

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Diagnosis and Treatment of Hepatoblastoma: An Update

Chengzhan Zhu, Bingzi Dong, Xin Chen and Qian Dong

Abstract

Hepatoblastoma is a rare but the most common solid tumor in children. The incidence is gradually increasing. The international collaboration among four centers in the world has greatly improved the prognosis of hepatoblastoma. They formed the Children's Hepatic Tumor International Collaboration (CHIC) to standardize the staging system (2017 PRETEXT system) and the risk factors for tumor stratification. Multimodal therapy has become the standard for the management of hepatoblastoma, including surgical resection, liver transplantation, chemotherapy, and so on. Surgery is the primary treatment of early stage hepatoblastoma. Three-dimensional reconstruction is helpful for preoperative evaluation of large tumors, assisting extended hepatectomy for patients in PRETEXT III or IV. Neoadjuvant therapy is useful for reducing the tumor volume and increasing the resectability. Primary liver transplantation is recommended for advanced hepatoblastoma. The lungs are the most common metastatic organ, the treatment of which is critical for the patient's long-term survival. We reviewed the recent progress in the diagnosis and treatment of hepatoblastoma.

Keywords: hepatoblastoma, PRETEXT, stratification, neoadjuvant, surgical resection, liver transplantation

1. Introduction

Hepatoblastoma is the third most commonly diagnosed intra-abdominal solid tumor [1]. It is also the most common primary hepatic malignancy in children [2]. More than 90% of hepatoblastoma occur in children under the age of 5 years [3, 4]. Although its absolute incidence is very low, its growth rate is gradually increasing, which increased from 1.89 per 1,000,000 in 2000 to 2.16 per 1,000,000 in 2015, with an annual percentage change of 2.2%. This increase mainly occurs in male children between 2 and 4 years of age, which was found to be an independent predictor for short overall survival [5]. With the development of multimodal treatment and cooperation between international organizations, the prognoses have been greatly improved in recent years [6].

2. Diagnosis

Clinical manifestations are not typical at the early stage of hepatoblastoma. There would be epigastric or total abdominal distention, nausea, vomit, loss of appetite, abdominal pain, diarrhea, jaundice, even varicosity of abdominal wall,

and dyspnea. Another clinical feature is often accompanied by fever, and the temperature can reach 39–40°C. About 3% of patients have sex hormone and sexual organ development abnormalities. And a few children have obvious osteoporosis and pathological fracture.

Physical examination could find diffuse or nodular enlargement of the liver, of which the volume varies, sometimes with splenomegaly and varicosity of the abdominal wall. Abdominal pain and abdominal muscle tension may be due to tumor rupture. In the late stage, the hepatoblastoma progresses rapidly and cachexia appeared soon.

Alpha fetoprotein (AFP) increases in more than 90% of patients, which is a specific indicator for hepatoblastoma and important for disease follow-up. Age should be considered when analyzing the clinical significance of AFP. The average AFP of the newborn is about 62.7ng/ml, and it reaches the peak in the first month after birth, the average AFP is about 1200 ng/ml. After three months, it decreases to 3.15ng/ml (the level of normal adult). In addition, the LDH, cholesterol, and alkaline phosphatase are also increased. The liver function is normal at early stage, middle, and late stage.

Imaging is necessary for diagnosis and preoperative evaluation, including tumor location, number, and the relationship with peripheral blood vessels and organs. The commonly used examination includes ultrasound, CT, MRI, angiography, etc.

Enhanced CT and MRI are important imaging studies, which are recommended. However, due to the difficulty of MRI examination for children, we usually choose enhance CT and reconstruct the images into three-dimensional images to understand the spatial structure of the tumor and the anatomical relationship with the blood vessels.

Additionally, the deep exploration of CT/MRI images is also important for the overall evaluation of hepatoblastoma. Identifying the CT/MRI image features of hepatoblastoma will help distinguish the more malignant tumor, which is potentially useful for guiding the clinical treatment. A study of 34 patients, aimed at studying contrast-enhanced CT characteristics of hepatoblastoma associated with metastatic disease and patient outcomes, found that irregular tumor margins, vascular invasion, capsule retraction, and PRETEXT staging are associated with poor patient prognosis. Among them, irregular tumor margins are the only imaging features that are significantly associated with more aggressive tumor subtypes [7]. For investigating the image characteristics, artificial intelligence has demonstrated remarkable progress in image recognition tasks. Radiomics is used to investigate the quantitative features that are invisible to the naked eye from conventional image with methods of artificial intelligence. The image features could be used to predict the pathology characteristics, therapeutic response, and survival. Previous studies have evaluated the value of radiomics in adult liver cancer. The results were achieved, particularly in the preoperative prediction of pathological features and postoperative recurrence [8, 9].

3. International collaboration

3.1 The children's hepatic tumor international collaboration (CHIC)

The four centers in the world that have performed prospective controlled studies of hepatoblastoma joined forces to form the CHIC. It includes the International Childhood Liver Tumor Strategy Group (SIOPEL), the Children's Oncology Group (COG), the German Society for Pediatric Oncology and Hematology (GPOH), and the Japanese Study Group for Pediatric Liver Tumors (JPLT). Such international

cooperation provides a large-scale database for clinical trials. The CHIC has developed a centralized online platform that combines data from eight completed clinical trials to form a database of 1605 hepatoblastoma cases treated between 1988 and 2008. The resulting data set has been used for investigating the relationship between the patient prognosis and the tumor characteristics and patient stratification for treatment selection and follow-up. And the collaboration has led to a uniform implementation of staging system (PRE-Treatment EXtent of tumor, PRETEXT), which is helpful for systemically evaluating the hepatoblastoma at diagnosis and useful for establishing consensus classification. Moreover, pathologists in the collaboration have established a new histopathological consensus classification for pediatric liver tumors. There have also been advances in chemotherapy treatments and liver transplantation for unresectable tumors. These advances will be further evaluated in the upcoming Pediatric Hepatic International Tumor Trial (PHITT) [10].

