1%)]
Extended hemihepatectomy	42	5 (11.9%) [2 (4.8%)]	4 (9.5%) [2 (4.8%)]	3 (7.1%) [2 (4.8%)]	1 (2.4%) [0]
Others	74	9 (12.2%) [3 (4.1%)]	6 (8.1%) [3 (4.1%)]	2 [1 (1.4%)]	2 (2.7%) [0)]
Unknown	27	3 (11.1%) [2 (7.4%)]	2 (7.4%) [1 (3.7%)]	2 (7.4%) [1 (3.7%)]	1 (3.7%) [1 (3.7%)]
Margin-negative	284	32 (11.3%) [14 (4.9%)]	18 (6.3%) [7 (2.5%)]	18 (6.3%) [10 (3.5%)]	8 (2.8%) [5 (1.8%)]
Margin-positive	33	3 (9.1%) [14 (4.8%)]	2 (6.1%) [0]	0 [0]	1 (3.0%) [0]
Microscopic-positive	31	2 [0]	1 [0]	0	1
Macroscopic-positive	2	1 [1]	1 [1]	0	0
Unknown	18	3 (16.7%) [3 (16.7%)]	2 (11.1%) [2 (11.1%)]	3 (16.7%) [3 (16.7%)]	2 (11.1%) [2 (11.1%)]

[a]One surgical dead case was excluded. [b]Three PD and two surgical dead cases were excluded.

Table 2: **Surgical resection, resectability and recurrence rates.**

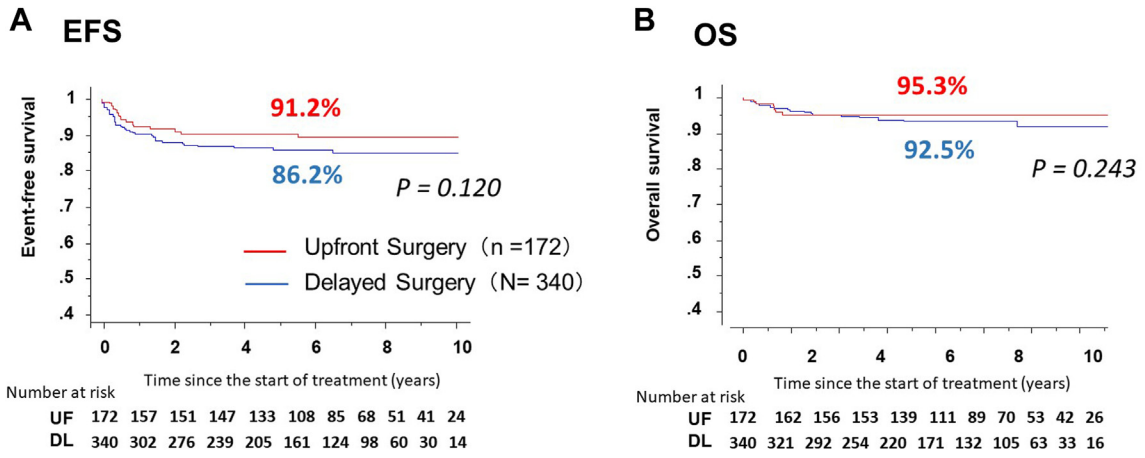

***Fig. 2*: Event-free (A) and overall survival (B) of the upfront (UF) and delayed (DL) surgery patients.** Five-year event-free survival (EFS) rates in the UF and DL cohorts were 90.6% and 86.2% and the 5-year overall survival (OS) were 95.3% and 92.5%, respectively; the 5-year EFS and 5-year OS were nearly comparable in both groups.

