

# Unresectable hepatoblastoma: current perspectives

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**Abstract:** Although rare, hepatoblastoma is the most common pediatric liver tumor. Complete resection is a critical component for cure; however, most patients will have tumors that are not resected at diagnosis. For these patients, administration of neoadjuvant chemotherapy renders tumors resectable in most patients. For patients whose tumors remain unresectable after chemotherapy, liver transplantation is indicated (in the absence of active unresectable metastatic disease). In patients whose tumors remain unresectable after conventional chemotherapy, interventional techniques may serve as a promising option to reduce tumor size, decrease systemic toxicity, decrease need for liver transplantation, and increase feasibility of tumor resection.

**Keywords:** hepatoblastoma, unresectable, pediatric

## Introduction

Although rare, hepatoblastoma (HB) is the most common pediatric liver tumor with at least 100 cases per year in the US and an increasing incidence.<sup>1-4</sup> Patients with HB typically present at <5 years of age, with an increased risk seen in patients with low birthweight, maternal tobacco exposure, familial adenomatous polyposis coli, and Beckwith-Wiedemann Syndrome.<sup>5-8</sup>

Complete resection is a critical component for cure; however, 60%–80% of patients' tumors are unresectable at diagnosis depending upon the surgical guidelines used.<sup>9,10</sup> The surgery-based Evans staging system, previously used in America, was based on an attempted resection at diagnosis in all patients. It classified tumors as stage I (upfront resection with negative microscopic margins), stage II (upfront resection with positive microscopic margins), stage III (unresectable at diagnosis without metastatic disease), and stage IV (metastatic disease). In the intergroup study INT0098 (1989–1992), 32% of patients were presented with stage I or II disease and 68% of patients were presented with stage III or IV tumors.<sup>9</sup> In Europe, the International Childhood Liver Tumors Strategy Group (SIOPEL) introduced a radiology-based staging system called PRETreatment EXtent of disease (PRETEXT).<sup>11</sup> The PRETEXT system classifies tumors into one of four groups based upon the number of tumor free liver sections. PRETEXT I tumors have three adjoining sectors free of tumor, PRETEXT II tumors have two adjoining sectors free of tumor, PRETEXT III tumors have one sector free of tumor, and PRETEXT IV tumors have no sectors free of tumor. In the most recent high risk (HR) SIOPEL trial SIOPEL 4 (which included patients with metastatic disease, PRETEXT IV tumors, extrahepatic abdominal disease, vascular

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invasion, and/or low alpha fetoprotein), the patients had 3%, 27%, 44%, and 26% PRETEXT I, II, III, and IV tumors, respectively.<sup>12</sup> In the most recent standard risk (SR) SIOPEL trial SIOPEL 3SR (which included patients without HR features), the patients had 8%, 52%, and 40% PRETEXT I, II, and III tumors, respectively.<sup>13</sup> In the most current Children's Oncology Group trial AHEP0731, the surgical guidelines were structured according to PRETEXT. Resection at diagnosis was recommended only for patients with PRETEXT I and II tumors with a 1 cm radiographic margin from the middle hepatic vein, the retrohepatic inferior vena cava, and the portal bifurcation. Following neoadjuvant chemotherapy, conventional resection is recommended for patients with resolution of major vascular involvement and POSTTEXT I, II, or III group. POSTTEXT refers to the tumor burden after neoadjuvant chemotherapy.

When tumors remain unresectable after chemotherapy, various therapeutic approaches may be employed to facilitate resection. These include consideration of liver transplantation, aggressive nonanatomic resection with vascular reconstruction, and/or interventional embolization depending on the tumor extent and available expertise.

## Chemotherapy

Neoadjuvant chemotherapy allows for delayed resection of the primary mass in some patients with HB; however, certain tumors remain amenable to complete resection only via liver transplantation. Cisplatin is generally considered to be the most active chemotherapy agent in HB treatment and has significantly affected rates of surgical resection and overall survival and is administered alone or in combination with

other chemotherapeutic agents (with doxorubicin being the second most common agent utilized).<sup>14,15</sup> Of note, previous studies have not performed a direct comparison of cisplatin with doxorubicin to determine which is the more active agent in HB treatment. For more advanced HB (including tumors with vascular involvement and those that are PRETEXT IV or metastatic at diagnosis), treatment has been based on multi-agent chemotherapy with a cisplatin backbone. For patients with less advanced tumors (eg, tumors without significant vascular involvement), the aim has been to maintain overall survival while decreasing chemotherapy toxicity.