3.2 2017 PRETEXT and risk stratification

Imaging is an important basis for disease assessment and treatment selection. The PRETEXT system has been firstly proposed for staging and risk stratification for hepatoblastoma in 1992 [11]. The PRETEXT system is used to classify the tumor extent before treatment, which has a good prognostic value in patients with hepatoblastoma. The PRETEXT system has been widely used to evaluate the hepatoblastoma in recent years, which could stratify patients into groups with different prognosis.

The 2017 PRETEXT has updated the 2005 PRETEXT definitions [12]. The liver was divided into four sections. For PRETEXT I, II, and IV groups, there were no obvious differences between 2017 PRETEXT and 2005 PRETEXT. For PRETEXT I group, the tumor involves only one of the two lateral sections (right posterior and left lateral section). For PRETEXT II group, the tumor involves the left lobe, right lobe, left medial section only, and right anterior section only; two separate tumors involves the two lateral sections or the caudate lobe only. For PRETEXT III group, the tumor involves three sections of the liver, leaving only one normal section. For PRETEXT IV group, the tumor involves all four sections. The 2017 PRETEXT has mainly standardized the PRETEXT annotation factors, preparing the future clinical trials. It includes hepatic venous/inferior vena cava involvement (V), portal venous involvement (P), extrahepatic disease contiguous with the main liver tumor (E), multifocality (F), and tumor rupture (R) [12].

Many single centers have put effort to investigate the prognostic factor of hepatoblastoma [13–16]. But the results were limited due to the small patients' number and the use of multiple disparate staging systems. CHIC has created a new staging system to staging and risk stratification in children with hepatoblastoma, named the Children's Hepatic tumors International Collaboration-Hepatoblastoma Stratification (CHIC-HS). Based on a 5-year event-free survival and clinical applicability, the system was established with risk factors including PRETEXT groups, metastatic disease, age, AFP concentration, PRETEXT annotation factors (VPEFR), and surgically resectable at diagnosis [17]. PRETEXT group is the primary and most important for risk stratification. If the tumor is resectable at diagnosis for patients of PRETEXT I/II group, they are in very low or low risk. After PRETEXT group, metastatic disease is the first risk factor for stratification. All patients with metastatic disease were defined as high risk. Then, age ≥ 8 years in PRETEXT I, II, and III group and age ≥ 3 years in PRETEXT IV group were high-risk factor. For younger patients, AFP ≤ 100 ng/mL was defined as high-risk group. And VPEFR+ patients were in intermediate-risk group. In PRETEXT I/II group, older patients showed a relatively poor prognosis. But many of these tumors can be surgically resected; they defined the patients at 3–7 year age in the lower-risk group; patients who had low

PRETEXT and positive VPEFR were placed in the intermediate-risk group; patients with PRETEXT I and low AFP (≤ 100 ng/mL) should not be stratified into high-risk group due to surgically resectable small tumors; patients with PRETEXT III group (younger than 8 years, no metastasis (M–) and AFP 100–1000 ng/mL) were defined as intermediate risk due to the poor 5-year event-free survival. CHIC-HS is by far the most complete system for risk stratification of pediatric hepatoblastoma and has important guiding significance for guiding individualized treatment [17]. Further study should also pay attention to the prognostic effect of treatment selection, such as anatomical or nonanatomical partial hepatectomy [18] and the dosage of chemotherapy [19, 20].

4. Treatment

Multimodal therapy is recommended for the management of hepatoblastoma, including surgical resection, liver transplantation, chemotherapy, or radiofrequency ablation [21]. Multimodal therapy can improve tumor remission rate of children with advanced hepatoblastoma and prolong the survival. Surgical resection is the preferred treatment of resectable hepatoblastoma at the time of diagnosis. Neoadjuvant chemotherapy could improve the rate and safety of complete surgical resection for unresectable hepatoblastoma. Liver transplantation is one of the main treatments for unresectable hepatoblastoma [22, 23]. Prognosis has been greatly improved due to advances in chemotherapeutic agents and dosing regimens as well as innovations in surgical procedures, including the preoperative three-dimensional reconstruction, the usage of energy device, and liver transplantation. The management of high-risk patients and patients with recurrent or metastatic disease remains challenging [21].

4.1 Surgical resection for hepatoblastoma

Hepatectomy is the first choice for hepatoblastoma. It is suitable for PRETEXT I, II, and part of III patients. For most PRETEXT III and IV patients, chemotherapy is preferred first. Then, reevaluate the tumor and decide the treatment, hepatectomy or liver transplantation. However, there is still controversy about whether surgery should be performed first or chemotherapy first and the selection of extended hepatectomy or liver transplantation.

