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Advanced Hepatoblastoma: A Review of Current Management Strategies

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Abstract

Hepatoblastoma (HB) is an embryonal tumor comprising nearly 1% of all pediatric malignancies and more than 90% of all liver tumors in patients under 5 years of age. The incidence of HB is increasing due to the rising prevalence of very low birth weight infants, a strong risk factor. Many cases are linked to congenital syndromes such as Beckwith-Wiedemann, Familial Adenomatous Polyposis, and trisomy 18. Wnt pathway activation and a concominant rise in intracytoplasmic levels of beta-catenin are the biochemical hallmarks of tumorgenesis. Innovative chemotherapy and medical advances has increased survival rates over the years to upwards of 80%. Staging systems such as PRETEXT and SIOPEL serve to guide therapy. Various chemotherapeutic regimens have been proposed with platinum based therapy as the mainstay of all treatment regimens. High risk tumors including those with PRETEXT 4, extrahepatic disease, or low AFP levels pose a particular challenge to treatment. Despite advances in medical therapy, surgery still remains at the forefront as a definitive cure, especially with advanced disease. Principles of general surgical liver resection based on segmental anatomy are applied with goal of achieving an en-bloc R0 resection. POST-TEXT IV disease is best managed with total hepatectomy and liver transplant. The SIOPEL 4 guidelines have outlined basic principles for utilization of liver transplant, which has shown to improve outcomes in patients with unresectable disease following neoadjuvant chemotherapy. Candidates eligible for liver transplant should be referred to a tertiary transplant center no later than 2 cycles following chemotherapy. Relapsed HB poses a challenge for the treating clinician. High dose chemotherapy (HD-CT) is a sensible option; however, there is no consensus on the optimal regimen currently. Despite medical research and development of novel chemotherapeutic regimens, the outcome for children with relapsed disease remains poor.

Keywords: Hepatoblastoma; Computed tomography; Liver transplant

Abbreviations: HB: Hepatoblastoma; HD-CT: High Dose Chemotherapy; VLWB: Very Low Birth Weight; IARC: International Agency for Research on Cancer; BWS: Beckwith Weideman Syndrome; FAP: Familial Adenomatous Polyposis; GSK-3β: Glycogen Synthase Kinase 3β; TERT: Telomerase Reverse-Transcriptase; AFP: Alpha-Fetoprotein; US: Ultrasound; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; COG: Children's Oncology Group; PRETEXT: Pretreatment Extent of Disease; LTX: liver transplant; TXP: Indications for Liver Transplant

Epidemiology and Risk Factors

Hepatoblastoma (HB) is the most common primary tumor of the liver in the pediatric population, accounting for 80% of all pediatric liver cancer, and 91% of liver cancer in patients younger than 5 years of age [1-3]. It comprises 1% of all pediatric malignancies, and approximately 100 new cases are diagnosed in the US each year [4]. With an incidence of 1.8 per million in children 18 years of age and under, it occurs more frequently in age groups <1 year and 1 – 4 years, with an incidence of 9.8 and 6.1 per million respectively [5]. Incidence has doubled since 1975, and continues to increase at a rate of 1.2–1.5 cases per million per year [4]. HB has a slight predilection for males, who also have a lower 5 yr survival rate of 78% when compared to 84% for their female counterparts [6].

The most documented and potent risk factor for HB is very low birth weight (VLWB), or <1500g, with relative risks reported from 16 to 70 [7-11]. The increasing incidence of HB may be related to the rising prevalence of immature infants, however preterm birth (<37 weeks) was not an independent risk factor for HB in any of the studies after adjustment. The association between HB and VLBW indicates either a patho-physiological overlap, or that therapeutic interventions for VLBW infants are causative. It is postulated that oxygen therapy, medications including furosemide, radiation, total parenteral nutrition, and plasticizers may be responsible for HB as they are shown to be carcinogenic [11,12]. However, this is difficult to prove given that VLBW infants are intrinsically sicker and are more likely to necessitate these therapies.

Maternal smoking has been well studied as a potential risk

factor for HB. The International Agency for Research on Cancer (IARC) has classified hepatoblastoma as a tobacco-related cancer [13]. Yet only 3 of 7 case-control studies have shown maternal smoking to be an independent risk factor for HB when adjusting for VLBW [10,14-18]. What is not debated is that maternal smoking is associated with VLBW [19] and therefore increases risk of HB. Maternal hypertension and infants conceived with use of assisted reproductive technology have also been shown to be associated with VLBW [10,20-22].

Other risk factors for HB that have been implicated include multiple births, small for gestational age, pre-eclampsia, and maternal age less than 20 years [9,23]. One study implicated higher rates of HB in infants of mothers exposed to metals (OR = 8.0, P = 0.01), petroleum products (OR = 3.7, P = 0.03), and paints or pigments (OR = 3.7, P = 0.05) [24].

