Review

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An update on diagnosis and treatment of hepatoblastoma

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SUMMARY Hepatoblastoma (HB) remains the most common paediatric liver tumour and survival in children with hepatoblastoma has improved considerably since the advent of sequential surgical regimens of chemotherapy based on platinum-based chemotherapeutic agents in the 1980s. With the advent of modern diagnostic imaging and pathology techniques, new preoperative chemotherapy regimens and the maturation of surgical techniques, new diagnostic and treatment options for patients with hepatoblastoma have emerged and international collaborations are investigating the latest diagnostic approaches, chemotherapy drug combinations and surgical strategies. Diagnosis of hepatoblastoma relies on imaging studies (such as ultrasound, computed tomography, and magnetic resonance imaging), alpha-fetoprotein (AFP) levels, and histological confirmation through biopsy. The standard treatment approach involves a multimodal strategy with neoadjuvant chemotherapy followed by surgical resection. In cases where complete resection is not feasible or tumors exhibit invasive characteristics, liver transplantation is considered. The management of metastatic and recurrent hepatoblastoma poses significant challenges, and ongoing research focuses on developing targeted therapies and exploring the potential of immunotherapy. Further studies are necessary to gain a better understanding of the etiology of hepatoblastoma, develop prevention strategies, and personalize treatment approaches. We aim to review the current status of diagnosis and treatment of hepatoblastoma.

Keywords PRETEXT staging, neoadjuvant chemotherapy, hepatectomy, recurrent hepatoblastoma

1. Introduction

Hepatoblastoma (HB) has been the most common primary pediatric liver malignancy in young children who developed liver cancer, accounting for 90% of malignant liver tumors in children younger than 5 years, and it is especially prevalent in children under the age of 3(*1,2*). With the development of imagining examination, the diagnostic method has been common and more precise staging can be applied through imaging tools (*3,4*). In the treatment of hepatoblastoma, since the application of platinum-based chemotherapy regimens and advances in surgical techniques and surgical tools, which facilitated precision hepatectomies and resection of focal metastasis, survival has greatly improved (*5*). After the International Childhood Liver Tumor Strategy Group (SIOPEL)-I study in the 1980s, which found that platinum-based chemotherapy regimens were quite effective in children with hepatoblastoma, more international collaborative organizations became involved in the trend of studying preoperative chemotherapy regimens in combination with sequential surgical treatment (*6-9*). Among these, the Children's Oncology Group (COG), Japanese study group for Pediatric Liver Tumor (JPLT), German Paediatric Oncology and Haematology Society (GPOH) and SIOPEL cohorts are the most authoritative and systematic. In subsequent studies, even though the basic chemotherapeutic drug combinations are relatively fixed, an increasing number of chemotherapy regimens have emerged, and the pursuit of better tumor remission, adjusting the dose of chemotherapy drugs within a reasonable range, and combining the use of other drugs to reduce the damage of chemotherapy side effects have become the goals of new chemotherapy regimens (*7,9-11*). At the same time, surgical resection of liver tumors has advanced dramatically over the past few decades (*12*). The use of more sophisticated surgical techniques has further increased the resection rate of patients with hepatoblastoma after chemotherapy. The identification of lesions, the removal of metastatic lesions and the implementation of extreme hepatectomy have increased the surgical benefit for patients(*5,13*). We aim to present the progression and current situation of diagnoses and treatments in hepatoblastoma.

2. Progress and current situation in diagnosis of hepatoblastoma

2.1. Symbols of hepatoblastoma

The most common presentation of hepatoblastoma is asymptomatic celiac mass, the accompanying symbol includes ascites, febrile, jaundice, feeding intolerance and weight loss, caused by the mass effect upon the stomach or intestine (*14,15*). Some symbols containing pseudo precocious puberty and thrombocytosis could help to make a clinical diagnosis (*16*). The serum alpha-feto protein (AFP) level is also an element in diagnosis of hepatoblastoma. The sensitivity and specificity of the abnormal increase of serum AFP in the diagnosis of hepatoblastoma were 98.0% (95%CI: 0.89-1.00) and 100% (95%CI: 0.88-1.00). The clinical diagnosis was consistent with the pathological diagnosis of hepatoblastoma (Kappa = 0.97, $P < 0.001$) (*17*). However, low-AFP level was highly associated with poor prognosis (*18*).

2.2. Imaging diagnosis of hepatoblastoma

2.2.1. Ultrasound

Ultrasound remains the first imaging study performed for screening and diagnosis of pediatric abdominal mass. By assessment the echo signal and significant mass effect on adjacent organs, ultrasound can confirm the hepatic mass origin (*19*). Hepatoblastoma can appear as a solitary mass, a dominant mass with satellite lesions, as multiple nodules throughout the liver or, rarely, a diffusely infiltrative mass involving the entire liver on sonography. Most tumors are hyperechoic relative to normal liver but are often nonhomogenous due to mesenchymal components. Calcifications may be present and appear as punctate or linear hyperechoic foci with posterior shadowing. Areas of internal hemorrhage and necrosis are not uncommon and will appear anechoic (*19*). Also, doppler ultrasound is sensitive to evaluate the invasion of hepatic and portal venous, which contributed to high-risk stratification in several studies conducted by international conjunction groups (*20*).