4.1.1 Preoperative or postoperative chemotherapy

Over the past 40 years, the management of hepatoblastoma has changed significantly. For patients with unresectable tumors, neoadjuvant chemotherapy has become the standard treatment which can lead to a significant reduction in preoperative tumors and sometimes even complete ablation [24]. Neoadjuvant chemotherapy may facilitate partial hepatectomy by withdrawal of the tumor boundary from the confluence of portal vein bifurcation, hepatic veins, and inferior vena cava. And the tumor volume of hepatoblastoma could be significantly resolved with increasing neoadjuvant chemotherapy cycles [25]. For patients who underwent cisplatin-based neoadjuvant and postoperative chemotherapy, microscopically positive resection margin did not affect the overall survival rate. And the “wait-and-see policy” is recommended [26].

For patients with hepatoblastoma that could be resected at diagnosis, postoperative chemotherapy with cisplatin, fluorouracil, and vincristine is useful to control the disease progression [27]. And for the subtype of pure fetal histology hepatoblastoma, complete surgical resection can achieve good survival without additional

chemotherapy. Further study should be performed to identify the patients for whom chemotherapy is not necessary [28].

4.1.2 Extended hepatectomy or liver transplantation

The management of patients in PRETEXT III or IV was difficult, including the selection between an aggressive liver resection and liver transplantation. There has been several study comparing the prognosis of partial hepatectomy and liver transplantation, the 5-year overall survival rate was 92% in patients who were performed partial hepatectomy, and about 83% in patients who underwent liver transplantation [29–32].

Although primary liver transplantation is recommended for POSTTEXT III and IV hepatoblastoma, some of the patients may be possible to perform extended hepatectomy after careful preoperative evaluation. In a prospective study that involved 18 patients with PRETEXT III and IV, extended major hepatic resection is safe and feasible with a comparable prognosis. The prognosis was similar with liver transplantation, while patients could avoid long-term immunosuppressive treatment. But there should always be a potential donor for salvage liver transplantation [33, 34]. A study including 24 patients performed liver transplantation or extensive liver resection. Two patients in five who underwent liver transplantation experienced tumor recurrence and death within a mean period of 6 months, while 6 patients were recurrent in the extended hepatectomy group, with 63.2% event-free survival and 94.7% overall survival rate. The results support extensive surgical resection in patients of advanced tumor [35]. Although the surgical resection is complicated and sometimes remains positive or close negative margins, the patients could have good outcomes. Combined with neoadjuvant therapy, extensive surgical resection may spare the morbidity of orthotopic liver transplantation. And it will offer an alternative treatment for patients who are ineligible for liver transplantation [36].

In our center, we have performed extended hepatectomy for 27 cases of PRETEXT or POSTEXT III and IV, the 3-year disease-free survival was 75.0%, and the overall survival was 87.5%.

4.1.3 Does postoperative complication affect prognosis

Neoadjuvant therapy has become the standard treatment for unresected hepatoblastoma. After neoadjuvant therapy, tumor volume may reduce, and surgical resection could be safely performed [37]. Although the patients may have good survival, neoadjuvant therapy may be related with postoperative complications. A study assessing the surgical outcomes focusing on resection margins, postoperative complications, 30-day mortality, and overall survival found that patients who underwent partial hepatectomy after chemotherapy experienced high rate of surgical complications (58%). But the complications were not detrimental to survival [29]. In another report, the incidence of complications after surgical resection following adjuvant chemotherapy is high and is associated with overall survival in high-risk hepatoblastoma. One of the possible reasons is that postoperative complication will delay the chemotherapy [38]. In our experience, precise preoperative evaluation of the anatomy of tumor and intrahepatic vascular with three-dimensional (3D) reconstruction and compare with the intraoperative situation will ensure the safety of surgery.

4.2 3D reconstruction facilitates surgical resection

Three-dimensional reconstruction has been widely used in preoperative evaluation and assisting hepatectomy [39] or living donor liver transplantation [40].

3D simulation software could reconstruct the whole liver, tumor, and intrahepatic vascular, clearly displaying the anatomical variation and the correlation of tumor with the surrounding vascular. It is helpful for making the precise surgical plan and enables individualized anatomic hepatectomy for each pediatric patient with hepatoblastoma. For surgical resection, precisely understanding the location of tumor and the relation of tumor with the surrounding vascular and accurately evaluating the remnant liver volume are important for safe hepatectomy of giant hepatoblastoma. In our center, we have used a novel virtual hepatectomy simulation software named Hisense CAS for preoperative evaluation. The Hisense CAS software could simulate a 3D liver image quickly and accurately with DICOM files of contrast-enhanced CT. With the Hisense CAS, we could confirm the anatomical relationship of tumor with the surrounding vascular from any direction, preoperatively mimic hepatectomy by extracting Glisson territory for anatomical liver resection or nonanatomical hepatectomy, automatically calculate the remnant liver volume, and navigate the liver resection during operation [41, 42]. As shown in **Figure 1**, with the help of 3D reconstruction, we performed extended hepatectomy for the patients. In total, we have performed extended hepatectomy for 27 patients in PRETEXT or POSTTEXT III and IV. All the hepatoblastoma were successfully removed with no complications. There were shorter operation time and less intraoperative bleeding in the reconstructing group. And the postoperative hospital stays tended to be shorter [41, 42].

4.3 Liver transplantation in unresectable hepatoblastoma

Although extended hepatectomy for advanced hepatoblastoma has achieved favorable results, liver transplantation is still the only treatment for unresectable hepatoblastoma.

