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Original Articles

Multidisciplinary effort in treating children with hepatoblastoma in China

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ABSTRACT

The purpose of this study is to report the first nationwide protocol (*Wuhan Protocol*) developed by Chinese Children's Cancer Group and the results of multidisciplinary effort in treating hepatoblastoma. In this study, we reported the final analysis, which includes 153 hepatoblastoma patients in 13 hospitals from January 2006 to December 2013. The 6-year overall survival and event-free survival rates were 83.3 ± 3.1% and 71.0 ± 3.7%, respectively, in this cohort. The univariate analysis revealed that female ($P = 0.027$), under 5 years of age ($P = 0.039$), complete surgical resection ($P = 0.000$), no metastases ($P = 0.000$), and delayed surgery following neoadjuvant chemotherapy ($P = 0.000$) had better prognosis. In multivariate analysis, male, 5 years of age or above, stage PRETEXT III or IV, and incomplete surgical resection were among the some adverse factors contributing to poor prognosis. The preliminary results from this study showed that patients who underwent treatment following *Wuhan Protocol* had similar OS and EFS rates compared to those in developed countries. However, the protocol remains to be further optimized in standardizing surgical resection (including liver transplantation), refining risk stratification and risk-based chemotherapy.

Introduction

Hepatoblastoma (HB) is one of the most common liver malignancies in children. Recent data showed that the incidence of HB has increased by 2.18% annually in patients under 20 years of age. Ninety percent of patients with liver malignancies under 5 years of age were diagnosed with HB [1]. In the past, the main treatment for HB was surgical resection; however, complete tumor resection could be achieved only in a few patients [2]. The use of chemotherapy improved the survival rate dramatically since 1970s [3]. The multidisciplinary team (MDT), which included pediatric surgeons, oncologists, radiologists, and pathologists, played an essential role in HB treatment, with a survival rate of over 80% reported elsewhere in the world [4]. However, there was no report on overall survival (OS) and event-free survival (EFS) study in pediatric HB patients in China. In 2006, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine developed a protocol and the preliminary data showed a satisfactory survival rate in 12 HB patients [5]. In order to improve the outcome in HB patients and standardize the

Abbreviations: AFP, α-fetoprotein; CCCG, Chinese Children's Cancer Group; CHIC, Children's Hepatic tumor International Collaboration; CI, confidence interval; COG, Children's Oncology Group; CT, computed tomography; CR, complete remission; EFS, event-free survival; GPOH, German Liver Tumor Study; HB, hepatoblastoma; HR, hazard ratio; JPLT, Japanese Study Group for Pediatric Liver Tumor; LT, liver transplantation; MDT, multidisciplinary team; MRI, magnetic resonance imaging; OS, overall survival; PD, progressive disease; PR, partial remission; PRETEXT, pretreatment extent of disease; SD, stable disease; SIOPEL, Société Internationale d'Oncologie Pédiatrique-Epithelial Liver Tumor Study Group.

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treatment regimens in China, using protocols from Société Internationale d'Oncologie Pédiatrique-Epithelial Liver Tumor Study Group (SIOPEL) and Children's Oncology Group (COG) as references, Chinese Children's Cancer Group (CCCG) developed the *Multidisciplinary Treatment Guideline for Chinese Children with Hepatoblastoma* in the city of Wuhan, Hubei Province, in 2009, also referred to as *Wuhan Protocol*. This protocol focused on pre-operative chemotherapy and MDT effort in treating HB patients; thirteen CCCG member hospitals adopted this protocol. The purpose of this study is to assess the feasibility and effectiveness of the first nationwide protocol and the results of multidisciplinary effort in treating HB in China.

Materials and methods

Inclusion and exclusion criteria

From January 2006 to December 2013, there were 162 cases of pediatric HB treated in 13 CCCG member hospitals following *Wuhan Protocol* but 153 patients were enrolled in this study. The enrollment criteria for patients in this study were: (1) patients must be younger than 18 years of age; (2) patients had not had any chemotherapy before inclusion; and (3) pathological diagnosis confirmed by ultrasound-guided fine-needle biopsy or surgical resection. Patients with great risk for biopsy at the onset were temporarily diagnosed with clinical findings, including age, clinical history, physical examination, serum α-fetoprotein (AFP) level, and computed tomography (CT) scan or magnetic resonance imaging (MRI). After two or more cycles of neoadjuvant chemotherapy, the diagnoses of all patients were pathologically confirmed after a subsequent surgical tumor resection. Patients who underwent treatment following *Wuhan Protocol* for less than one cycle of chemotherapy were excluded from this study. The medical records of all enrolled cases were retrospectively reviewed, and their information (including medical history, physical examination, CT/MRI images, serum AFP, chemotherapy regimens, surgery, and outcome) was collected and verified by CCCG senior pediatricians and radiologists (CT/MRI images were used to define the stage). The Ethics Committee of each individual hospital had reviewed and approved this study. The consent from each patient's parents or legal guardians was obtained before treatment.

Stage, pathology, and risk stratification

Patients were classified using PRETEXT (pretreatment extent of disease) system [6] before treatment and COG staging [7] after surgery. The stage of each patient was verified by Dr. Yu-Hua Li, a CCCG senior pediatric radiologist from Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China. Based on WHO pathological diagnostic criteria [8], patients were divided into the pure fetal pattern, the combined fetal and embryonal epithelial pattern, the mixed epithelial and mesenchymal pattern, and other patterns (including the macrotrabecular, the small cell undifferentiated and the mixed with teratoid feature patterns). The paraffin sections from the tumor specimens of all patients were reviewed by Dr. Min-Zhi Yin, a CCCG senior pathologist at Shanghai Children's Medical Center, Shanghai, China.