2.2.2. Computed Tomography (CT)

The CT presentation of hepatoblastoma depends on the histologic composition of the tumor and is highly variable. Calcification may be present in the epithelial pathological subtype and are usually small and fine, whereas in mixed mesenchymal-epithelial tumors the calcifications are coarse and extensive (*19*). After contrast injection, hepatoblastoma generally shows heterogeneous enhancement and is less enhanced than the surrounding normal liver. If imaging is performed in the arterial phase, there may be an enhanced peripheral margin. The tumor may involve one, two, three or all four hepatic segments. Although coronal and sagittal reconstructed CT images help to define the tumor margins, sometimes it is difficult to define the margins on CT. In such cases, MRI can provide additional information.

Since approximately 20% of portions of hepatoblastoma patients were diagnosed with lung metastasis initially, pulmonary CT was required and can be used to scan abdomen at the same time (*3*).

2.2.3. Magnetic Resonance Imaging (MRI)

MRI is more widely used in the diagnosis of hepatoblastoma due to its ability to reflect more accurately the location of the tumor in relation to the vital tissue vessels and to determine roughly the pathological type of the tumor by the presentation of many different sequences (*21*). Epithelial tumors are generally homogeneous, appearing as hypodense on T1-weighted images and dense on T2-weighted. Mixed epithelial-mesenchymal tumors are usually heterogeneous due to varying amounts of internal haemorrhage, necrosis, fibrosis, calcification, cartilage and septa (*19*). However, MRI takes longer to perform and therefore sedation is usually required for paediatric patients.

2.3. Biopsy of hepatoblastoma

Though imaging tools played a vital role in diagnosis in hepatoblastoma, only biopsy can confirm it. It's obliged in children under 6 months old and over 3 years of age undergoing tumor biopsy, because various tumors could present at the former group and a high-AFP level may be attributed to the age of the child, and to tell if hepatoblastoma and hepatocellular carcinoma occurs in older children. To children between 6 months and 3 years old, diagnostic biopsy is controversial (*16*). Biopsy tissue can be obtained through percutaneous core, laparoscopic core or wedge, or open biopsies, which depend on the balance between the risk of bleeding and acquiring enough of target tissue. It's recommended to obtain five cores of tumor and one core of normal liver or at least three cores for pathological examination (*6*).

Since the forge of staging systems (PRETEXT, COG *et al*) and risk stratification were mature in recent years, histological subtype is raising great importance in formulating treatment protocols (*8,9,18,22*). Not only histological subtype, but also the results of immunohistochemical testing could guide the chemotherapy algorithms. The clinical meaning revealed by immunohistochemistry differs a lot. Integrase interactor 1(INI 1) negative epithelial hepatoblastoma with low serum AFP level may suggest a rhabdoid originated tumor and receive a compromised chemotherapy regimen. Comparison between PRETEXT stage I/II and stage III/IV have shown that CD44 is higher expressed in the latter (*23*). Abnormal expression

of CD 90, CD133 and CD44 were associated with disease progression and decreased survival in hepatoblastoma (*24*). Studies concentrated on new immunohistochemical markers are conducted globally. A report from AHEP 0731 has shown that pretreatment percutaneous biopsy of pediatric liver tumors yielded the lowest frequency of clinically significant hemorrhaging requiring transfusion, without evidence of sacrificing diagnostic accuracy (*10*).

2.4. Hepatoblastoma risk stratifying staging system

The first risk stratifying system was pre-treatment extent of tumor system (PRETEXT system), reported by SIOPEL in 1992. Evan's risk stratification was adopted by Children's Oncology Group (COG), and the stratification was based on initial surgery. Since the advances applied in imagine techniques, PRETEXT system has been a hybrid to apply serial trails conducted by international cooperative groups. In 2017, four international cooperative groups (SIOPEL, COG, JPLT, GPOH) have collaborated to write a new staging system- CHIC-HS. CHIC-HS is a stratification based on PRETEXT system, and was used by ongoing hepatoblastoma trials.

2.4.1. PRETEXT staging system

The Société Internationaled' Oncologie Pédiatrique Epithelial Liver Tumor Study Group (SIOPEL) first described the pre-treatment extent of tumor system (PRETEXT system) in 1992 to stratify the risk stage for children diagnosed with hepatoblastoma prior to neoadjuvant chemotherapy (Figure 1). The PRETEXT system contains content concerning standardized imaging evaluation at the same time (*25*). A consequence of SIOPEL trials reported PRETEXT system stratified risk patients distinctly, and easily to be reproduced in clinical practice (*13,22,26-29*). The PRETEXT system was contributed by two components: the PRETEXT group and annotation factors. The former depicted the intrahepatic extent of hepatoblastoma and the latter was used to reveal characters like vascular invasion (including portal vein or hepatic vein/ inferior vena cava), extrahepatic disease, multifocality, tumor rupture and metastatic disease (to both the lungs and lymph nodes).