Liver transplantation can achieve a good prognosis for patients with hepatoblastoma, with a 5-year survival rate of 86% and a 10-year survival rate of about 80% [32, 43]. Compared with deceased donor transplantation, the prognosis of living liver transplantation was a little better (5-year survival rates were 83.3 and 77.6%). And compared with salvage liver transplantation, primary liver transplantation has a better prognosis (5-year survival rates were 82 and 30%) [31]. Compared with liver transplantation performed before 2010, patients who received liver transplantation after 2010 have a better prognosis (5-year survival rates were 82.6 and 75.1%) [43]. Preoperative liver metastasis, tumor lysis after chemotherapy, and perioperative anticoagulation can significantly improve the prognosis of patients with liver transplantation. And the outcome was not affected by tumor pathology [44]. For unresectable hepatoblastoma, vascular infiltration and poor resection are often present, and liver transplantation has become the first choice [45]. Adjuvant chemotherapy after transplantation can significantly improve the long-term prognosis of patients [22]. For unresectable hepatoblastoma, the pretransplantation trend of alpha-fetoprotein levels after live donor liver transplantation can be used as an indicator of predictive recurrence. Since the AFP response cannot be accurately predicted before each chemotherapy cycle, liver transplantation may be appropriate if the AFP level does not decrease after the last cycle and before AFP levels are found to rise again [46].

4.4 Treatment after metastasis

The lung is the most common metastatic organ of hepatoblastoma. In addition to lung, brain and bone metastases have also been reported [12, 47]. At the first diagnosis of hepatoblastoma, 17% of patients had pulmonary metastases [48]. Patients with lung

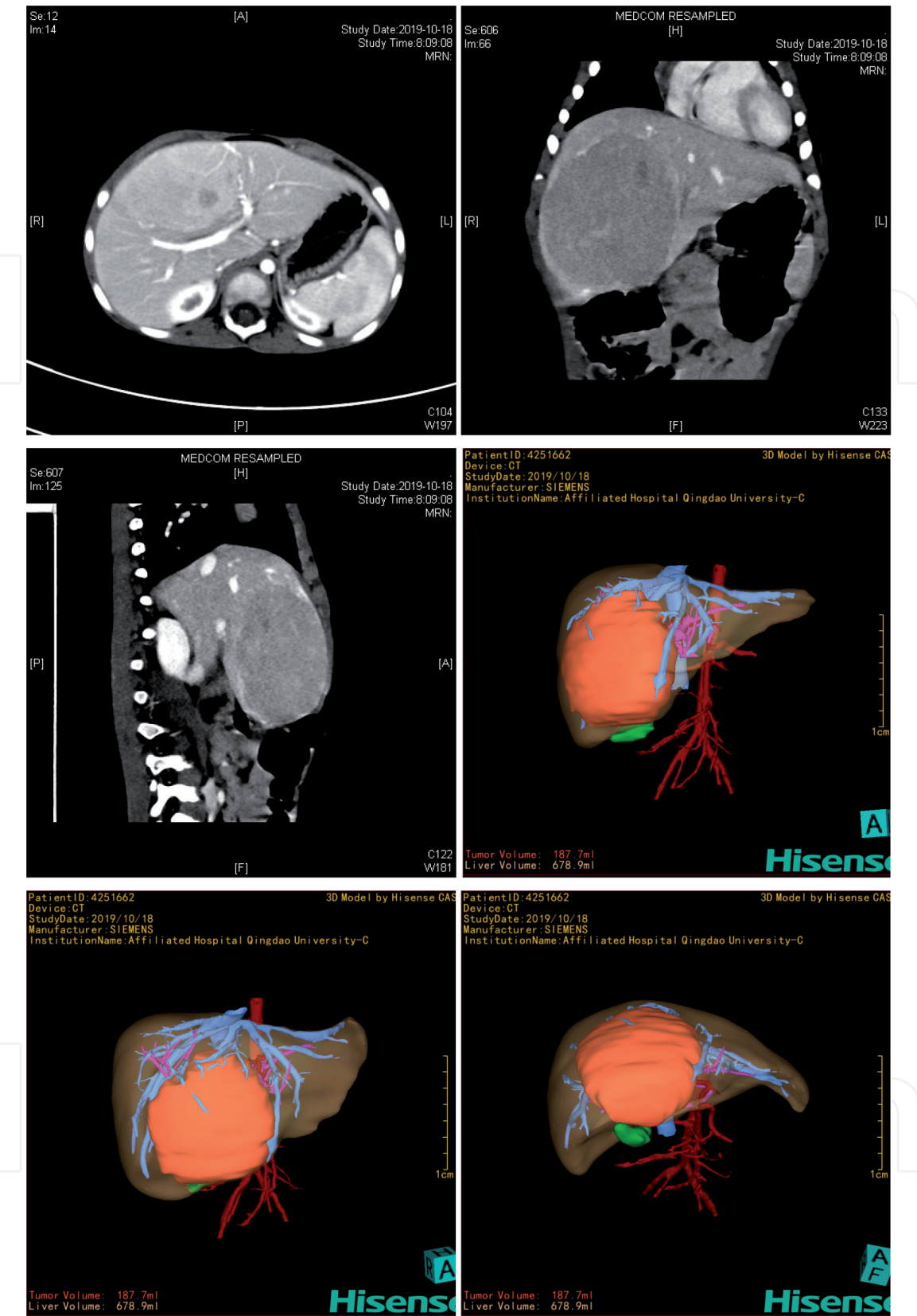


Figure 1.
Precise evaluation of hepatoblastoma with 3D reconstruction software.

metastasis will have a poor overall prognosis. Therefore, a CT scan of the lung should be performed before treatment to determine whether there is lung metastasis. Treatment after lung metastasis is also critical to extend the prognosis of patients. Comprehensive treatment of primary and metastatic lesions can improve the prognosis of patients.