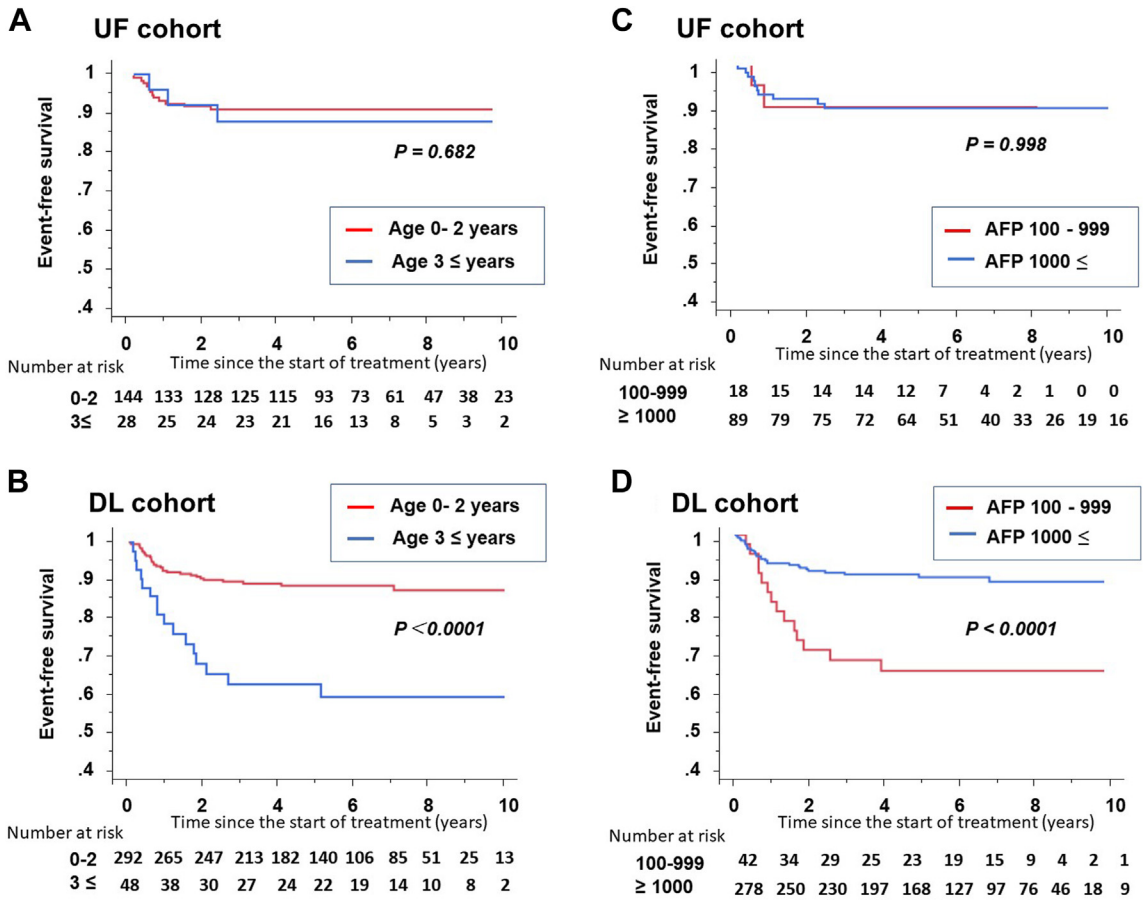

***Fig. 3*: Event-free survival (EFS) of the upfront (UF) and delayed (DL) surgery patients by age at diagnosis (A and B) and by AFP level at diagnosis (C and D).** A. In the UF cohort, 5-year EFS of the patients over 3 years old at diagnosis was slightly worse than other patients, but not significantly. B. In the DL cohort, 5-year EFS of the patients over 3 years old at diagnosis was significantly worse than other patients ($P < 0.0001$). C. In the UF cohort, 5-year EFS of the patients with an AFP level 100–999 ng/mL at diagnosis was comparable to other patients. D. In the DL cohort, 5-year EFS of the patients with an AFP level 100–999 ng/mL at diagnosis was significantly worse than other patients ($P < 0.0001$).