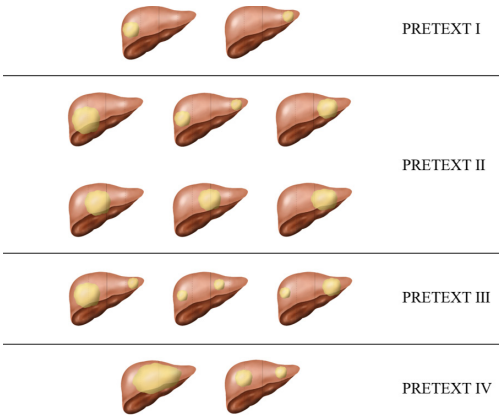

Figure 1. PRETEXT staging. (I = one section involved, three sections tumour free; II= one or two sections involved, two sections tumour free; III = two or three sections involved, one section tumour free; IV = four sections involved).

PRETEXT system was revised several times since the first publication in 1992, and several trails conducted by Children's Oncology Group (COG), the International Childhood Liver Tumors Strategy Group (SIOPEL), and the Japanese Study Group for Pediatric Liver Tumor (JPLT, now part of the Japan Children's Cancer Group) have some differences in definitions of annotation factors.

In 2017, these organization wrote a common set of definitions to be used in future trials together (*3*). The modified PRETEXT annotation contains **V:** Hepatic or vena cava involvement, **P:** Portal vein involvement, **E:** Extrahepatic adjacent tissue involvement, **M**: Distal tissue involvement, **C:** Caudate lobe involvement, **F**: Intrahepatic multiple tumor nodules, **R**: Pre-diagnostic tumor rupture. These definitions will be used in the forthcoming Trial to Pediatric Hepatic International Tumor Trial (PHITT) (*3*).

2.4.2. Evan's surgical stage

In trial INT-0098, which was conducted by Children's Oncology Group (COG), presented Evan's surgical stage based on initial surgical intervention prior to neoadjuvant chemotherapy. With the development of imaging techniques, COG has used a staging system mixed with PRETEXT and Evan's system (Table 1).

2.4.3. PRETEXT: pre-treatment extent of tumor system

In order to create a standard staging system, SIOPEL, COG, JPLT and GPOH cooperated to summarize their clinical trial data. The Children's Hepatic Tumors International Collaboration (CHIC)has reviewed these data and formed CHIC-HS risk stratification (Table 2). The new system uses PRETEXT groups and PRETEXT annotation factors, as well as age and alpha-fetoprotein (AFP) levels, to determine treatment cohorts on the new Trial to Pediatric Hepatic International Tumor Trial (PHITT).

Table 1. Evan's surgical stage

Stage	Specifics
I	Complete gross resection with clear margins
II	Gross total resection with microscopic residual disease at margin of resection
III	Gross total resection with nodal involvement or tumor spill or incomplete resection with gross residual intrahepatic disease
IV	Metastatic disease with either complete or incomplete resection

3. Treatments of hepatoblastoma

3.1. Pre/Post-operative chemotherapy

Since the apparent reduction of tumor volume caused by cisplatin-based chemotherapy was reported in the 1980s, neoadjuvant chemotherapy with sequential surgery became a paradigm of treatment of hepatoblastoma gradually (*30,31*). In consecutive trials conducted by SIOPEL, the children were treated with chemotherapy prior to surgery (*29*). The COG believes that very low risk, low risk patients should have surgery first; medium to high-risk patients should have neoadjuvant chemotherapy in combination with surgery and adjuvant chemotherapy (*32*). GPOH and JPLT preferred to apply surgery to relatively early-stage patients and administer post-operative chemotherapy(*9,33*). Both GPOH and JPLT are now increasingly advocating the use of pre-operative chemotherapy. However, patients suitable for surgery at initial diagnosis and undergoing surgery were recommended for postoperative chemotherapy by COG, GPOH and JPLT (*7,9*). The summarization of these collaborations is shown in Table 3.

Table 2. Risk stratification of CHIC-HS

Risk Stratification	Specifics
Very low	PRETEXT I, M(-), VEGFR(-), resectable at diagnosis
	PRETEXT II, M(-),< 8 years, VEGFR(-), AFP > 1,000 ng/mL, resectable at diagnosis
Low	PRETEXT I, M(-),VEGFR(-), non-resectable at diagnosis
	PRETEXT II, M(-),< 8 years, VEGFR(-), AFP > 1,000 ng/mL, non-resectable at diagnosis
	PRETEXT III, M(-), < 8 years, VEGFR(-), AFP>1,000 ng/mL
Intermediate	PRETEXT I, M(-), < 8 years, VEGFR(+)
	PRETEXT II, M(-), < 8 years, VEGFR(+), AFP > 1,000 ng/mL
	PRETEXT III, M(-),< 8 years, VEGFR(+)/ AFP 100-1,000 ng/mL
	PRETEXT IV, M(-), < 3 years, AFP>100ng/mL
High	Any PRETEXT, M(+)
	PRETEXT I, M(-), > 8 years, VEGFR(+)
	PRETEXT II/III, M(-), <8 years, AFP ≤ 100 ng/mL
	PRETEXT II/III, M(-), > 8 years
	PRETEXT IV, M(-), < 3 years, AFP ≤ 100 ng/mL
	PRETEXT IV, M(-), > 3 years