The treatment of patients with synchronous lung metastasis and hepatoblastoma has been systemically reviewed [49]. To summarize, if the primary lesions and

metastases are resectable, combine resection; if unresectable, eradicate or reduce the metastasis by neoadjuvant chemotherapy and then flowing combined resection. For single lung metastatic nodule, surgical resection is safe and feasible for the treatment [50]. Neoadjuvant chemotherapy combined with surgical resection of primary and metastatic lesions can achieve a better prognosis for patients with lung metastases. Most lung metastatic lesions are sensitive to chemotherapy. About half (26/60) of patients can achieve complete remission by chemotherapy. Then flowing surgical removal of primary lesion, the patient's survival could be significantly improved (3-year survival rate 67.2%) [51]. For the patients whose lung metastasis cannot be completely eradicated by chemotherapy, the prognosis is relatively poor [52]. For patients who cannot achieve complete remission, increasing the intensity of chemotherapy or expanding the scope of surgical resection may prolong the patient's prognosis. In addition, the patients will experience poor prognosis if it occurs as lung metastases while on treatment [52]. If the primary liver lesion is resectable, chemotherapy-resistant lung lesions should be surgically removed before, after, or at the same time as liver tumor surgery. In patients with unresectable primary liver tumor, liver transplantation combined with metastasectomy can be performed after chemotherapy, the 5-year survival rate of which can reach 86%. For patients with an unremovable hepatoblastoma and residual lung metastasis, overall tumor burden may be an important prognostic factor for these patients [53]. Local treatment (e.g., transcatheter arterial chemoembolization or radiofrequency ablation) may be considered to reduce tumor size [49, 54]. Sometimes it is difficult to diagnose whether there is viability of residual lung lesions after chemotherapy; it will affect the operation for the primary tumor. It is difficult to determine the pathology of tiny lesions in imaging and find the lesions during intraoperative exploration; indocyanine green fluoroscopy may be helpful. But further study is necessary to verify the usefulness [55].

4.5 Adult hepatoblastoma

Compared with pediatric hepatoblastoma, adult hepatoblastoma has a lower incidence and a higher degree of malignancy [56]. There is no significant gender difference in the incidence of adult hepatoblastoma, and the average age of onset is 42 years [57]. About 25% of adult hepatoblastomas are associated with hepatitis and cirrhosis, while it is rare in pediatric patients. Abdominal pain is the main clinical manifestation, and abdominal mass is the most common sign. As with children, surgical resection is the first choice for adult hepatoblastoma. Most hepatoblastomas are unresectable at diagnosis; chemotherapy can be used for patients who cannot be resected to gain opportunities for surgery [58]. Chemotherapy protocols are not standardized, and there was no statistically significance in survival rate between patients treated with drugs or TACE and patients not treated [57]. Due to low incidence, liver transplantation has yet to be fully evaluated. The prognosis of adult hepatoblastoma is extremely poor. The median survival time was 8 months and a 1-year survival rate of 39.2% after treatment [59]. And patients had a longer survival if operation was performed [59]. Compared with nonsurgical treatment, surgery has a better prognosis. Hepatic multilobed involvement, embryonic histology, multifocal nodules, and AFP <100 or AFP > 1000 are the poor prognostic factors [60].

5. Conclusions

In summary, surgical resection is the primary treatment for hepatoblastoma. Preoperative three-dimensional reconstruction can improve the resection rate

of the tumor and the safety of the resection. For patients who cannot be directly resected, the tumor volume can be reduced by neoadjuvant therapy and then surgically treated. Liver transplantation is the best treatment for unresectable hepatoblastoma and has a good prognosis. For patients with distant metastasis, chemotherapy or metastasis resection combined with primary resection can effectively control disease progression.

Acknowledgements

This research was funded by the National Natural Science Foundation of China (81600490 and 81600691), the Research and Development Project of Shandong Province (2016GSF201221), China Postdoctoral Science Foundation (2016M602098 and 2018M640615), and Qingdao Postdoctoral Science Foundation (2016046).

Conflict of interest

The authors declare no conflict of interest.

Author details

Chengzhan Zhu^{1,2}, Bingzi Dong², Xin Chen³ and Qian Dong^{2,3*}


1 Department of Hepatobiliary and Pancreatic Surgery, The Affiliated Hospital of Qingdao University, Qingdao, China

2 Shandong Key Laboratory of Digital Medicine and Computer Assisted Surgery, The Affiliated Hospital of Qingdao University, Qingdao, China