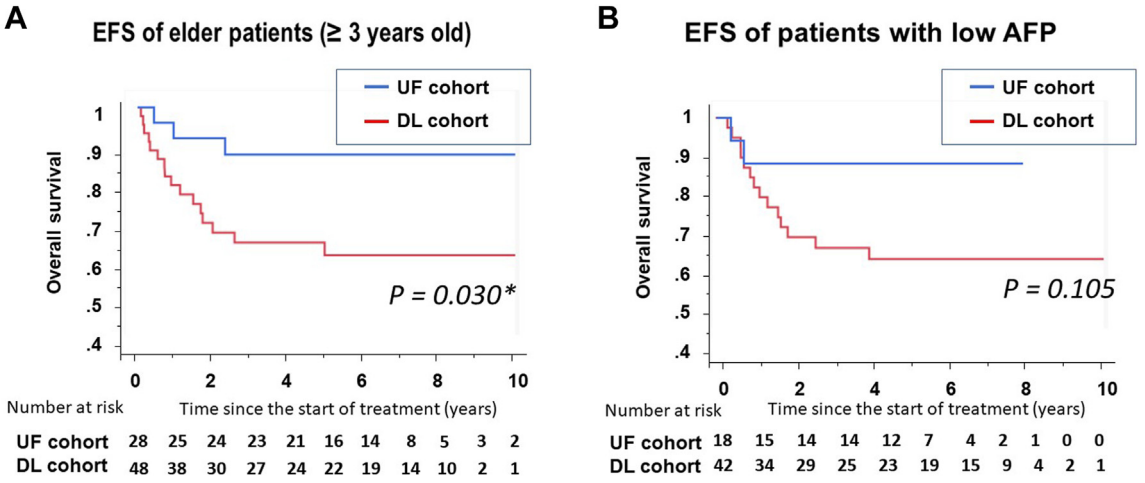

Fig. 4: **Event-free survival (EFS) of the upfront (UF) and delayed (DL) surgery patients in the subgroup of over 3 years old at diagnosis and that with low AFP levels.** In the patients who were diagnosed at more than 3 years old, 5-years EFS was significantly poor (P = 0.030). In the patients with an AFP level 100–999 ng/mL at diagnosis seemed worse but not significantly (P = 0.105).

UF and DL groups in the 4 subgroups divided by age at diagnosis (Appendix page 3). The EFS in DL group seemed progressively worse in the patients whose age at diagnosed at the 3–4 years old and in those whose age at diagnosis at more than 5 years old, but not significantly due to the small number of this cohort. In the multivariable Cox regression analysis in the whole cohort, significant risk factors for events were old age (≥3 years old) and low AFP (100–999 ng/mL) at diagnosis (P = 0.003, P = 0.003) (Table 3). In the Cox analysis of the UF cohort, no significant variables for events were detected but in that of the DL cohort, old age (≥3 years old) and low AFP (100–999 ng/mL) at diagnosis were significant for events (P < 0.001, P = 0.001) (Table 4). But these factors were not significant risk factors in OS, except for relative significance of annotation factor (portal or hepatic vein involvement) in total cohort and PRETEXT in DL cohort (Appendix pages 4 and 5). There were no significant difference of surgical type and eight study trials.

Late complications

Ototoxicity occurred in 35 (20.3%) of 172 patients in the UF cohort and 90 (26.5%) of 340 patients in the DL cohort. SMNs occurred in 1 patient in the UF cohort and 2 patients in the DL cohort; there was no significant difference between the groups.

Discussion

Complete resection is a critical component of surgical treatment to achieve cure in HB. However, 60%–80% of tumors are unresectable at the time of diagnosis.[1,27] The remaining 20%–40% of tumors are considered resectable at the time of diagnosis but, due to the rarity of HB, it has been difficult to conduct a randomized study to

Variable	Hazard ratio (95% CI)	P value
Age at diagnosis		
<3 vs 3 ≤	2.362 (1.329, 4.198)	0.003[a]
Gender		
Male vs Female	0.785 (0.449–1.373)	0.396
PRETEXT		
I vs II	1.565 (0.661, 3.704)	0.308
F (multifocality)		
0 vs 1	1.581 (0.519, 4.816)	0.420
P (portal vein involvement)		
0 vs 1	2.724 (0.918, 8.082)	0.071
V (hepatic vein involvement)		
0 vs 1	3.658 (0.909, 14.717)	0.068
AFP at diagnosis		
100–999 vs 1000≤	0.372 (0.204, 0.689)	0.003[a]
Surgery		
UF vs DL	1.263 (0.585, 2.728)	0.552
Surgical extent		
HT	1 (reference)	
EXT	1.071 (0.436, 2.627)	0.882
Others	0.913 (0.460, 1.812)	0.769
Unknown	2.365 (0.893, 6.184)	0.083
Studies		
HB89	1 (reference)	
HB99	2.927 (0.729, 11.748)	0.130
INT0098	1.065 (0.191, 5.938)	0.943
JPLT1	3.416 (0.716, 16.307)	0.123
JPLT2	3.276 (0.816, 13.148)	0.094
P9645	0.658 (0.133, 3.260)	0.608
SIOPEL2	1.454 (0.276, 7.645)	0.659
SIOPEL3	1.962 (0.472, 8.147)	0.354

HT: hemihepatectomy, EXT: extended hemihepatectomy, AFP: alpha-fetoprotein. [a]P < 0.01.