3.1.1. SIOPEL

The SIOPEL initiative of cisplatin-based neoadjuvant chemotherapy in combination with surgery and postoperative chemotherapy has shown a significant improvement in patient prognosis (*22*). The first HB prospective clinical trial (SIOPEL-1) used a cisplatin + adriamycin regimen (PLADO) with a 5-year event-free survival (EFS) and overall survival (OS) of 66% and 75%, respectively, for the entire group (*29*). In subsequent trials, SIOPEL-2 has stratified patients into standard-risk group and high-risk group depending on the PRETEXT system and lung metastasis. Cisplatin alone (CDDP 80 mg/m^2) was shown to be comparable to cisplatin combined with adriamycin for the standard-risk group (3-year EFS (83% *vs.* 85%) and OS (95% *vs.* 93%) and relapse rate (15% *vs.* 12%) (*29*). For the treatment of patients in the high-risk group, the SIOPEL-4 study increased the preoperative cisplatin dose density from

Table 3. Summarization of chemotherapy of international collaborations

International collaborations	Risk stratification	PRETEXT staging and disease manifestations	Preoperative chemotherapy	Postoperative chemotherapy
SIOPEL-4	Standardize risk	PRETEXT I/II/III and AFP > 100 ng/mL	CDDP*4	C5V-DOXO*2
	High risk	PRETEXT IV or M,H,P,E,R, AFP < 100 ng/mL	CDDP*4 alternate CARBO/DOXO*3	C5V-DOXO alternate CARBO/DOXO*2
AHEP0731 (COG)	Very low risk	PRETEXT I with pure fetal histology hepatoblastoma	N	N
	Low risk	PRETEXT I/II, non-small-cell undifferentiated disease	N	C5V*2
	Intermediate risk	PRETEXT I/II with small-cell undifferentiated histology or PRETEXT III hepatoblastoma	C5V and DOXO*4-6	C5V-DOXO
	High risk	PRETEXT IV and Any stage disease with AFP <100 ng/mL	Vincristine (V) and Irinotecan (I)*2 and C5V-DOXO*6	-
HB99 (GPOH)	Standardize risk	Potentially resectable after chemotherapy	IPA*2-3	IPA
	High risk	Non-resectable Multifocal Vessel involvement Positive lymph nodes	Carboplatin + etoposide * 2	CDDP*1 alternate CARBO/ DOXO * 2
JPLT-2		PRETEXT I/II	N	CITA (50% dose)
		PRETEXT II	CITA*2	CITA (50% dose)
		PRETEXT III/IV OR PRETEXT I/II with annotation	CITA+ITEC (high dose)	CITA*2

CDDP: cisplatin; C5V: vincristine; DOXO: doxorubicin; CARBO: carboplatin; IPA: ifosfamide+cisplatin+doxorubicin, cisplatin and doxorubicin CITA: CDDP + 4'-O-tetrahydropyranyladriamycin ITEC: cisplatin, pirarubicin or pirarubicin, ifosfamide/carboplatin.

22. 9 mg/(m^2 -week) to 47. 5 mg/(m^2 -week), and after high-dose cisplatin + adriamycin preoperative chemotherapy and carboplatin + adjuvant chemotherapy, patients had an increase in complete remission rates of approximately 20% compared to SIOPEL3, with 3-year EFS and OS of 76% and 83%, respectively (*22,34*). The prognosis of patients in the high-risk group was significantly better than before, with 77% and 73% 3-year OS in patients with metastases or PRETEXT stage IV, respectively, suggesting that weekly application of cisplatin may improve patient survival (*22*). In SIOPEL IV, postoperative chemotherapy was applied to patients who underwent sequential surgery after neoadjuvant chemotherapy. The postoperative chemotherapy protocols were doxorubicin (20 mg/m²) and carboplatin6 mg/mL per min per day) (*22*).

3.1.2. COG

The COG initially favored a post-operative chemotherapy regimen based on Evans classification criteria. In COG-INT0098, a postoperative chemotherapy protocol based on cisplatin, fluorouracil and vincristine (C5V) regimen were applied to avoid adriamycin cardiotoxicity with improved prognosis (*35*). In 1993, the COG first demonstrated the efficacy of the C5V regimen, with a 5-year EFS of 90% in Evan's stage I and II patients and a poorer prognosis in later stage patients (*36*). Subsequent studies comparing C5V and cisplatin + adriamycin regimens found similar overall survival rates (5-year OS 69% *vs.* 72%), with the former having a slightly higher recurrence rate (5-year EFS 57% *vs.* 69%) but less toxic side effects (*36*). AHEP0731 further optimized the chemotherapy regimen for the low-risk group, suggesting that in children with completely resectable tumors, reducing the C5V regimen by 2 courses postoperatively would reduce drug accumulation and ensure efficacy, and reduce the total cisplatin dose by 1/2 (*8*). Also, the AHEP0731 study used vincristine/irinotecan for the pre-treatment of high-risk HB. The 3-year EFS and OS were 49% and 62%, respectively (*37*). In 2021, the COG suggested that the C5V regimen combined with adriamycin (C5VD regimen) could further improve outcomes in children with HB, with a 5-year EFS and OS of 88% and 95%, respectively, in children with unresectable disease at diagnosis (*11*).