3 Pediatric Surgery Department, The Affiliated Hospital of Qingdao University, Qingdao, China

*Address all correspondence to: 18661801885@163.com

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Hung GY, Lin LY, Yu TY, et al. Hepatoblastoma incidence in Taiwan: A population-based study. *Journal of the Chinese Medical Association*. 2018;**81**(6):541-547. DOI: 10.1016/j.jcma.2017.11.012
- [2] Hadzic N, Finegold MJ. Liver neoplasia in children. *Clinics in Liver Disease*. 2011;**15**(2):443-462, vii-x. DOI: 10.1016/j.cld.2011.03.011
- [3] Allan BJ, Parikh PP, Diaz S, et al. Predictors of survival and incidence of hepatoblastoma in the paediatric population. *HPB: The Official Journal of the International Hepato Pancreato Biliary Association*. 2013;**15**(10):741-746. DOI: 10.1111/hpb.12112
- [4] Hung GY, Horng JL, Lee YS, et al. Cancer incidence patterns among children and adolescents in Taiwan from 1995 to 2009: A population-based study. *Cancer*. 2014;**120**(22):3545-3553. DOI: 10.1002/cncr.28903
- [5] Feng J, Polychronidis G, Heger U, et al. Incidence trends and survival prediction of hepatoblastoma in children: A population-based study. *Cancer Communications (London)*. 2019;**39**(1):62. DOI: 10.1186/s40880-019-0411-7
- [6] Ismail H, Broniszczak D, Kalicinski P, et al. Changing treatment and outcome of children with hepatoblastoma: Analysis of a single center experience over the last 20 years. *Journal of Pediatric Surgery*. 2012;**47**(7):1331-1339. DOI: 10.1016/j.jpedsurg.2011.11.073
- [7] Baheti AD, Luana Stanescu A, Li N, et al. Contrast-enhanced CT features of hepatoblastoma: Can we predict histopathology? *Clinical Imaging*. 2017;**44**:33-37. DOI: 10.1016/j.clinimag.2017.03.023
- [8] Miranda Magalhaes Santos JM, Clemente BO, Araujo-Filho JAB, et al. State-of-the-art in radiomics of hepatocellular carcinoma: A review of basic principles, applications, and limitations. *Abdominal Radiology(NY)*. 2019. DOI: 10.1007/s00261-019-02299-3
- [9] Hosny A, Parmar C, Quackenbush J, et al. Artificial intelligence in radiology. *Nature Reviews. Cancer*. 2018;**18**(8):500-510. DOI: 10.1038/s41568-018-0016-5
- [10] Aronson DC, Meyers RL. Malignant tumors of the liver in children. *Seminars in Pediatric Surgery*. 2016;**25**(5):265-275. DOI: 10.1053/j.sempedsurg.2016.09.002
- [11] MacKinlay GA, Pritchard J. A common language for childhood liver tumours. *Pediatric Surgery International*. 1992;**7**(4):325-326
- [12] Towbin AJ, Meyers RL, Woodley H, et al. 2017 PRETEXT: Radiologic staging system for primary hepatic malignancies of childhood revised for the paediatric hepatic international tumour trial (PHITT). *Pediatric Radiology*. 2018;**48**(4):536-554. DOI: 10.1007/s00247-018-4078-z
- [13] Liu APY, Ip JJK, Leung AWK, et al. Treatment outcome and pattern of failure in hepatoblastoma treated with a consensus protocol in Hong Kong. *Pediatric Blood and Cancer*. 2019;**66**(1):e27482. DOI: 10.1002/pbc.27482
- [14] Qiao GL, Chen Z, Wang C, et al. Pure fetal histology subtype was associated with better prognosis of children with hepatoblastoma: A Chinese population-based study. *Journal of Gastroenterology and Hepatology*. 2016;**31**(3):621-627. DOI: 10.1111/jgh.13165
- [15] Yuan XJ, Wang HM, Jiang H, et al. Multidisciplinary effort in treating

- children with hepatoblastoma in China. *Cancer Letters*. 2016;**375**(1):39-46. DOI: 10.1016/j.canlet.2016.02.051
- [16] Shi Y, Commander SJ, Masand PM, et al. Vascular invasion is a prognostic indicator in hepatoblastoma. *Journal of Pediatric Surgery*. 2017;**52**(6):956-961. DOI: 10.1016/j.jpedsurg.2017.03.017
- [17] Meyers RL, Maibach R, Hiyama E, et al. Risk-stratified staging in paediatric hepatoblastoma: A unified analysis from the children's hepatic tumors international collaboration. *The Lancet Oncology*. 2017;**18**(1):122-131. DOI: 10.1016/S1470-2045(16)30598-8
- [18] Hiyama E, Hishiki T, Watanabe K, et al. Resectability and tumor response after preoperative chemotherapy in hepatoblastoma treated by the Japanese study group for pediatric liver tumor (JPLT)-2 protocol. *Journal of Pediatric Surgery*. 2016;**51**(12):2053-2057. DOI: 10.1016/j.jpedsurg.2016.09.038
- [19] Wang TY, Pan C, Tang JY, et al. A follow-up report of childhood hepatoblastoma from 74 cases in a single center. *Zhonghua Er Ke Za Zhi*. 2017;**55**(5):364-368. DOI: 10.3760/cma.j.issn.0578-1310.2017.05.011
- [20] Zsiros J, Brugieres L, Brock P, et al. Dose-dense cisplatin-based chemotherapy and surgery for children with high-risk hepatoblastoma (SIOPEL-4): A prospective, single-arm, feasibility study. *The Lancet Oncology*. 2013;**14**(9):834-842. DOI: 10.1016/S1470-2045(13)70272-9
- [21] Kremer N, Walther AE, Tiao GM. Management of hepatoblastoma: An update. *Current Opinion in Pediatrics*. 2014;**26**(3):362-369. DOI: 10.1097/MOP.0000000000000081
- [22] Pham TA, Gallo AM, Concepcion W, et al. Effect of liver transplant on long-term disease-free survival in children with Hepatoblastoma and hepatocellular cancer. *JAMA Surgery*. 2015;**150**(12):1150-1158. DOI: 10.1001/jamasurg.2015.1847
- [23] Perilongo G, Malogolowkin M, Feusner J. Hepatoblastoma clinical research: Lessons learned and future challenges. *Pediatric Blood and Cancer*. 2012;**59**(5):818-821. DOI: 10.1002/pbc.24217
- [24] Sharma D, Subbarao G, Saxena R. Hepatoblastoma. *Seminars in Diagnostic Pathology*. 2017;**34**(2):192-200. DOI: 10.1053/j.semdp.2016.12.015
- [25] Murphy AJ, Ayers GD, Hilmes MA, et al. Imaging analysis of hepatoblastoma resectability across neoadjuvant chemotherapy. *Journal of Pediatric Surgery*. 2013;**48**(6):1239-1248. DOI: 10.1016/j.jpedsurg.2013.03.019
- [26] Aronson DC, Weeda VB, Maibach R, et al. Microscopically positive resection margin after hepatoblastoma resection: What is the impact on prognosis? A childhood liver tumours strategy group (SIOPEL) report. *European Journal of Cancer*. 2019;**106**:126-132. DOI: 10.1016/j.ejca.2018.10.013
- [27] Katzenstein HM, Langham MR, Malogolowkin MH, et al. Minimal adjuvant chemotherapy for children with hepatoblastoma resected at diagnosis (AHEP0731): A children's oncology group, multicentre, phase 3 trial. *The Lancet Oncology*. 2019;**20**(5):719-727. DOI: 10.1016/S1470-2045(18)30895-7
- [28] Malogolowkin MH, Katzenstein HM, Meyers RL, et al. Complete surgical resection is curative for children with hepatoblastoma with pure fetal histology: A report from the children's oncology group. *Journal of Clinical Oncology*. 2011;**29**(24):3301-3306. DOI: 10.1200/JCO.2010.29.3837
- [29] Busweiler LA, Wijnen MH, Wilde JC, et al. Surgical treatment