Table 3: **Multivariate analysis for event-free survival by Cox regression analysis.**

analyze the benefit of UF over DL.[28,29] In these patients, although resection at the time of diagnosis might be possible, many have historically argued that neoadjuvant chemotherapy for all might facilitate an easier resection of the tumor and promptly treat micro (-circulating or distant) disease thereby decreasing surgical morbidity and leading to improved outcomes.[30,31] From the point of view of the initial COG legacy studies, exploratory laparotomy at the time of diagnosis was recommended to attempt surgical resection when feasible.[1,6,32] In the subsequent COG AHEP0731 trial, upfront resection was recommended for patients with PRETEXT I or II disease, provided that preoperatively radiographic imaging suggested adequate margin with a simple, non-extended, hemihepatectomy.[28,33] In the JPLT and GPOH groups, the PRETEXT I or II cases underwent resection at the time of diagnosis if possible.[3–5,18,34] In contrast, the SIOPEL group recommended neoadjuvant chemotherapy in all cases.[2,7–9] To evaluate both strategies, an analysis with a large number of HB patients with comparable resectable tumors was needed. Therefore, in the current study we compared patients with PRETEXT I and II tumors who underwent UF with those who underwent DL following neoadjuvant chemotherapy using the CHIC database.

In the comparison of these two cohorts, PRETEXT I cases were significantly higher in UF. Since age, sex, annotation factors of venous involvement (P1 or V1) and multifocality (F) and the AFP levels at diagnosis were not different, UF might be selected in the patients by location and size of tumors except for SIOPEL studies. In the 194 cases whose histology was reclassified by review of experts in the CHIC project,[13] the most common one is epithelial type. The proportion of HBs with mixed epithelial and mesenchymal histology was significantly increased in the DL cohort, suggesting that mesenchymal differentiation seen in this mixed type might be induced by neoadjuvant chemotherapy. Other types including small-cell undifferentiated (SCU), macrotrabecular, and hepatocellular neoplasm not otherwise specified (HCN–NOS) were identified in only 4 cases and one DL case died of tumor. Therefore, such unfavorable histology HBs might be rare in the PRETEXT I/II tumors without major annotation factors and the outcome of these cases could not be explained by the histological classification.

Focusing on the UF cohort, 19 patients did not receive any adjuvant chemotherapy. According to the COG protocol,[32] the patients with completely resected pure fetal tumors with low mitotic activity (well-differentiated fetal HB), which is well-known subtype of epithelial HB with better outcomes, were followed without chemotherapy. As shown in the results of this trial, all these 16 patients were alive and disease-free. However, two of the remaining 3 patients with other histologies experienced relapse. Therefore, in PRETEXT I/II HB patients, adjuvant chemotherapy would seem to be advisable for all but well-differentiated fetal tumors. Unfortunately, the diagnosis of well-differentiated fetal HB is not possible with small biopsy sample but requires the whole tumor specimen. The diagnosis of this type is an advantage in UF surgery for avoiding unnecessary adjuvant chemotherapy. In future, given that we now have a better histological and even molecular way to stratify risk for these patients, as well the histological heterogeneity of these tumors, UF whenever possible followed by careful histological and molecular profiling would allow for individualized management and avoid overtreating patients with low risk tumors.

The SIOPEL delayed resection strategy hypothesizes that resection will be facilitated by first administering chemotherapy because the tumor becomes more solid, less prone to bleed and more demarcated from the remaining healthy liver parenchyma, thus easier to be removed by the surgeon.[8,35–37] Interestingly, the rates of complete resection were similar between the UF and DL cohorts but the number of extended hemihepatectomies