3.1.3. GPOH

GPOH has led three clinical trials, HB89, HB94 and HB99, in which the indications for initial surgical procedures have become increasingly stringent (*38-40*). In GPOH 99, the protocol allowed the primary resection only in very small tumors confined to one liver segment on the liver margin, which was equal to PRETEXT I, and PRETEXT system used to stratify parallel patients (*40*). The German GPOH prospective studies of HB89, HB94 and HB99 using IPA (isocyclophosphamide + cisplatin + adriamycin), PA-cont (cisplatin + adriamycin continuous therapy) and Carbo/VP16 (carboplatin + etoposide) had 3-year OS of 75%, 77% and 89%, respectively, but the GPOH regimen did not outperform the SIOPEL and COG regimens over the same period. HB94 had a slightly improved prognosis (29% *vs.* 36%) in advanced, relapsed refractory HB with IPA and Carbo/VP16 (*33*). High-dose Carbo/VP16 chemotherapy combined with autologous HSCT had limited efficacy in the high-risk group, with a 5-year OS of only 58% (*7*).

3.1.4. JPLT

The first clinical trial of JPLT (JPLT-1) used a cisplatin + adriamycin regimen with 3-year and 6-year OS of 77. 8% and 73. 4%, and a 3-year EFS of < 50% after doubling the cisplatin dose in patients with advanced disease (stages IIIB and IV) (*9,41*). In JPLT-2, patients staged PRETEXT I/II were recommended to undergo surgery first, and remaining patients received cisplatin + pirarubicin (CITA) used as the first-line regimen; isocyclophosphamide, pirarubicin. VP-16 and carboplatin (ITEC) were used as the second-line regimen, with a 5-year EFS of 71. 6-84. 8%. However, ITEC second-line regimen and autologous stem cell transplantation has limited efficacy (*9*). The effectiveness and safety of the SIOPEL-4 regimen was confirmed by JPLT3-H (*42*).

3.2. Common chemotherapy adverse reactions and management

3.2.1. Cisplatin

Cisplatin is indispensable for HB treatment, but can cause irreversible Ototoxicity in children and reduce quality of life. In SR patients treated with cisplatin monotherapy, SIOPEL-6 found a significantly lower incidence of grade 1+ hearing loss in the sodium thiosulfate group compared to the control group (33% *vs.* 63%), with no difference in 3-year EFS and OS between the two groups, confirming that sodium thiosulfate significantly reduced cisplatin ototoxicity without compromising efficacy (*43*). This was corroborated by the results of the COG's ACCL0431 trial, which showed a 27. 8% reduction in hearing loss in children with cancer in the sodium thiosulfate group (28.6% *vs.* 56.4%). However, the prognosis was worse in the sodium thiosulfate group in patients with metastases, suggesting that sodium thiosulfate may diminish the effect of cisplatin and may not be used in the high-risk group (*44*). Amifostine has a hearing protective effect but unfortunately does not work in HB (*45*).

3.2.2. Anthracyclines

The main side effects of chemotherapy with anthracyclines are cardiotoxicity, including acute

myocardial injury and chronic impairment of cardiac function. The former is transient and reversible myocardial localised ischaemia, which may manifest as panic, shortness of breath, chest tightness and precordial discomfort; the latter is irreversible congestive heart failure, which is related to the cumulative dose of the drug (*46*). Once cardiac function tests suggest an ejection fraction < 55% or an axis shortening fraction < 28%, anthracycline antibiotics may be continued if abnormal left heart function can be demonstrated to be related to bacterial infection, otherwise they should be suspended until the ejection fraction is ≥ 55% or the axis shortening fraction is ≥ 28% (*47*). Dexrazoxane and levocarnitine are chosen according to the dose of anthracycline used or the degree of myocardial damage (*15*).

3.3. Surgical treatment of hepatoblastoma

Surgery remains the most vital intergradient in the cure of hepatoblastoma even though chemotherapy has become sophisticated through these decades. The timing and extent of hepatectomy or liver transplantation contingent on the POSTTEXT classification (staged in the same way as PRETEXT but used to describe status after receiving neoadjuvant chemotherapy), response to neoadjuvant and tumor biology (*3*). The advent of many new techniques has also broadened the scope of resectable hepatoblastoma, making surgery safer and more effective.

3.3.1. Hepatectomy

On the timing of surgical resection of hepatoblastoma, this varies between collaborative groups. The International Childhood Liver Tumors Strategy Group (SIOPEL) recommends preoperative neoadjuvant chemotherapy for all staged children to reduce the extent of hepatic resection, avoid aggressive surgery and reduce surgical trauma (*13*). In the COG, GPOH and JPLT studies, an upfront resection strategy was adopted for patients with PRETEXT I/II and, according to the COG study, pure fetal hepatoblastoma with PRETEXT I can be cured with radical surgery (*48,49*). The COG surgical guidelines recommend: segmental or lobectomy for children with PRETEXT stages I and II; lobectomy or trilobectomy for children with POST-TEXT stages II and III without involvement of large vessels; and complex hepatectomy or liver transplantation for children with POST-TEXT stages III and IV with involvement of large vessels, which should be assessed by an experienced team with competence in liver transplantation (*50-52*). Although the protocols used by the various collaborative groups differed, the final outcomes were generally similar according to the Children's Hepatic tumors International Collaboration (CHIC) (*18*).