A majority of HB cases are sporadic, however, many cases have been linked to syndromes such as Beckwith Weideman Syndrome (BWS), Familial Adenomatous Polyposis (FAP), and trisomy 18, as well as congenital anomalies. A case–control study conducted through the Children's Oncology Group found a significant association between HB and kidney and bladder abnormalities (OR=4.75; 95%CI: 1.74–13) [25]. Elevated but non-significant ORs were found for spinal anomalies including spina bifida, and large or multiple birthmarks. In fact, the incidence of congenital anomalies in HB patients has been reported up to 50%.

Pathology

HB is an embryonal tumor that originates from the hepatoblast, a hepatic progenitor cell. A range of epithelial and mesenchymal patterns of differentiation defines the different histologic subtypes, with some variants resembling specific stages of liver development [26]. In March 2011, The Liver COG Committee held an international symposium to develop a consensus classification system to define the histologic subtypes and standardize treatment algorithms [27]. These subtypes consist of: epithelial only, which includes pure fetal or mixed fetal/embryonal histology; and mixed epithelial/mesenchymal. Other components may be seen which include macrotrabecular clusters, undifferentiated small cells, cholangioblastic cells, stromal derivatives, and teratoid features. Pure fetal histology is defined by clusters of hepatocytes with two cell thick laminae, recapitulating those of the fetal liver. They can range from well-differentiated with low mitotic activity to anaplastic with abnormal mitosis. Well-differentiated pure fetal subtype offers a favorable prognosis and is found in approximately 7% of all HB [26]. Embryonal histology is defined by primitive elements, high nuclear-to-cytoplasmic ratio, and is typically arranged in ribbons, rosettes and papillary formations. Undifferentiated small cells are found in 5% of HB and are associated with particularly aggressive behavior and resistance to chemotherapy [28].

HB more commonly involves the right lobe of the liver. On gross pathology, it appears as a tan, bulging mass with a pseudocapsule. Although it may appear well-circumscribed, microvascular invasion is frequently seen beyond the extent of the pseudocapsule.

Beta-catenin and the Wnt Signaling Pathway

Beta-catenin has been established as an important player in carcinogenesis [29]. In comparison to normal hepatocytes, HB cells contain elevated cytoplasmic levels of beta-catenin. Beta-catenin is normally located at the plasma membrane of epithelial cells, along with with E-cadherin, alpha-catenin, and alpha-actinin, occuring in adherens junctions, and having a significant impact on cell-cell adhesion [30]. It also has an established role in signal transduction as a downstream component of the Wnt signaling pathway, facilitating stem cell maintenance, differentiation, proliferation, and metabolic zonation of the liver [31-34].

In the absence of Wnt signaling, β-catenin is phosphorylated by a destruction complex consisting of APC, Axin, and Glycogen Synthase Kinase 3β (GSK-3β), and targeted for the proteasome where it is degraded [35]. Activation of the Wnt pathway prevents phosphorylation of β-catenin, resulting in its accumulation in the cytoplasm and subsequent translocation to the nucleus, where it interacts with the high mobility group transcription factors Tcf/LEF. This interaction leads to activation of oncogenic target genes that regulate cellular growth, apoptosis, angiogenesis, and invasion [33-37].

In the developing liver, suppression of Wnt signaling is required for endodermal proliferation. This is later followed by activation of Wnt to enhance liver growth [37,38]. Aberration of Wnt signaling following hepatoblast differentiation leads to interference of hepatic morphogenesis and cell death [39].

It has been observed that b-catenin is over expressed in a variety of tumor components at various stages of differentiation including mesenchymally-derived cells [40]. This indicates that uninterrupted b-catenin activation interferes with signaling that differentiates tissue types at early stages of hepatogenesis. This also suggests that epithelial and mesenchymal derivatives seen in mixed HBs may develop from the same pluripotent stem cell [41].

Exon 3 of the b-catenin gene has four serine and threonine residues at its N-terminus that act as targets for phosphorylation by GSK-3β. The frequency of mutations at this locus (CTNNB1) in HB is reported to be 48 – 89%, implicating Wnt signaling as an integral component in the pathogenesis of sporadic hepatoblastoma [40,42-46]. The role of the Wnt pathway is further implicated by the over expression of the Wnt antagonists Nkd-1, B-TrCP, and AXIN2 [47]. However, intracellular accumulation of b-catenin is seen in HB cells that do not possess a mutation at CTNNB1, indicating that other mechanisms may be involved [43]. In recent studies, telomerase activation by telomerase reverse-transcriptase (TERT) promoter mutations was seen in HB cells that did not possess CTNNB1 mutation, and conferred a poorer prognosis [48,49]. Other reported mutations include AXIN1/AXIN2 loss of function, ubiquitin ligase complex mutation, Notch activation, p53 mutation, microsatellite instability, HGF/C-Met phosphorylation of b-catenin, and IGF2/H19 hypermethylation [26,45,50-55].

Syndromic Hepatoblastoma

The association between familial adenomatous polyposis (FAP) and HB is well documented. The risk of HB is 750 – 7500

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times higher in children of FAP kindred, and the incidence of HB in FAP patients is roughly 2.5% [56-59]. While sporadic HB is slightly more common in boys, HB associated with FAP is primarily seen in boys [60-61]. Prognosis is similar between sporadic and syndromic cases [61].