To compare the treatment outcome among different risk groups with *Wuhan Protocol* and provide the basis for risk-based chemotherapy in future revision of the protocol, we retrospectively classified the patients into two groups based on the criteria of SIOPEL risk stratification [9,10]: standard-risk group and high-risk group. Standard-risk is defined as PRETEXT I, II or III, without any manifestation listed in high risk group; high-risk is defined as PRETEXT IV, or any PRETEXT stage with tumor infiltration of the inferior vena cava (IVC)/hepatic veins (+V), portal vein (+P), extrahepatic abdominal (+E), distant metastases (+M), the small cell undifferentiated (SCU), AFP <100 ng/mL, or tumor rupture.

Treatment procedure

Patients who were diagnosed with HB and met the enrollment criteria were treated following *Wuhan Protocol*. In this protocol (shown in Fig. 1), PRETEXT I patients were recommended to have surgical tumor resection followed by either two or four courses of post-operative chemotherapy. The preferred regimen was C5V, which consisted of cisplatin (90 mg/m^2, >1 year old, or 3 mg/kg, <1 year old) on day 1, vincristine (1.5 mg/m^2 with a maximum dose of 2 mg) and 5-fluorouracil (600 mg/m^2) on day 2.

All PRETEXT II, III, and IV patients usually received the same two courses of chemotherapy (C5V regimen) after diagnosis, with a 21-day interval between two courses. Patients' AFP level and CT scan were repeated after the second course of chemotherapy (defined as the first evaluation). Based on the first evaluation results, MDT members made a decision as when to have surgery. If the patients had complete surgical tumor resection, they were followed by either two or four courses of post-operative chemotherapy (C5V regimen). The total courses of chemotherapy for these cases were four to six.

Patients who could not undergo surgery after the first evaluation would receive two more courses of chemotherapy (C5V regimen). However, the patients whose first evaluation showed no response to initial chemotherapy (without reduced serum AFP level or tumor size), or the tumor was progressing, were subsequently switched to PLADO regimen. As an alternative regimen, PLADO was consisted of cisplatin (80 mg/m^2) on day 1, and doxorubicin (30 mg/m^2/d) on day 2 and day 3. The results of second evaluation by MDT after four courses of chemotherapy were used to determine the proper time-point of surgery. Patients with complete surgical resection received two to four more courses of post-operative chemotherapy. There would be a total of six to eight courses of chemotherapy. Those patients whose tumors could not be resected completely continued to receive two more courses of PLADO regimen. After the third evaluation, some of the patients underwent surgery and then received two to four courses with C5V or PLADO regimen.

Those patients who had finished six courses of pre-operative chemotherapy, but not responding to the chemotherapy as determined during the evaluations at different intervals, were excluded from *Wuhan Protocol*. These patients would be adjusted with other regimens (e.g. C5VD, ICE, and cyclo/topo) based on drug sensitivity results; each patient received an individual treatment plan.

Statistical analysis

Data statistics were performed using SPSS (Statistical Package for the Social Sciences), version 19.0 (SPSS Inc, Chicago, IL, USA). Survival curves were estimated by Kaplan–Meier method; the survival rates were reported as mean ± standard error (SE). Log-rank test was used to analyze prognostic univariate. Variables with a P-value <0.05 in univariate analysis were entered into the multivariate Cox proportional-hazards regression model. A P-value <0.05 was considered to be of statistical significance.

Follow-up

The last follow-up date for this study was May 31, 2015. Overall survival (OS) was calculated as time (in months) from diagnosis to death of any cause. Event-free survival (EFS) was calculated as time (in months) from definitive clinical diagnosis to event happening (including disease progression, recurrence, abandonment or death of any cause, whichever occurred first). Complete remission (CR) means that there is no evidence of tumor in CT or MRI, and normal serum AFP level for at least 4 weeks. Partial remission (PR) means a decrease of at least 50% in size of all measurable lesions, with no evidence of new lesions or progression in any lesion. Stable disease (SD) refers to any remission without an increase in tumor size and new lesions. Progressive disease (PD) refers to an increase of at least 25% in the size of any lesion, any new lesion, or a rising AFP level. Lost to follow-up is defined as that patient who failed to be followed up for at least 6 months.

Follow-ups were conducted in patients' primary hospital for at least 5 years from the date of treatment completion or the cut-off date for this report. The AFP level was checked monthly in the first year of follow-up, then every three months in the second year and third year, and every six months in the fourth and fifth years. MRI or CT scan was performed every two months in the first year, every three months in the second year, every six months in the third year, and annually during the last two years.