In the Chinese guidelines for the diagnosis and management of hepatoblastoma, the indications for primary surgical resection are: (1) American Society of Anesthesiologists grade 1 to 2; (2) residual liver tissue greater than 35% of the original volume and functionally capable of meeting metabolic needs as assessed by imaging; (3) a single tumor lesion in PRETEXT stage I or II with adequate clearance (≥ 1 cm) from important vessels; (4) an anticipated microscopic single tumor lesion in PRETEXT stage I and II with sufficient clearance from important vessels (≥ 1 cm); (5) expected microscopic residual (COG stage II) without secondary surgery. (6) For children with PRETEXT stage III or IV, deferred surgery should be performed after neoadjuvant chemotherapy with a clear diagnosis on biopsy; (7) For children with POSTTEXT stage I or II or POST-TEXT stage III without significant vascular involvement (portal vein or inferior vena cava) after chemotherapy, lobectomy or segmental resection of the liver is feasible; (8) For children with PRETEXT stage I or II, lobectomy or segmental resection of the liver is feasible. (9) Children with PRETEXT stage IV and POSTTEXT stage III with inferior vena cava (V+) or portal vein (P+) involvement after chemotherapy should be transferred to a hospital with complex hepatic segmental resection or liver transplantation capability as soon as possible; (10) Children with single metastatic lesions in the lung or brain remaining after chemotherapy should be surgically resected for residual lesions.

The use of surgical adjuvant techniques also provides a guarantee of safety and effectiveness in hepatoblastoma surgery. Along with the development of laparoscopic techniques, laparoscopic liver tumor resection is becoming increasingly sophisticated. With the assurance of less trauma, less bleeding and faster postoperative recovery, laparoscopic surgery offers adequate safety and efficacy. In the JPLT-2 study, non-anatomical partial hepatectomy and incomplete tumor resection were suggested as risk factors associated with a high risk of recurrence. Combined with the use of intraoperative ultrasound, laparoscopic liver resection can accomplish precise resection of liver segments and complete removal of the lesion. However, due to the small abdominal space in paediatric patients, patient selection for surgery should be considered in relation to the location, size and response to chemotherapy of the paediatric tumor.

Indocyanine green (ICG) fluorescence imaging has been widely used in laparoscopic surgery and paediatric liver resection, and there are international reports of ICG being used in hepatoblastoma resection (*53-55*). Since healthy liver tissue rapidly clears ICG, while tumor tissue retains ICG, preoperative injection of ICG facilitates intraoperative determination of the resection line and identification of residual tumor (*56*). ICG (0.5-1 mg/kg) is currently administered intravenously 48-72 hours prior to surgery to ensure hepatic clearance (*55*). In addition, indocyanine green staining can be applied to indicate resection of distant metastases from hepatoblastoma. See 3.4 of this chapter for details. However, the following

deficiencies remain when using indocyanine green for staining indication of hepatoblastoma. First, for hepatoblastoma with good differentiation, indocyanine green can maintain a good fluorescence image, while for special hepatoblastoma, indocyanine green does not maintain well. Second, most patients with hepatoblastoma received preoperative chemotherapy, and the activity of the tumor is significantly reduced, which also affects the absorption and excretion of indocyanine green by the tumor tissue (*57*).

With regard to the prognostic impact of positive postoperative pathological examination margins, although residual tumor was found to be a high-risk factor for recurrence in the JPLT-2 study, in the SIOPEL study, positive microscopically seen margins did not affect outcome with a median follow-up of 67 months, with local recurrence occurring in 3/58 (5%) patients with microscopically positive resection margins and 23/371 (6%) patients with complete resection. The 5-year overall and event-free survival rates were 91% and 86%, respectively (*58,59*). The more widely shared view is that in patients with hepatoblastoma treated with platinum-based protocols, even if a positive microscopic margin is found after surgery, there is no significant impact on patient survival. The results of some studies suggest that there is no significant difference in the prognosis of patients with positive margins even when compared to patients in complete remission after platinum-based therapy (*59,60*). The reasons for this phenomenon may be as follows: first, the positive margins of the patient's resected liver specimen may not mean that tumor cells remain in the patient's liver body because liver sections are routinely cauterized during liver surgery; second, even small amounts of residual tumor tissue are still more easily controlled or even in complete remission under the control of platinum-based chemotherapy regimens (*59*). In some cases of postoperative recurrence of non-R0 resection, this may also be due to the presence of potential metastases at the time of diagnosis. The survival was not significantly different even after postoperative distant metastases due to good control of distant metastases with platinum-based agents (*60*). This provides some theoretical basis for the acceptance of hepatectomy in patients with POSTTEXT stage III/IV. Indeed, studies by Joerg Fuchs *et al*. and El-Gendi A *et al*. have suggested a survival benefit for patients undergoing hepatectomy in POSTTEXT stage III, with 3-year overall survival rates of 86.6% for the former and 5-year overall survival rates of 80.7% for the latter (*13,61*). Although such clinical practice may be beneficial in diverting the need for allogeneic liver transplantation in advanced patients, the possibility of liver transplantation should always be considered. In addition, a surgical strategy of ex vivo liver resection and autotransplantation (ELRA) may be attempted for those who still have invasion of important tissue structures after chemotherapy treatment and whose growth location is difficult to be directly resected. According to Kang *et al*, an autologous liver transplantation with ex vivo hepatectomy was performed in a 1.5-year-old female child. The patient's AFP level returned to normal rapidly after surgery and the perioperative period was uneventful, providing preliminary evidence of the potential feasibility of the ex vivo hepatectomy combined with the autologous liver transplantation technique for patients who are not suitable for conventional hepatectomy (*62*).