Variable	Upfront surgery (n = 172)		Delayed surgery (n = 340)	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age at diagnosis				
<3 vs 3 ≤	0.949 (0.227, 3.976)	0.943	3.434 (1.728, 6.822)	<0.001[a]
Gender				
Male vs Female	0.693 (0.203, 2.360)	0.557	0.826 (0.431, 1.582)	0.564
PRETEXT				
I vs II	1.593 (0.437, 5.808)	0.480	1.399 (0.392, 4.989)	0.605
F				
0 vs 1	8.559 (0.795, 92.203)	0.077	0.614 (0.104, 3.623)	0.077
P				
0 vs 1	2.572 (0.235, 28.100)	0.439	2.577 (0.725, 9.161)	0.144
V				
0 vs 1	0.629 (0.027, 14.464)	0.772	10.15 (1.931, 53.34)	0.060
AFP at diagnosis				
100–999 vs 1000≤	0.897 (0.200, 4.029)	0.888	3.434 (1.728, 6.822)	0.001[a]
Surgical extent				
HT	1 (reference)		1 (reference)	
EXT	0.000 (0.000, 0.000)	0.938	5.323 (1.380, 20.542)	0.015
Others	1.842 (0.435, 7.802)	0.407	1.168 (0.458, 2.978)	0.745
Unknown	4.059 (0.528, 31.237)	0.178	0.601 (0.259, 1.399)	0.238
Studies				
HB89	1 (reference)		1 (reference)	
HB99	3.903 (0.531, 28.667)	0.181	0.000 (0.000, 0.000)	0.984
INT0098	0.817 (0.096, 6.993)	0.854	1.375 (0.598, 4.693)	0.326
JPLT1	1.429 (0.107, 19.143)	0.788	0.000 (0.000, 0.000)	0.977
JPLT2	1.035 (0.110, 9.768)	0.976	2.325 (0.702, 7.706)	0.165
P9645	0.281 (0.020, 2.360)	0.350	2.276 (0.938, 5.523)	0.069
SIOPEL2	–	–	0.194 (0.029, 1.307)	0.092
SIOPEL3	–	–	0.737 (0.244, 2.223)	0.588

F: multifocality, P: portal vein involvement, V: hepatic vein involvement, HT: hemihepatectomy, EXT: extended hemihepatectomy, AFP: alpha-fetoprotein. [a]$P < 0.01$.

Table 4: **Multivariate analysis for event-free survival in UF and DL cohorts by Cox regression analysis.**

was significantly higher in the DL cohort ($P < 0.01$). The non-SIOPEL groups might have selected larger tumors, despite resectable at the time of diagnosis, to be treated with DL, thus increasing the frequency of PRETEXT II cases and extended hemihepatectomies in the DL cohort in the comparison of UF cohort. Among DL cohort patients, only three did not undergo surgery and one patient underwent liver transplantation. Although it is unlikely that tumors progressed during neoadjuvant chemotherapy,[8,38] some DL cases were reported to be upstaged during neoadjuvant chemotherapy in SIOPEL studies. In the DL cohort, 3 cases who had resectable PRETEXT II tumors at diagnosis could not undergo surgery due to progression during neoadjuvant chemotherapy. Among them, one was 6 years old and one had low AFP tumor. Recent study revealed the different histological and biological characteristics of the tumors in elder or low AFP patients.[21] Therefore, the upstaging tumors should be resected earlier for examination of histology as well as biological heterogeneity of the whole tumor and biology.

No difference in the occurrence of distant recurrences between the UF and DL groups suggests that the concept of the importance of the immediate treatment of distant microscopic disease, does not hold true.[10,38] Previous reports indicated that atypical resection of tumors might induce dissemination of tumor cells in the liver, which could predispose to a recurrence.[39,40] In the current study, the recurrence rates were slightly higher in the patients with non-anatomic resections compared to those with anatomical resections but not significantly. The local recurrence rate (30%) of microscopic residual cases in UF cohort was also high, but not significantly due to the small numbers of cases. The recurrence rate did not increase in patients who had a microscopic complete resection in the DL cohort. Adjuvant chemotherapy might be effective to reduce local recurrence in these cases, but also burned or coagulated tissue existing at the liver remnant may have helped to prevent a recurrence, so a microscopic residual might not increase the local recurrence rate.[36,41] In some trials the safety margin from tumor to main liver vasculature vessels was advocated to be > 1 cm in patients who have not received neoadjuvant chemotherapy, but there is no evidence for this statement[4,28] Another analysis indicated a worse outcome of the patients whose tumor were resected with microscopic positive margin compared to a complete excision, but this cohort included the more advanced HBs and a smaller number of patients.[42] Therefore, three cases of 10 marginal positive cases in the UF cohort might depend on the viability of residual tumor cells at surgical margin, indicating that complete resection should be performed in UF group. The requirement of safety margin for resection in HB will be further explored by the Pediatric Hepatic International Tumor Trial (PHITT) in the future.[11]