Comparison of different chemotherapeutic regimens has been difficult due to different staging systems, risk stratification schema, and surgical approaches utilized by cooperative groups. Resectability in less advanced tumors is often determined by the expertise, approach, and preference of the treating surgeon. In addition, in North America, the emphasis has been to resect at diagnosis when possible, whereas delayed resection has been advocated in European studies. Event-free survival in patients with HB not resected at diagnosis varies depending on additional prognostic factors as well as the different staging systems and surgical approaches but generally approaches at least ~65%–70% (Table 1). The upcoming international trial will be based on resection at diagnosis when possible and will utilize a single-risk stratification system. Nonetheless, general retrospective comparisons can be made between the different treatment regimens (Table 1).

Chemotherapy for unresectable HB in North America has historically been based on a cisplatin backbone in combination with 5-fluorouracil and vincristine (C5V) and, most

**Table 1** Resection rates and outcomes in patients with advanced HB

Time (location)	Study	Patient population	Chemotherapy	No of patients	Not resected at diagnosis, n	Eligible for delayed definitive resection <sup>a</sup> , n	Resected after neoadjuvant chemotherapy, n (%)	EFS <sup>b</sup>
1989–1992 (North America)	INT0098 <sup>2</sup>	Stage III or IV	Cisplatin 5-Fluorouracil Vincristine or cisplatin and doxorubicin	182	123	104	47 (45)	Stage III: 64% Stage IV: 25%
1998–2004 (Europe and International)	SIOPEL 3HR <sup>16</sup>	HR <sup>c</sup>	Cisplatin Carboplatin Doxorubicin	153	151	127	115 (91)	65%
2005–2009 (Europe and International)	SIOPEL 4 <sup>12</sup>	HR <sup>c</sup> or tumor rupture	Cisplatin Carboplatin Doxorubicin	62	61	55	52 (95)	76%

**Notes:** <sup>a</sup>This total excludes patients without data available for analysis. <sup>b</sup>Five years for INT0098 and 3 years for SIOPEL studies. <sup>c</sup>HR for SIOPEL studies: patients with PRETEXT IV tumor, extrahepatic abdominal disease, vascular invasion, low alpha fetoprotein, or metastatic disease.

**Abbreviations:** HB, hepatoblastoma; EFS, event-free survival; HR, high risk.

recently, addition of doxorubicin (C5VD) for upfront unresectable patients. In INT0098, 47 patients with unresectable HB (45% of those with tumors not resected at diagnosis and eligible for a delayed resection) underwent complete resection after neoadjuvant chemotherapy.<sup>9</sup> These patients received in a randomized manner either C5V or cisplatin/doxorubicin before the definitive surgery. On close inspection of the INT0098 results, the cisplatin/doxorubicin regimen was actually superior to C5V in terms of disease progression; however, due to excess toxicity, the eventual survival was not statistically different. Given that supportive care measures have improved since then, and with some favorable results from European regimens including doxorubicin, it was decided for the current trial (AHEP0731) that patients with stage III HB should have doxorubicin added to C5V (C5VD). Analysis of patients proceeding to conventional resection or liver transplantation after this new regimen is pending.

Chemotherapy for HB not resected at diagnosis in Europe has consisted of cisplatin alone for patients with SR HB (localized, PRETEXT I, II, or III tumors) or a combination with carboplatin and doxorubicin for patients with HR HB (PRETEXT IV, metastatic disease, or other HR features on SIOPEL IV).<sup>12,13,16</sup> In SIOPEL 3SR, 126 patients received either cisplatin monotherapy or cisplatin and doxorubicin with 95% and 93% of patients, respectively, able to undergo delayed complete resection.<sup>13</sup> In SIOPEL 3HR, 150 patients received either cisplatin, carboplatin, and doxorubicin with 56% able to undergo delayed conventional resection and 21% proceeding to liver transplantation.<sup>16</sup> The subsequent SIOPEL study for HR HB (SIOPEL IV) incorporated intensification of the timing of the cisplatin dosing in combination with carboplatin and doxorubicin.<sup>12</sup> In SIOPEL IV, 74% of patients were able to undergo delayed complete resection (35% with liver transplantation and the remaining 65% with conventional resection).