3.3.2. Liver transplantation

There is no unified indication for liver transplantation for hepatoblastoma in international collaborations, but liver transplantation should still be considered first for patients with PRETEXT stage III/IV, or with large vessel or bile duct invasion. Liver transplantation is a more complete eradication of the lesion than hepatectomy, but is limited by the adverse effects of immunosuppressive therapy and an insufficient number of donors, and has been commonly used as a salvage treatment for end-stage HB. So, liver transplantation for hepatoblastoma can be divided into two options: primary liver transplantation and salvage liver transplantation. Salvage liver transplantation may be considered for remaining intrahepatic recurrences that occur after initial liver resection. Based on previous literature, the postoperative survival benefit of salvage liver transplantation is similar to that of initial liver transplantation (*63*). Also, the pathological type of hepatoblastoma, waitlist time, log-fold decrease in AFP and number of adjuvant chemotherapy cycles had a significant effect on the time to EFS after liver transplantation in patients with hepatoblastoma (*63*). Thanks to the use of preoperative chemotherapy and the maturation of surgical techniques, the survival prognosis of liver transplantation in patients with unresectable hepatoblastoma has been significantly improved and the number of liver transplants performed on patients with hepatoblastoma has increased more than 20-fold (*64*). Due to preoperative chemotherapy regimens and improved surgical techniques, liver transplantation for hepatoblastoma now has a 5-year survival rate of 60-80% (*65*). A restorative clinical study based on the Surveillance, Epidemiology, and End Results Program (SEER) database suggests that children with hepatoblastoma who undergo liver transplantation have a 5-year survival rate of 86.5% (*66*). In recent years, studies have confirmed that postoperative survival rates are significantly higher in children who have undergone first-stage liver transplantation than in children who have undergone recurrent remedial liver transplantation after hepatectomy. Therefore, a more positive attitude towards liver transplantation is required in clinical practice.

3.3.3. Assistive technology

Trans-catheter arterial chemo-embolization (TACE) may

be indicated for patients who have had a poor response to chemotherapy and are not candidates for liver resection or liver transplantation (*67,68*). Jiang *et al*. treated 17 patients with PRETEXT stage III-IV with the A combined with B approach, and 14 of them achieved good results. Tumor markers were reduced to normal (*69*). The results of another randomized controlled trial suggested that 110 patients with unresectable hepatoblastoma treated with High Intensity Focused Ultrasound (HIFU) combined with TACE regimen had higher survival rates of 100%, 84%, and 16% at 1, 3, and 5 years, respectively (*70*). The above results support that TACE and various treatment options in combination with TACE may have some efficacy in difficult-to-resect hepatoblastoma, leading to longer survival times. In addition, portal vein embolisation (PVE) or associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has the potential to promote normal liver volume gain and safeguard liver function in the perioperative period in patients who have insufficient future liver remnant (FLR) but still require liver resection. The world's first patient with hepatoblastoma treated surgically with ALPPS was reported in 2014 by Chan *et al* (*71*). The use of ALPPS in paediatric liver tumors is still in its infancy and has only been carried out in a small number of experienced paediatric hospitals, and is mostly reported as a case study (*72,73*). However, some studies now show that rapid tumor recurrence and metastasis may occur after ALPPS, which may be related to changes in the immune microenvironment within the liver (*74*).

3.4. Treatment of metastatic lesions

The most common distant metastatic organ for hepatoblastoma is the lung, with 20% of children having lung metastases at diagnosis. In patients with hepatoblastoma found at initial diagnosis and with pulmonary metastases, surgical resection of the still present pulmonary metastases after chemotherapy helps to prolong overall survival (*13,75,76*). According to the JPLT-2 and SIOPEL-3 studies, more than half of patients who received intensive neoadjuvant chemotherapy experienced complete remission of their lung lesions (*13,77*). For patients with complete remission of lung lesions who undergo resection of the primary lesion, the overall survival rate at 3 years can exceed 80% (*78*). Whereas in patients with residual lung lesions despite chemotherapy, residual lung lesions are a significant risk factor for reduced EFS and OS and undergoing lung nodule resection is a viable means of doing so. Wanaguru *et al*. reported on the resection of eight patients with hepatoblastoma with long-term curative results (*76*). Intraoperative identification and resection of lung metastases can now also be achieved with the aid of ICG fluorescent labelling. Kitagawa *et al* reported that ICG can detect lung lesions as small as 0.062 mm. In a study of 10 patients, all pathologically positive lesions were significantly fluorescence positive (*79*). In contrast, survival data for pulmonary recurrence after surgery vary widely, but the basic treatment idea is also based on surgical options after chemotherapy or relying on chemotherapy alone for disease control, but in general, the prognosis for patients with this condition is relatively poorer than for patients with lung metastases at the time of initial diagnosis, perhaps due to the development of resistance to chemotherapy in postoperative recurrent tumors (*80*). The difference in survival of patients with recurrent lung disease, however, may be due to differences in patient metastasis, with shorter survival for patients who also have extra-pulmonary recurrent lesions compared to those with limited intrapulmonary recurrence (*81,82*). Currently, the common surgical approach for resection of lung lesions is irregular resection or wedge resection of the lung, rather than resection of the complete lung lobes or segments. Also, simultaneous and heterochronic resection is controversial in patients with metastatic lesions in both lungs (*83*). Although heterochronic surgery is less invasive, the interval between surgical procedures may affect the development and implementation of the patient's postoperative chemotherapy regimen. The procedure is also more invasive and more likely to affect the patient's respiratory function, requiring more careful assessment of the patient's surgical and respiratory tolerances. In addition, radiofrequency ablation can be used for the treatment of pulmonary metastatic lesions (*84*).