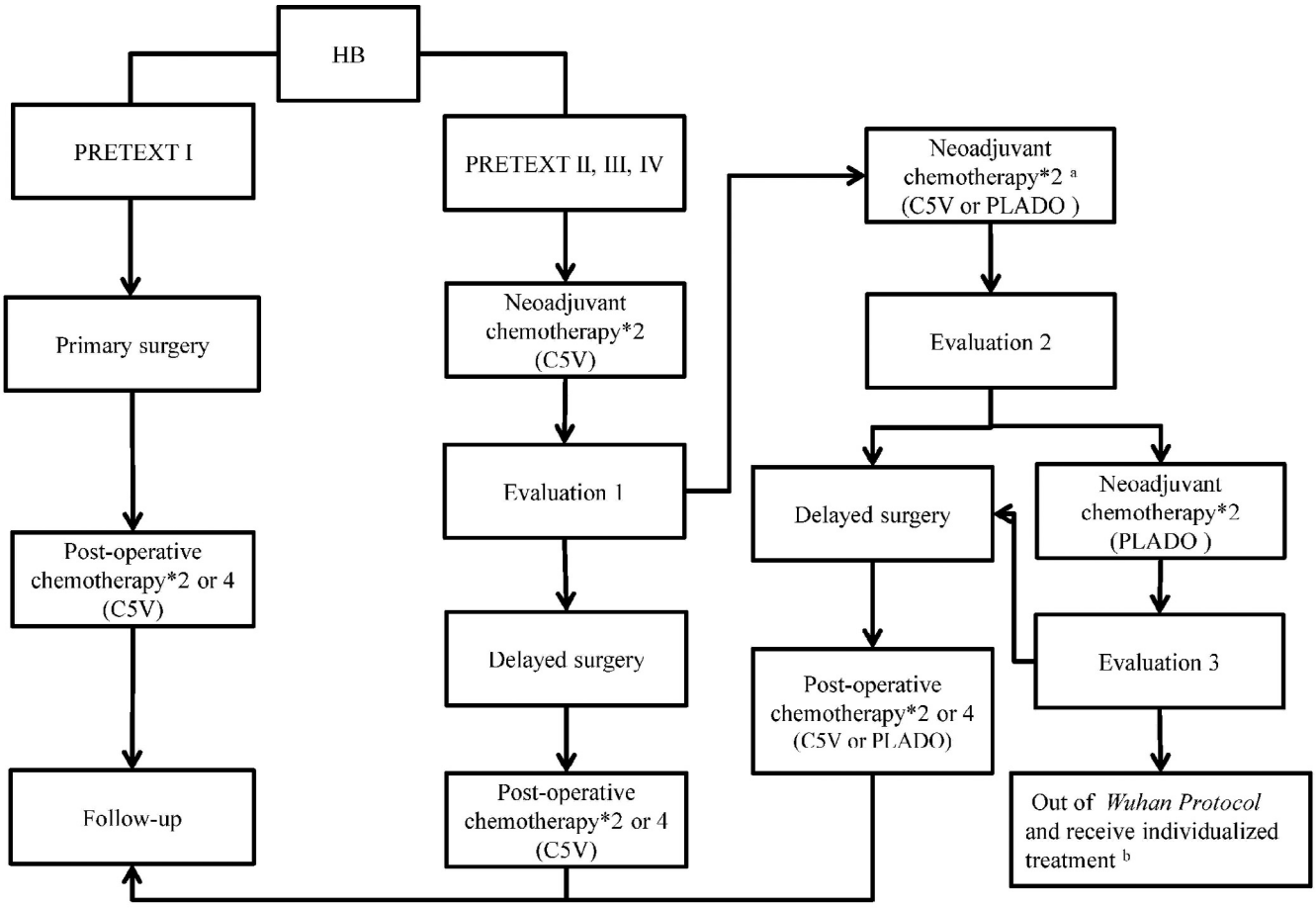
Results

Patients' characteristics

From January 2006 to December 2013, a total of 162 patients from 13 CCCG member medical centers were registered for this study. Nine cases were excluded from the cohort, of which 4 patients abandoned treatment (two of which abandoned treatment due to financial reasons and the other two suffered from heart failure), one patient was misdiagnosed with HB (the patient was clinically diagnosed with HB, but the pathological result after a subsequent surgery was confirmed as yolk sac tumor after 4 cycles of chemotherapy), and 4 cases lacked complete documentations. Therefore, 153 cases were included, analyzed and reported in this study. The group included 104 males and 49 females (the male to female ratio was 2.1:1); the median age at diagnosis was 16.0 (1.3–132.0) months, median follow-up time was 52.9 (1.0–116.6) months. The demographic and clinical characteristics of 153 HB patients were listed in Table 1. There were 6 (6/153, 3.9%) preterm patients and none was very low birth weight infant.

Staging, metastases and risk stratification

Patients were staged according to PRETEXT system before treatment. The number of cases of PRETEXT I is 16 (10.4%), PRETEXT II



a. Patients would be switched to PLADO regimen if the evaluation showed no response or progressive disease after two cycles of C5V regimen chemotherapy.
b. Patients would be out of the protocol and receive individual treatment plan based on drug sensitivity results if the evaluation showed no response or progressive disease after six courses of C5V or PLADO regimen.

Fig. 1. Treatment plan of *Wuhan Protocol*. The protocol mainly includes two parts: (a) Patients with PRETEXT I stage will have primary surgery and post-operative chemotherapy; (b) PRETEXT II, III, or IV patients will have neoadjuvant chemotherapy, delayed surgery, and post-operative chemotherapy.

is 29 (19.0%), PRETEXT III is 64 (41.8%), and PRETEXT IV is 44 (28.8%). Among all cases, three patients had hepatic vein tumor infiltration and none had tumor rupture or portal vein involvement. After surgical resection, 143 patients were classified based on COG system subsequently with cases in stage I: 109 (76.2%), stage II: 11 (7.7%), stage III: 8 (5.6%), and stage IV: 15 (10.5%) cases.