Taking into account all patients with unresectable HB, there is a subset of patients, as seen in SIOPEL 3SR, for whom less chemotherapy is indicated.<sup>13</sup> Acute and late toxicities from chemotherapy are significant for patients with HB. The common acute side effects include myelosuppression, malnutrition, febrile neutropenia, and neuropathy. The late effects of chemotherapy for HB include hearing loss, cardiomyopathy, nephrotoxicity, and second neoplasms. Further reduction in chemotherapy exposure with fewer agents and lower cumulative doses will be studied on the upcoming international trial for patients with less advanced HB not resected at diagnosis.

For the higher risk population with unresectable HB without metastatic disease, the optimal chemotherapeutic

approach remains to be determined. For patients with unresectable HB not amenable to conventional resection, liver transplantation is the mainstay for cure. Prolonged chemotherapy administration beyond four cycles in an attempt to proceed with conventional resection has been shown to be ineffective in increasing the ability to proceed to conventional resection and may induce drug resistance.<sup>17,18</sup>

## Surgical approaches

The recommendations for transplant used in the most recent cooperative group studies are: 1) tumor at diagnosis clearly involving all four sections of the liver, especially those with extensive multifocality as judged by MRI or CT angiography and 2) tumor location so close to both main portal vessels at the hilum of the liver and/or all three hepatic veins that it is unlikely that a tumor-free excision plane will be achieved without risking life-threatening hemorrhage. These patients should be identified early in their treatment, and their clinical course and imaging should be followed closely throughout their initial chemotherapy in consultation with a surgeon from a liver specialty center. An occasional patient with an extensively multifocal PRETEXT IV tumor or with tumor thrombosis in the main portal vein might be recommended for primary transplant with minimal preoperative chemotherapy.<sup>19</sup> The upcoming international trial for HB (Pediatric Hepatic International Tumor Trial) will incorporate risk stratification by the Children's Hepatic Tumors International Collaboration including surgical guidelines based on PRETEXT.

Multifocal PRETEXT IV HB in the absence of any metastatic disease after chemotherapy (POSTTEXT IV + multifocal/F – metastases/M) is a clear indication for liver transplantation. Clinicians should resist the temptation to intensify chemotherapy in a vain effort to avoid transplant because of the high likelihood of inducing tumor resistance to chemotherapy.<sup>17,18</sup> Apparent clearance of tumor nodules from one section of liver after preoperative chemotherapy should not distract from transplant because of the high probability of persistent microscopic viable neoplastic cells despite apparent radiographic clearance.<sup>10</sup> Children's Oncology Group and SIOPEL recommend transplant in these patients, although there are reports of successful piecemeal resections of such tumors.<sup>20</sup> The patients with large solitary PRETEXT IV tumors usually receive neoadjuvant chemotherapy, and many of these tumors may “downstage” to POSTTEXT III with clear retraction of the tumor from the anatomic border of one lateral section, allowing for performance of a trisectionectomy. A unifocal POSTTEXT IV tumor without metastatic disease is a clear indication for transplant.

In a subgroup of patients with PRETEXT II and III tumors, there will be major vascular invasion that does not clear with neoadjuvant chemotherapy. For patients with persistent vascular involvement of all three major hepatic veins, both portal veins, and/or the retrohepatic vena cava (POSTTEXT + venous involvement/V and/or + portal involvement/P), referral for nonconventional liver resection or liver transplantation is recommended. Resection in the face of major venous invasion runs the risk of leaving viable neoplastic tissue behind if the surgeon peels off viable tumor directly from the involved vein. Some have argued in favor of venous resection and reconstruction (“extreme” or “complex” resection) as opposed to transplant in these cases.<sup>21</sup>

Unresponsive or progressive metastatic disease in the face of neoadjuvant chemotherapy is a relative contraindication to transplant because even if the nodules can be surgically resected, microscopic foci of chemoresistant tumor are highly probable.<sup>22–24</sup> Lung metastases in a patient that seem to respond to chemotherapy, but which do not entirely clear, should be surgically resected.<sup>10,25</sup> Some have advocated sternotomy and bilateral lung palpation, rather than unilateral wedge resection, although this remains controversial.