- of childhood hepatoblastoma in the Netherlands (1990-2013). *Pediatric Surgery International*. 2017;**33**(1):23-31. DOI: 10.1007/s00383-016-3989-8
- [30] Finegold MJ, Egler RA, Goss JA, et al. Liver tumors: Pediatric population. *Liver Transplantation*. 2008;**14**(11):1545-1556. DOI: 10.1002/lt.21654
- [31] Otte JB, Pritchard J, Aronson DC, et al. Liver transplantation for hepatoblastoma: Results from the International Society of Pediatric Oncology (SIOP) study SIOPEL-1 and review of the world experience. *Pediatric Blood and Cancer*. 2004;**42**(1):74-83. DOI: 10.1002/pbc.10376
- [32] Triana Junco P, Cano EM, Dore M, et al. Prognostic factors for liver transplantation in unresectable hepatoblastoma. *European Journal of Pediatric Surgery*. 2019;**29**(1):28-32. DOI: 10.1055/s-0038-1668148
- [33] El-Gendi A, Fadel S, El-Shafei M, et al. Avoiding liver transplantation in post-treatment extent of disease III and IV hepatoblastoma. *Pediatrics International*. 2018;**60**(9):862-868. DOI: 10.1111/ped.13634
- [34] Fuchs J, Cavdar S, Blumenstock G, et al. POST-TEXT III and IV hepatoblastoma: Extended hepatic resection avoids liver transplantation in selected cases. *Annals of Surgery*. 2017;**266**(2):318-323. DOI: 10.1097/SLA.0000000000001936
- [35] de Freitas Paganoti G, Tannuri ACA, Dantas Marques AC, et al. Extensive hepatectomy as an alternative to liver transplant in advanced hepatoblastoma: A new protocol used in a pediatric liver transplantation center. *Transplantation Proceedings*. 2019;**51**(5):1605-1610. DOI: 10.1016/j.transproceed.2019.03.004
- [36] Fonseca A, Gupta A, Shaikh F, et al. Extreme hepatic resections for the treatment of advanced hepatoblastoma: Are planned close margins an acceptable approach? *Pediatric Blood and Cancer*. 2018;**65**(2). DOI: 10.1002/pbc.26820
- [37] Sunil BJ, Palaniappan R, Venkitaraman B, et al. Surgical resection for hepatoblastoma-updated survival outcomes. *Journal of Gastrointestinal Cancer*. 2018;**49**(4):493-496. DOI: 10.1007/s12029-017-0005-z
- [38] Becker K, Furch C, Schmid I, et al. Impact of postoperative complications on overall survival of patients with hepatoblastoma. *Pediatric Blood and Cancer*. 2015;**62**(1):24-28. DOI: 10.1002/pbc.25240
- [39] Aoki T, Murakami M, Fujimori A, et al. Routes for virtually guided endoscopic liver resection of subdiaphragmatic liver tumors. *Langenbeck's Archives of Surgery*. 2016;**401**(2):263-273. DOI: 10.1007/s00423-016-1385-4
- [40] Mochizuki K, Takatsuki M, Soyama A, et al. The usefulness of a high-speed 3D-image analysis system in pediatric living donor liver transplantation. *Annals of Transplantation*. 2012;**17**(1):31-34
- [41] Zhang G, Zhou XJ, Zhu CZ, et al. Usefulness of three-dimensional(3D) simulation software in hepatectomy for pediatric hepatoblastoma. *Surgical Oncology*. 2016;**25**(3):236-243. DOI: 10.1016/j.suronc.2016.05.023
- [42] Zhao J, Zhou XJ, Zhu CZ, et al. 3D simulation assisted resection of giant hepatic mesenchymal hamartoma in children. *Computer Assisted Surgery (Abingdon, England)*. 2017;**22**(1):54-59. DOI: 10.1080/24699322.2017.1358401
- [43] Ezekian B, Mulvihill MS, Schroder PM, et al. Improved contemporary outcomes of liver transplantation for pediatric hepatoblastoma and hepatocellular

carcinoma. *Pediatric Transplantation*. 2018;**22**(8):e13305. DOI: 10.1111/ptr.13305