A total of 23 patients had metastasis at time of diagnosis, 18 patients (78.3%) had lung metastases, of which 2 also had brain or hepatic vein involvement; 2 cases (8.7%) had hepatic vein metastasis; 3 cases (13.0%) had bone, gall bladder, or ascites metastasis, respectively.

Based on SIOPEL risk stratification criteria, we retrospectively classified all the patients into standard-risk group (n = 104) and high-risk group (n = 49).

Treatment

Treatment path

Over half of the patients (99/153, 64.7%) received neoadjuvant chemotherapy initially after diagnosis (Fig. 2), but only 89 patients could have surgical resection. Of those 89 patients, 4 (4.5%) were treated with two courses of C5V regimen before surgery, 25 cases (28.1%) received four courses of C5V or PLADO regimen before

Table 1
Demographic and clinical characteristics of 153 HB patients.

Characteristics	Case number, n (%)
Gender	
Male	104 (68.0)
Female	49 (32.0)
Age	
Under 5 years of age	143 (93.5)
5 years of age or above	10 (6.5)
Main **c**linical manifestations	
Abdominal mass	122 (79.7)
Abdominal distention	11 (7.2)
Abdominal pain	10 (6.5)
Fever	6 (3.9)
Jaundice	4 (2.6)
Serum AFP level at diagnosis	
<100 ng/mL	2 (1.3)
100–100,000 ng/mL	35 (22.9)
>100,000 ng/mL	116 (75.8)
Pathological subtypes	
Pure fetal pattern	34 (22.2)
Fetal and embryonal	55 (35.9)
Epithelial and mesenchymal	50 (32.7)
Others	6 (3.9)
Unknown	8 (5.2)
Metastasis at the onset	
With	23 (15.0)
Without	130 (85.0)

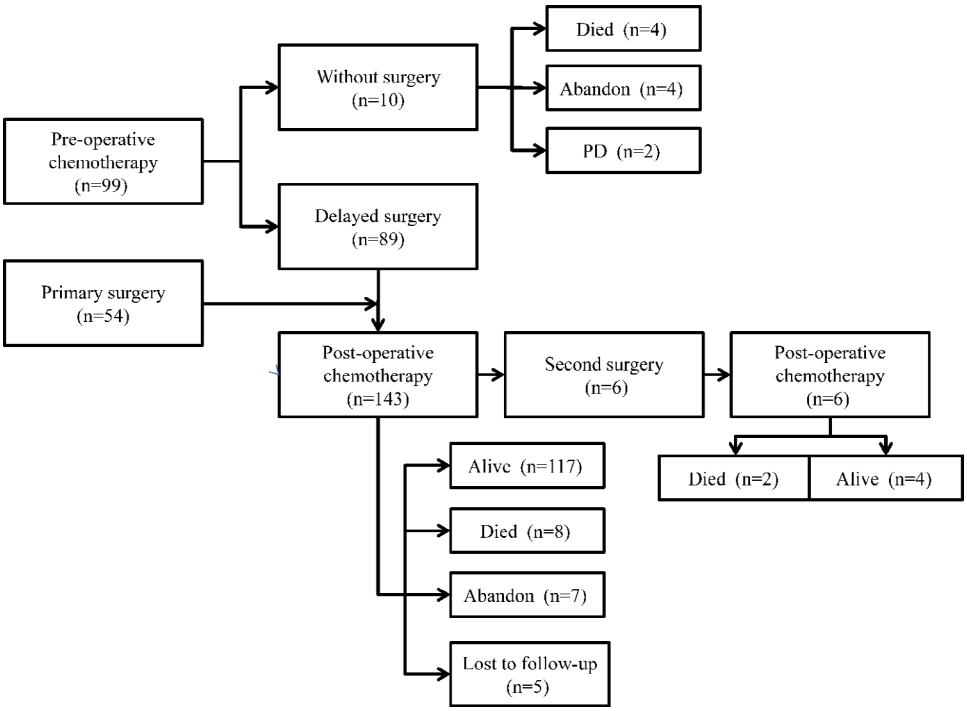


Fig. 2. Treatment path and outcome of 153 HB patients. Ninety-nine patients received chemotherapy and fifty-four cases underwent surgery at diagnosis. A total of 143 children had post-operative chemotherapy.

resection, 33 cases (37.1%) had six courses of pre-operative chemotherapy, and another 27 patients (30.3%) accepted more than six courses of neoadjuvant chemotherapy, including individualized treatment plan after six courses. The remaining 10 patients did not have surgery; two died from primary disease and the other two died from sepsis, 4 cases abandoned treatment due to primary disease progressing, and two patients manifested progressive disease after six courses of chemotherapy. Fifty-four (35.3%) patients underwent surgical resection after they were clinically diagnosed with HB. One hundred and forty-three cases received post-operative chemotherapy, 6 cases had a second surgery (including one relapsed in liver, five had incomplete resection in first surgical attempt).