3.5. Treatment of recurrent hepatoblastoma

The most common sites of recurrence of hepatoblastoma are intrahepatic recurrence and pulmonary metastases. Recurrence of hepatoblastoma is relatively common in patients who are not sensitive to first-line therapy, with less than 12% of patients in complete remission to first-line therapy experiencing recurrence, according to the SIOPEL study and combined treatment with chemotherapy and surgical removal of the tumor is essential for long-term survival (*85*). Chemotherapy as well as surgery is still recommended for the treatment of recurrent hepatoblastoma. In the aforementioned SIOPEL study, 31 of 59 patients with recurrence achieved a secondary complete remission and 15 of 21 patients with local recurrence in the liver were treated with radical surgery (*85*). Salvage liver transplantation may also be considered for those with complex localised recurrent lesions in the liver that make reoperation difficult. However, the long-term survival of salvage liver transplantation is currently poor, with a 5-year survival rate of only about 30%-40% compared to the 5-year overall survival rate of over 80% for primary liver transplantation (*86,87*). Management of metastatic lung lesions with the same chemotherapeutic and aggressive surgical approach does not achieve similar results as in intrahepatic recurrences. In the SIOPEL series, a

second remission could be achieved by resection in 15 of 27 patients with pulmonary recurrence (*85*). Shi *et al* reported the surgical experience of 10 patients with pulmonary recurrence, one of whom had bilateral pulmonary metastases. eight were effectively treated by pulmonary metastasectomy for long-term survival (*81*). Multiple thoracotomies can be repeated as needed to remove pulmonary recurrences to prolong disease-free interval. However, its value in prolonging long-term overall survival remains to be demonstrated. For patients with recurrent hepatoblastoma after initial liver transplantation, re-hepatectomy is still an effective treatment. Liu *et al* reported that 18 patients with recurrent hepatoblastoma after liver transplantation underwent hepatic resection and significant prolonged survival time was observed (*88*).

4. Outlook

The efforts of international collaborations have led to significant advances in the treatment of hepatoblastoma, with significant increases in cure rates and long-term survival for children. However, there are still issues to be addressed.

As hepatoblastoma is a relatively rare type of tumor, the etiology of hepatoblastoma still needs to be further investigated. Although several studies have suggested that low birth weight and tobacco intake during pregnancy are risk factors for the development of hepatoblastoma (*89*). However, no epidemiological models have been successfully constructed to guide the primary prevention of hepatoblastoma. With unprecedented close collaboration and information sharing among international clinical research groups on hepatoblastoma, it is expected that future research on the etiological mechanisms of hepatoblastoma will be deepened and a preventive mechanism for the disease will be constructed from an etiological perspective.

In addition, despite promising improvements in survival rates for children with hepatoblastoma due to advances in chemotherapy and surgical techniques, there are still some children who are not sensitive to conventional chemotherapy regimens or whose tumors have recurred and metastasized after surgery. In the treatment of hepatocellular carcinoma, targeted combination immunotherapy regimens have shown significant efficacy and may also be useful in subsequent clinical trials for the treatment of recurrent or refractory hepatoblastoma (*90*). Small clinical trials have found that sorafenib (SFN) and irinotecan (CPT-11) resulted in remission in approximately 80% of patients with relapsed/refractory HB, and the combination of the two drugs still holds promise for partial response (PR) in patients with single agent resistance (*91*). Some phase I studies by the COG have shown the effectiveness of Aurora kinase inhibitors and the multi-receptor tyrosine kinase inhibitor pazopanib in HB (*92*). In immunotherapy, case reports have shown that immunotherapy with pabolizumab controlled HB disease progression for up to 22 months (*93*). Studies on the efficacy of GPC3, CAR-T cells for AFP or the humanized antibody codrituzumab in HB are ongoing (*92*). The limited inhibitory effect of anti-PD-1 monoclonal antibodies on HB may be related to the low mutational load of the tumor, and further studies are needed to determine whether the prognosis of HB can be improved by mutation screening or in combination with conventional chemotherapy (*93*).

5. Conclusion

Advances in diagnostic techniques and treatment options have led to survival benefits for children with hepatoblastoma. In light of the advancements in imaging technology, the diagnosis, preoperative assessment, and staging of hepatoblastoma have become more accessible, thus facilitating treatment modalities and surgical strategizing. New chemotherapy regimens are increasingly looking at ways to reduce the side effects of chemotherapy in addition to seeking higher rates of disease remission. Meanwhile, advances in surgical techniques have expanded surgical indications to further achieve a better survival benefit.

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