There was no difference in the intensity of the chemotherapy regimens consisting of cisplatin and anthracycline in the eight trials. There was a significant increase in the total number of chemotherapy cycles administered in the DL cohort because the adjuvant chemotherapy cycles were set to the same number in the UF and DL regimen in each trial. In the UF cohort reducing the chemotherapy dose is expected to reduce toxicity and late complications. In contrast, UF might delay the start of chemotherapy, which may be a disadvantage in some UF cases, but no difference in the chemotherapy start day after surgery between cases with recurrence and others, indicating that recurrences in UF cohort patients did not correlate with a delay in starting the chemotherapy.

In this study the EFS of the cases patient who were diagnosed at more than 3 years and those with an AFP level of 100–999 ng/mL at the time of diagnosis were significantly worse in the DL cohort but not in the UF cohort. The subgroup analysis revealed delayed surgery after neoadjuvant chemotherapy might be inappropriate for some patient who were diagnosed at more than 3 years and some with low AFP tumors. Although there was some bias for selection of the UF cohort, the usual chemotherapy might be ineffective in the cases with low AFP tumors or in elder patients.[19,43] This result suggested that an HB with a comparatively low expression of AFP (100–999 ng/mL) or HB in elder patients (≥3 years old) might be a biologically more aggressive tumor and perhaps less likely to respond to chemotherapy in the DL cohort.[44] In the multivariate analysis including adjusted covariates remained significant factors in the whole cohort as well as in the DL cohort, suggesting the existence of different subtypes of HB. Analysis of age at diagnosis in HB using the CHIC database already revealed the correlation with low AFP and the importance of age as prognostic factor for the outcome of the patients.[19] Therefore, these tumors might be biologically more aggressive, so that initial upfront resection for resectable tumors consequently showed favorable outcome but the selection of DL treatment showed less EFS rates in these biologically aggressive tumors. Indeed, in the subgroup of low AFP, no significant difference of EFS between UF and DL cases, which might be due to small number of cases analyzed. But there is a possibility to correlate with poor biological characteristics in these subgroups because some UF cases showed events early after resection. Recent studies have reported an increased proportion of HCN–NOS is older patients and identified molecular biomarkers in a subset of these tumors that overlap with carcinomas (HBs with carcinoma features) which could explain the aggressive clinical behavior of these tumors, including chemoresistance).[44] Since histological classification except for pure fetal HB were not correlated with outcomes in the resectable PRETEXT I or II HBs, this subset of patients should be analyzed further to identify

biological markers to classify the malignant grade of resectable HB.

Despite the promising data, this study had several limitations. Firstly, all studies included in this analysis are multi-center non-randomized controlled trials in design, which may be inclined to cause selection bias and exaggerate the effect of the approaches. Especially, SIOPEL studies did not permit the upfront resection in all cases and other trials permit upfront resection by institutional selection, which may be inclined to cause selection bias and alter the effect of the surgical approaches. Secondly, the CHIC database does not include data on the tumor size at diagnosis which might correlate with selection of upfront surgery. Thirdly, the biology data were not included and there was lack of pathology data in 318 cases, which precluded the detailed evaluation of biology and heterogeneity in the tumors.

In conclusion, the outcomes, surgical resectability, complications, and recurrence were not significantly different between the UF and DL groups. However, subgroup analysis indicated that some DL cases with a low AFP level or older age at diagnosis showed recurrence or progression. The concept that DL allows micrometastases to be treated earlier, thus giving rise to less distant metastases, does not seem to hold through. It appears that UF has an advantage of reducing chemotherapy and patients with potential risk factors such as a low AFP level or older age might undergo upfront resection when feasible.

Contributors

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All the authors have contributed to the manuscript in significant ways, and have reviewed and agreed upon the manuscript content.

Data sharing statement

The data from this study are not publicly available, however data sharing may be considered following publication upon reasonable written request to the CHIC organizing committee. Requests will be considered on a case by case basis.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102811.

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