Chemotherapy

One hundred and eight patients (70.6%) were treated only with regimens per *Wuhan Protocol*, including 63 cases (58.3%) with C5V regimen, others with both C5V and PLADO regimens. However, 46 patients (30.1%) showed no response (without reduced serum AFP level or tumor size) to both C5V and PLADO treatment. Among them, 27 cases accepted more than six courses of neoadjuvant chemotherapy, including individualized management plan after six courses; 10 patients received chemotherapy only without surgical resection, and 9 patients underwent surgical resection at diagnosis, but had recurrence or progressive disease in the post-operative treatment and thus treated with other individualized regimens. The individualized management included ICE regimen (carboplatin, ifosfamide, and etoposide), C5VD regimen (cisplatin, 5-fluorouracil, vincristine, and doxorubicin), or cyclophosphamide combined with topotecan.

Surgery

A total of 143 (93.5%) patients with HB underwent surgery; 88 of them (61.5%) had right hemihepatectomy, 35 (24.5%) had left hemihepatectomy, and 20 (14.0%) cases had the other surgical approaches (the combined right and left hemihepatectomy, or hepatic caudate lobectomy). Five patients had post-operative complications including biliary leakage (n = 2), peritonitis (n = 1), chylous ascites (n = 1), and pneumonia (n = 1). There was no patient receiving liver transplantation in this study.

Treatment outcome

Of a total of 153 HB patients in this study, 106 (69.3%) achieved complete remission (CR); one (0.6%) had stable disease (SD); 14 patients (9.2%) had progressive disease (PD), of which 5 abandoned subsequent treatment, 1 lost in follow-up, 1 died, and 7 patients were still alive; 21 patients (13.7%) relapsed with the median recurrence time of 15.0 (4.0–36.97) months, 15 of them had recurrence in liver, 3 in brain, and 3 in lungs, respectively, and among them 7 patients died in the following treatment, 3 cases abandoned and 1 case lost in follow-up respectively, the remaining 10 patients still survived; 6 cases (3.9%) died during the course of this study, 3 cases from primary disease, and 3 from sepsis; 2 patients (1.3%) abandoned the treatment due to financial reasons and 3 cases (2.0%) were lost in follow-up. There was no case with hearing loss, heart failure, or other major organ failure.

Among the 23 patients with metastasis at diagnosis, the metastatic loci in 8 cases (34.8%) completely disappeared after chemotherapy and surgical resection and those patients achieved complete remission. There were 7 cases (30.4%) whose metastases resolved after chemotherapy; however 4 cases relapsed at the same loci and 3 patients at other location during the following treatment. Eight cases (34.8%) had events during the treatment, two of them died from primary disease and 6 patients developed progressive disease.

Three patients had multinodular PRETEXT IV HB, two of them had also extrahepatic disease. Even with chemotherapy and surgery, one patient with extrahepatic disease died from disease progression and the remaining two remained alive.

There were 108 patients with PRETEXT III or IV in this group; after more than two cycles of neoadjuvant chemotherapy, 69 of them (63.9%) had complete surgical resection (COG I stage), 8 cases (7.4%)