[44] Cruz RJ Jr, Ranganathan S, Mazariegos G, et al. Analysis of national and single-center incidence and survival after liver transplantation for hepatoblastoma: New trends and future opportunities. *Surgery*. 2013;**153**(2):150-159. DOI: 10.1016/j.surg.2012.11.006

[45] Uchida H, Sakamoto S, Sasaki K, et al. Surgical treatment strategy for advanced hepatoblastoma: Resection versus transplantation. *Pediatric Blood and Cancer*. 2018;**65**(12):e27383. DOI: 10.1002/pbc.27383

[46] Isono K, Ohya Y, Lee KJ, et al. Pretransplant trends in alpha-fetoprotein levels as a predictor of recurrence after living donor liver transplantation for unresectable hepatoblastoma: A single-institution experience. *Pediatric Transplantation*. 2018;**22**(5):e13221. DOI: 10.1111/ptr.13221

[47] Yadav SS, Lawande MA, Patkar DA, et al. Rare case of hemorrhagic brain metastasis from hepatoblastoma. *Journal of Pediatric Neurosciences*. 2012;**7**(1):73-74. DOI: 10.4103/1817-1745.97634

[48] Czauderna P, Haeberle B, Hiyama E, et al. The children's hepatic tumors international collaboration (CHIC): Novel global rare tumor database yields new prognostic factors in hepatoblastoma and becomes a research model. *European Journal of Cancer*. 2016;**52**:92-101. DOI: 10.1016/j.ejca.2015.09.023

[49] Angelico R, Grimaldi C, Gazia C, et al. How do synchronous lung metastases influence the surgical management of children with hepatoblastoma? An update and systematic review of the literature. *Cancers (Basel)*. 2019;**11**(11):1693. DOI: 10.3390/cancers11111693

[50] Shi Y, Geller JI, Ma IT, et al. Relapsed hepatoblastoma confined to the lung is effectively treated with pulmonary metastasectomy. *Journal of Pediatric Surgery*. 2016;**51**(4):525-529. DOI: 10.1016/j.jpedsurg.2015.10.053

[51] Hishiki T, Watanabe K, Ida K, et al. The role of pulmonary metastasectomy for hepatoblastoma in children with metastasis at diagnosis: Results from the JPLT-2 study. *Journal of Pediatric Surgery*. 2017;**52**(12):2051-2055. DOI: 10.1016/j.jpedsurg.2017.08.031

[52] Wanaguru D, Shun A, Price N, et al. Outcomes of pulmonary metastases in hepatoblastoma—Is the prognosis always poor? *Journal of Pediatric Surgery*. 2013;**48**(12):2474-2478. DOI: 10.1016/j.jpedsurg.2013.08.023

[53] O'Neill AF, Towbin AJ, Krailo MD, et al. Characterization of pulmonary metastases in children with hepatoblastoma treated on children's oncology group protocol AHEP0731 (the treatment of children with all stages of hepatoblastoma): A report from the children's oncology group. *Journal of Clinical Oncology*. 2017;**35**(30):3465-3473. DOI: 10.1200/JCO.2017.73.5654

[54] Yevich S, Calandri M, Gravel G, et al. Reiterative radiofrequency ablation in the management of pediatric patients with hepatoblastoma metastases to the lung, liver, or bone. *Cardiovascular and Interventional Radiology*. 2019;**42**(1):41-47. DOI: 10.1007/s00270-018-2097-7

[55] Kitagawa N, Shinkai M, Mochizuki K, et al. Navigation using indocyanine green fluorescence imaging for hepatoblastoma pulmonary metastases surgery. *Pediatric Surgery International*. 2015;**31**(4):407-411. DOI: 10.1007/s00383-015-3679-y

[56] Rougemont AL, McLin VA, Toso C, et al. Adult hepatoblastoma: Learning

from children. *Journal of Hepatology*. 2012;**56**(6):1392-1403. DOI: 10.1016/j.jhep.2011.10.028

[57] Celotti A, D'Amico G, Ceresoli M, et al. Hepatoblastoma of the adult: A systematic review of the literature. *Surgical Oncology*. 2016;**25**(3):339-347. DOI: 10.1016/j.suronc.2016.07.003

[58] Nakamura S, Sho M, Kanehiro H, et al. Adult hepatoblastoma successfully treated with multimodal treatment. *Langenbeck's Archives of Surgery*. 2010;**395**(8):1165-1168. DOI: 10.1007/s00423-010-0630-5

[59] Duan XF, Zhao Q. Adult hepatoblastoma: A review of 47 cases. *ANZ Journal of Surgery*. 2018;**88**(1-2): E50-E54. DOI: 10.1111/ans.13839

[60] Brotto M, Finegold MJ. Distinct patterns of p27/KIP 1 gene expression in hepatoblastoma and prognostic implications with correlation before and after chemotherapy. *Human Pathology*. 2002;**33**(2):198-205. DOI: 10.1053/hupa.2002.31294