## Interventional approaches

Interventional radiology is defined as the use of imaging techniques to guide a minimally invasive procedural intervention. Interventional techniques have long been utilized in pediatrics to obtain central venous access, image the vascular tree, obtain diagnostic tissue via needle biopsy, drain fluid collections, and perform genitourinary and gastroenterology procedures.<sup>26,27</sup> While the use of interventional techniques to treat adult oncology patients is well established, the translation of these techniques to the pediatric realm continues to evolve. This evolution has been limited by the slow development and approval of new devices for use in children, patient size limitations, and the hesitation to test novel treatment approaches in pediatric patients.<sup>28</sup> There are numerous interventional radiology modalities available for the treatment of oncology patients, particularly those with liver tumors, with a range of experiences already published in the adult literature.<sup>29–32</sup> More recently, these interventional approaches have been introduced to the pediatric population as detailed in the following.

Transarterial chemoembolization (TACE) has been widely used in adult hepatocellular carcinoma (HCC) and secondary (colon cancer) liver metastases. It provides the advantage of concentrated chemotherapy administration, increased dwell time, and decreased systemic toxicity.<sup>29</sup> For hepatic metastases and HCC, TACE can not only be used in combination with radiofrequency ablation (RFA) to treat diffuse disease

but may also serve as a neoadjuvant approach to improve the feasibility of local control options such as surgical resection or orthotopic liver transplant.<sup>30,31,33</sup> TACE and RFA have been trialed in pediatric oncology patients, with patient selection and suitability for intervention extrapolated from the adult experience. Presurgical TACE has been used for pediatric HB in an attempt to reduce tumor volume and aid with surgical intervention. Published series are of various sizes and document a combination of chemotherapeutic agents used. However, nearly all cases demonstrate reduction in tumor size and resultant intratumoral necrosis and decreased intraoperative bleeding. While many publications reported increased ease of surgical resection, not all cases resulted in a complete resection.<sup>34–36</sup>

High-intensity frequency ultrasound is a technique that allows for the focal delivery of high-intensity ultrasound beams directly to the tumor to enhance cell death. High-intensity frequency ultrasound has been trialed with variable success, in combination with TACE, in the pediatric HB patients with upfront unresectable or metastatic tumors.<sup>37,38</sup>

Transarterial radioembolization with yttrium-90, while routinely pursued in the adult community, is relatively new to the pediatric community with experiential case reports limited to the palliative setting.<sup>39</sup>

While RFA has been used extensively in adult liver tumor patients, it has been trialed sparingly in pediatric patients. RFA has the benefit of providing immediate pain relief with a more targeted focus than conventional radiotherapy.<sup>40</sup> Its use has been reported successfully, albeit for small numbers, in patients with recurrent HB and Wilms tumor liver metastases and in a Phase I/pilot study for all solid tumors in which one patient with fibrolamellar HCC underwent multiple procedures.<sup>40–43</sup> Postprocedural pain was moderate with prolonged hospitalization more frequently reported. Serious complications were more commonly seen secondary to pulmonary RFA for lung lesions.

## Radiation therapy

Few cases have been reported in the literature incorporating external beam radiation therapy for patients with unresectable HB. Radiation therapy is not indicated during the initial treatment of HB, and its role in recurrent HB or in HB not resectable by other means (including patients who are not candidates for liver transplantation) remains to be determined.<sup>44–46</sup>

## Stem cell transplantation

Autologous stem cell transplantation has been explored for patients during upfront treatment as well as in relapse; thus far, it has not been proven beneficial.<sup>47,48</sup> The specific role of

stem cell transplantation in rendering HB tumors resectable remains undetermined but is likely to add toxicity in patients who may otherwise be candidates for liver transplantation instead of conventional resection.<sup>49</sup>

## Conclusion

For patients with HB, resection of the primary tumor (and metastatic sites where applicable) is the goal for curative treatment. When tumors are deemed to be unresectable at diagnosis, chemotherapy can be utilized to render most of them resectable. For patients without active metastatic disease but with primary tumors not amenable to conventional resection, liver transplantation is indicated. It stands to reason that for patients with upfront unresectable disease, interventional techniques may serve as a promising option to reduce tumor size, decrease systemic toxicity, and increase ease of tumor resectability. The upcoming international trial for HB aims to decrease toxicity from chemotherapy for patients with unresectable HB while maintaining good survival.

## Disclosure

The authors report no conflicts of interest in this work.

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