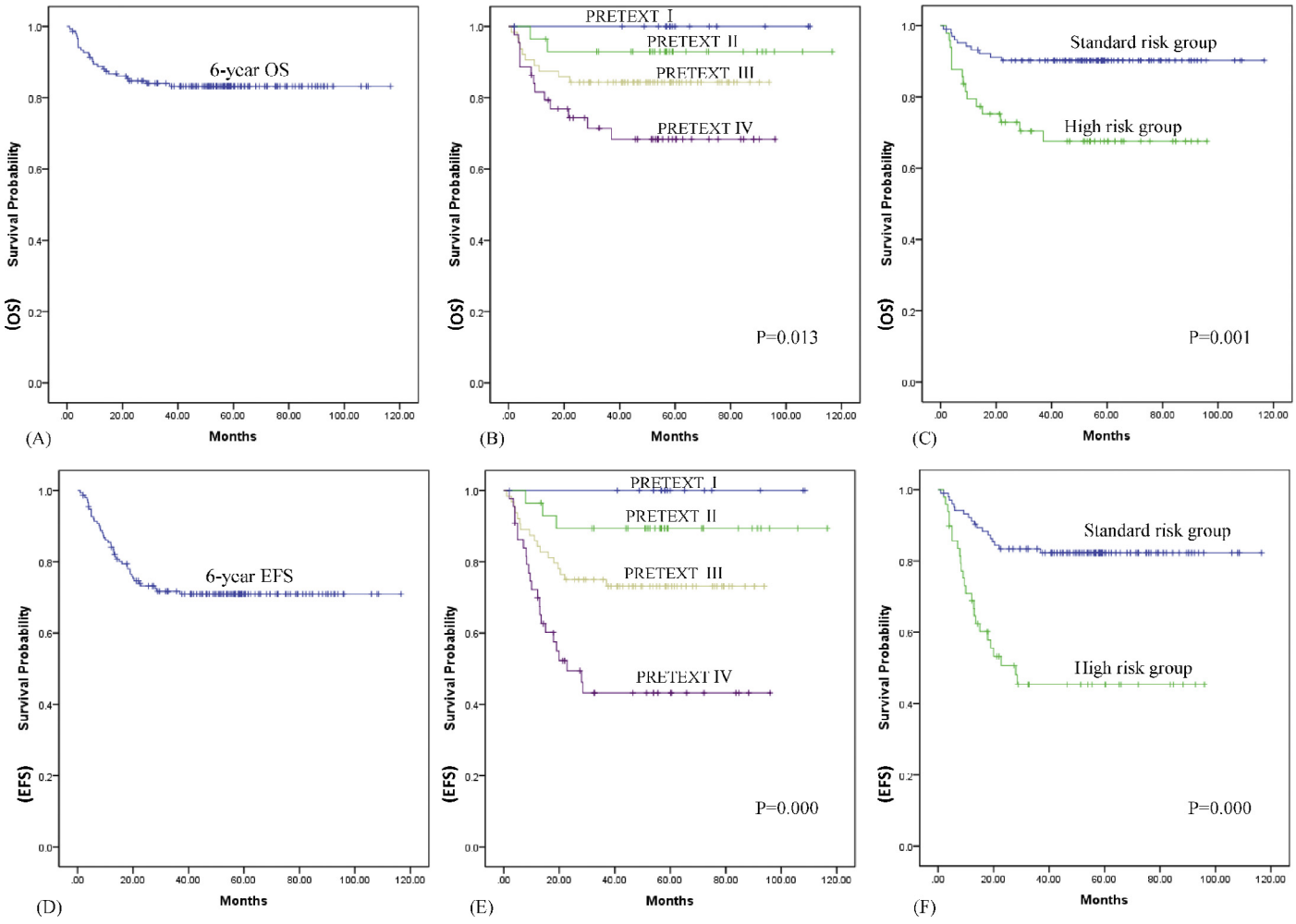


Fig. 3. Kaplan–Meier of 6-year OS and 6-year EFS rates. (A) The 6-year OS rate of all patients was 83.3 ± 3.1%; (B) OS rates stratified by PRETEXT stage: 100% in PRETEXT I, 93.0 ± 4.8% in PRETEXT II, 84.4 ± 4.5% in PRETEXT III, and 68.4 ± 7.4% in PRETEXT IV (P = 0.013); (C) OS rates stratified by SR and HR risk groups: 90.3 ± 2.9% in SR group and 67.6 ± 7.0% in HR group (P = 0.001); (D) The 6-year EFS rate for all patients was 71.0 ± 3.7%; (E) EFS rates stratified by PRETEXT stage: 100% in PRETEXT I, 89.4 ± 5.8% in PRETEXT II, 73.2 ± 5.6% in PRETEXT III, and 43.3 ± 8.0% in PRETEXT IV (P = 0.000); (F) EFS rates stratified by SR and HR risk groups: 82.3 ± 3.8% and 45.4 ± 7.5% (P = 0.000), respectively.

had microscopic residual (COG II stage) and 4 cases (3.7%) had gross tumor residual (COG III stage), 17 (15.7%) had metastasis, and 10 (9.3%) of them could not undergo surgery. Overall, half of the advanced HB patients had complete surgical resection after neoadjuvant chemotherapy.

Survival analysis

The 6-year OS rate was 83.3 ± 3.1% (100% in PRETEXT I, 93.0 ± 4.8% in PRETEXT II, 84.4 ± 4.5% in PRETEXT III, and 68.4 ± 7.4% in PRETEXT IV ($P = 0.013$) (Fig. 3A and B), whereas the 6-year EFS rate was 71.0 ± 3.7% among all patients (100% in PRETEXT I, 89.4 ± 5.8% in PRETEXT II, 73.2 ± 5.6% in PRETEXT III, and 43.3 ± 8.0% in PRETEXT IV ($P = 0.000$) (Fig. 3D and E). The 6-year OS rates of standard-risk and high-risk patients were 90.3 ± 2.9% and 67.6 ± 7.0% ($P = 0.001$), respectively (Fig. 3C), while the 6-year EFS rates were 82.3 ± 3.8% and 45.4 ± 7.5% ($P = 0.000$) (Fig. 3F). Patients treated under *Wuhan Protocol* had better OS (Fig. 4A) and EFS rates as compared with those patients treated with combined regimens (6-year OS rate: 87.6 ± 3.2% vs. 72.7 ± 6.7%, $P = 0.025$; 6-year EFS rate: 78.9 ± 4.0% vs. 52.3 ± 7.6%, $P = 0.000$). The 6-year OS rate for delayed surgery with neoadjuvant chemotherapy (Fig. 4B) was 90.8 ± 3.1%, whereas 83.0 ± 5.2% in patients with primary surgery and post-operative chemotherapy. Patients with chemotherapy only had an OS rate of mere 20.0 ± 12.6% ($P = 0.000$).

The univariate analysis showed that female (6-year OS rate: 93.8 ± 3.5%, $P = 0.027$, Fig. 4C), patients under five years of age (6-year OS rate: 85.0 ± 3.0%, $P = 0.039$, Fig. 4D), complete surgical resection (6-year OS rate: 93.5 ± 2.4%, $P = 0.000$, Fig. 4E), and no metastases at diagnosis (6-year OS rate: 89.0 ± 2.8%, $P = 0.000$, Fig. 4F) had better prognosis as shown in Fig. 4. All above factors were drawn into multivariate Cox proportional-hazards regression model, which revealed that male ($P = 0.039$, 95%CI 1.04–5.50), PRETEXT III ($P = 0.019$, 95%CI 1.27–14.90), PRETEXT IV ($P = 0.034$, 95%CI 1.11–14.73), and incomplete surgical resection ($P = 0.000$, 95%CI 2.61–15.10) could be considered as individual factors contributing to poorer prognosis (Table 2).

Discussion

In this retrospective study, for the first time, we reported a large number of pediatric HB patients in China treated under *Wuhan Protocol*. It was also the first time for CCCG to summarize the current therapy for HB children in China. Compared to acute lymphocytic leukemia and brain tumor, which are common childhood malignancies [11], the incidence of HB is extremely low. Therefore,

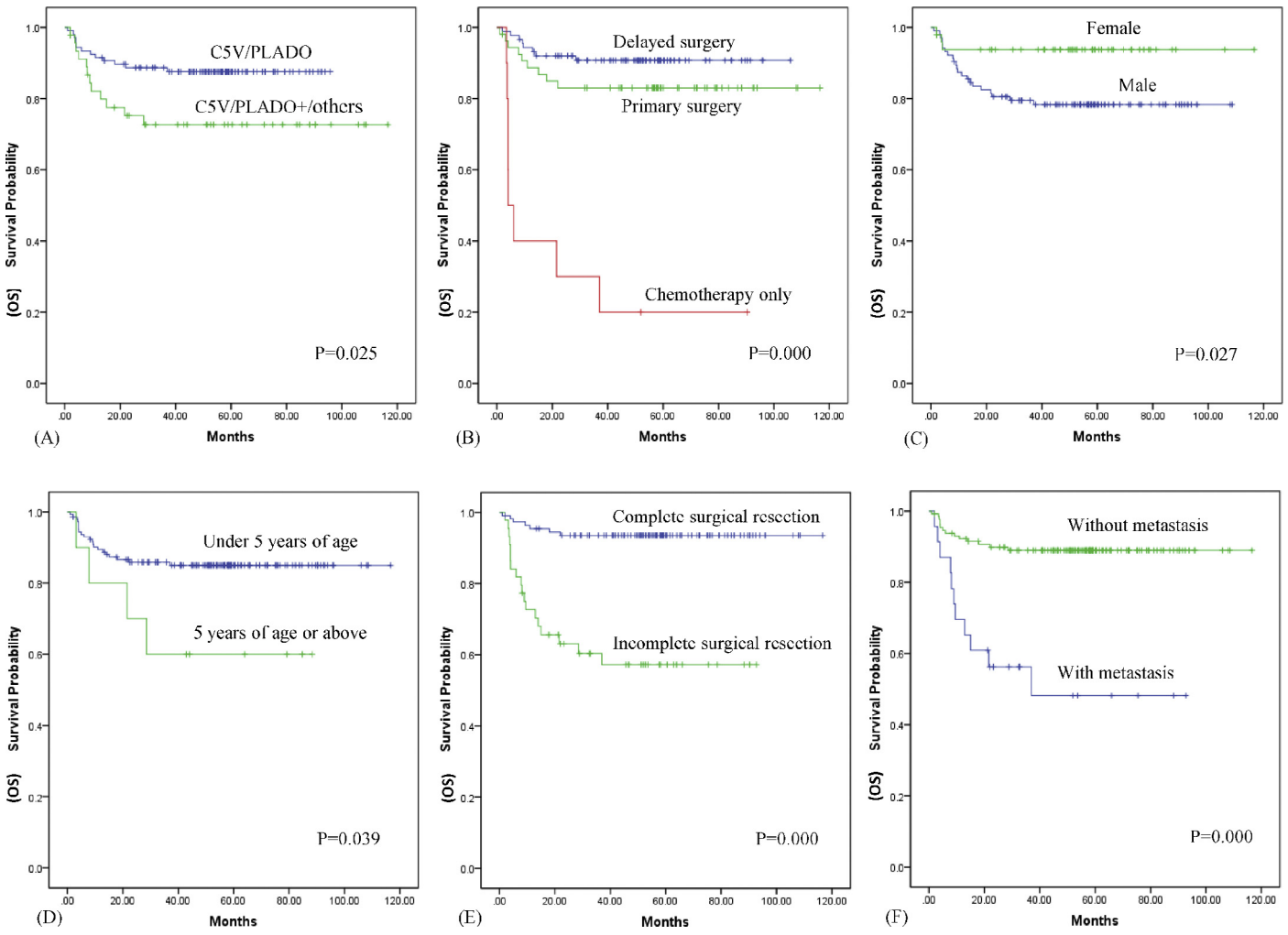


Fig. 4. The univariate analysis of HB estimated by 6-year OS rate. (A) Different chemotherapy regimens (C5V/PLADO vs. C5V/PLADO combined with others: 87.6 ± 3.2% vs. 72.7 ± 6.7%, P = 0.025); (B) Treatment modalities (delayed surgery vs. primary surgery vs. chemotherapy only: 90.8 ± 3.1% vs. 83.0 ± 5.2% vs. 20.0 ± 12.6%, P = 0.000); (C) Gender (female vs. male: 93.8 ± 3.5% vs. 78.4 ± 4.1%, P = 0.027); (D) Age (age under five years vs. age five years or above: 85.0 ± 3.0% vs. 60.0 ± 15.5%, P = 0.039; (E) Surgical respectability (complete surgical resection vs. incomplete surgical resection: 93.5 ± 2.4% vs. 57.1 ± 7.8%, P = 0.000); (F) Metastasis (without metastasis vs. with metastasis: 89.0 ± 2.8% vs. 48.2 ± 13.6%, P = 0.000).

multi-center cooperation plays an important role in standardizing HB treatment protocols. In the past 40 years, several major HB study groups have been established [12–15]. In order to facilitate better international communication and cooperation, the Children's Hepatic tumor International Collaboration (CHIC) was formed to combine the results of multi-center trials by SIOPEL, COG, German Liver Tumor Study (GPOH), and Japanese Study Group for Pediatric Liver Tumor (JPLT) [4,16]. CCCG was established in 1997 in China, and the liver tumor subgroup began collecting the data on HB patients since 2006, and 13 member hospitals participated in this effort.

Table 2
The multivariate analysis with COX regression.

Factor	Number	HR[a]	95% CI[a]	P value[b]
Male	104	2.40	1.04–5.50	0.039
Age 5 years old and over	10	1.15	0.44–3.00	0.781
PRETEXT III	64	4.35	1.27–14.90	0.019
PRETEXT IV	44	4.17	1.11–14.73	0.034
Incomplete resection	109	6.27	2.61–15.10	0.000

[a] HR stands for hazard ratio, CI stands for confidence interval.
[b] P < 0.050 indicates statistical significance at the 5% level.

Multidisciplinary cooperation is also the fundamental in HB treatment, especially neoadjuvant chemotherapy, which is the cornerstone in the development of solid tumor treatment. In 1982, Evans et al. [17] first suggested that when pre-operative chemotherapy (neoadjuvant chemotherapy) was used in HB treatment, the 3-year OS rate had risen from 20–25% to 30–40%. Recently, a series of clinical trials demonstrated that complete resection rate was over 90% after neoadjuvant chemotherapy [10]. The 3-year OS rate could also be as high as 70–80% in high-risk group [18]. In our study, 63.9% advanced patients achieved complete surgical resection (COG stage I) after neoadjuvant chemotherapy. Comparing the survival rates between delayed surgery (after pre-operative neoadjuvant chemotherapy) and primary surgery (without pre-operative but post-operative chemotherapy), the former group had a better survival rate (90.8 ± 3.1% vs. 83.0 ± 5.2%, *P* = 0.000). Complete resection plays a key role in treating HB and enables an optimal outcome [19]; it also strongly suggests that neoadjuvant chemotherapy before surgery significantly improves total resection rate as well as the survival rate in children with HB. As compared with complete surgical resection, the patients who had partial tumor resection achieved lower 6-year OS rate (57.1 ± 7.8% versus 93.5 ± 2.4%, *P* = 0.000). Besides conventional surgery for tumor resection, new surgical approaches

should be explored, such as liver transplantation (LT) [20], transcatheter arterial chemoembolization [21] and high intensity focused ultrasound [22]. LT has become the standard treatment for multinodular HB since 2004 [23] and remained currently recommended in patients with multinodular PRETEXT IV HB without extrahepatic disease, even though some of these children were probably over-treated. However, in this study there was no patient who received LT due to the limited number of medical centers that are qualified to perform LT. In addition, the rarity of appropriate donors and the high cost associated to LT are two other additional factors that directly affect LT in China. Furthermore, it needs an accurate evaluation of the benefits for each case to balance the chances of cure versus organ availability [24].

With the use of neoadjuvant chemotherapy and surgery, the 6-year OS and EFS rates were 83.3 ± 3.1% and 71.0 ± 3.7%, respectively, in this cohort. Recent literature review of clinical trials revealed that the majority of 3-year OS rates were above 80% [4]. In SIOPEL, 3-year OS rates for standard-risk and high-risk groups were 93–95% (n = 255) and 83% (n = 62), respectively [18,25]. In JPLT study, the 5-year OS rate for 212 patients with HB was 80.9% [26]. The 3-year OS rate for patients in GPOH was 89%, and for standard-risk group and high-risk group were 90% and 55%, respectively [14]. The survival rate in our study was similar to that obtained by other international study groups, which indicated the effectiveness of current protocol in China. To further analyze and optimize *Wuhan Protocol*, all patients were retrospectively classified into the standard and high-risk groups; the 6-year OS rates were 90.3 ± 2.9% and 67.6 ± 7.0% ($P = 0.001$), respectively. Standard-risk group with C5V regimen had achieved a satisfactory result; however, the prognosis of high-risk group was still gloomy. We believe it is necessary to adjust the treatment intensity based on risk-stratification, which means reducing the intensity in standard-risk group and increasing the intensity in high-risk group.

Some adverse factors that produce poor prognosis in HB had been identified, such as age (above 5 years old), PRETEXT stage (III or IV) [27], pathology subtypes (the SCU type) [28], serum AFP level (AFP <100 ng/mL) [29], and metastasis [30]. We have also analyzed the relationship between prognosis and these factors, such as gender, age, PRETEXT stage, COG stage, pathology subtypes, AFP levels and metastasis at diagnosis. The results demonstrated that female, age over 5 years, PRETEXT III, PRETEXT IV, incomplete surgical resection, and with metastasis had poorer prognosis; our findings are in agreement with those reported previously. In our cohort, only 2 patients were diagnosed with SCU subtype and died for relapse during follow-up. There were two patients whose AFP was <100 ng/mL at diagnosis, one died during follow-up due to relapse, and another is still surviving.

The treatment of HB has been making great progress in the past forty years. The preliminary results of *Wuhan Protocol* demonstrated reduced side-effects and similar OS or EFS rate compared to those in developed countries. However, standardizing surgical resection, LT, refining risk stratification, and risk-based chemotherapy remain to be further optimized.

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Conflict of interest

None.

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