FAP is an autosomal dominant syndrome characterized by a mutation in the APC gene on the long arm of chromosome 5 (5q21). The APC gene is a tumor suppressor gene that plays a key role in regulating levels of b-catenin [61]. While sporadic cases are due to mutations in the β-catenin gene that disrupt the wnt pathway, FAP associated HB stems from a mutation of the APC gene. In fact, multiple studies found no APC mutations in patients with the sporadic type [62-63]. Interestingly, these APC mutations are found outside the hotspot cluster region for FAP, almost always occurring 5' to this hotspot [61,63].

While there are no standard guidelines for screening FAP patients for HB, it is universally accepted that infants with FAP should have regular liver screening. Kennedy et al. recommends liver ultrasound and serum AFP levels by 6 months of age, repeated every 6 months until 6 years of age. They also recommend that children with HB should undergo genetic testing to look for an APC mutation [59].

Beckwith-Wiedemann syndrome (BWS) is characterized by various anomalies including abdominal wall defects, diaphragmatic defects, visceromegaly, gigantism, hemihypertrophy, microcephaly, and absent gonads [64]. The link between BWS and intra-abdominal malignancy is well described, frequently associated with Wilms tumor, hepatoblastoma, adrenal cortical carcinoma, neuroblastoma, and rhabdomyosarcoma [65]. DeBraun et al found that the relative risk of HB in BWS patients is >2000, and that hemihypertrophy was the only clinical feature associated with an increased RR of cancer [66].

BWS results from mutations or epigenetic events involving imprinted genes at chromosome 11p15. In HB patients with BWS, the genetic culprit appears to be loss of imprinting of IGF2 [67].

Again, there are no standard guidelines for screening BWS patients for HB. Clericuzio et al. recommends liver ultrasound and serum AFP levels every 2 – 3 months until 4 years of age [68].

Tumor Biomarkers

Alpha-fetoprotein (AFP) is a serum protein synthesized by fetal liver cells (Table 1). It is well known as a nonspecific biomarker found in a spectrum of germ cell and liver tumors, as well as non-carcinogenic liver pathology. AFP levels are significantly elevated in HB, often in the 100,000 to 300,000 mcg/ml range [69]. Its poor specificity precludes its use as a diagnostic tool, and mainly limits its value to therapeutic response. However, studies are finding its potential as a pretreatment prognostic indicator. The German Cooperative Pediatric Liver Tumor Study observed a relationship between extremes of AFP levels (<100 or >1,000,000 mcg/ml) and poor prognosis in HB.

Aside from AFP, there are currently no standard biomarkers utilized in patients with HB. The SIOPEL trials have allowed for the investigation of potential candidates, enabling researchers to analyze large numbers of tumor samples for prospective markers of diagnosis and prognosis. Purcell et al found increased expression of Cyclin D1 and Ki-67 in HB patients with poorer outcomes, as well as a correlation between Cyclin D1 and mixed epithelial/mesenchymal histology [70]. Murphy et al found that CBP/P-300 interacting transactivator 1 (CITED1), a transcriptional co-activator that is undetectable in developed livers, is over expressed in mixed fetal/embryonal histology, and is therefore associated with a poorer prognosis [71]. Lee et al showed 100% sensitivity for increased expression of high mobility group AT-hook 2 in patients with HB [72]. While it is clear that headway is being made, more research is needed before a practical and reliable marker will impact diagnostic and therapeutic strategies.

Table 1: Diagnostic Studies.

STUDY	FINDINGS
Serum Analysis	AFP: >100,000 CBC: normocytic anemia, thrombocytosis LFTs: normal or elevated
Ultrasound	calcifications, necrosis, hepatic or portal venous invasion
CT Scan	Heterogenous enhancement Hypoattenuated compared to liver parenchyma Peripheral enhancement during arterial phase

Presentation and Diagnosis

Patients with HB are commonly asymptomatic at the time of diagnosis. Symptoms indicating advanced disease include anorexia and severe osteopenia. Patients with syndromic HB may show sequelae of FAP, BWS, etc, prompting the workup for HB. On exam, patients may have a palpable abdominal mass.

Complete blood count often shows a normocytic anemia with thrombocytosis [69]. Liver function tests are elevated in a minority of patients. As mentioned earlier, while AFP levels are not specific for HB, they will likely be elevated.

Imaging techniques used to aid in the diagnosis of HB include ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). There is a paucity of data regarding which technique is superior and therefore all 3 are commonly used for each patient. The first imaging modality typically obtained is the least invasive, US. On US, HB can appear in many forms, ranging from a solitary mass to multiple nodules throughout the liver. Calcifications and necrosis may be present but are not specific to HB. Factors that favor malignancy include detection of hepatic and portal invasion and the presence of high velocity flow within the tumor on Doppler [73,74]. US are also useful in staging as it is superior to other modalities in distinguishing small peritoneal nodules from peripheral liver nodules.

CT with portal and venous phase contrast is a suitable method for delineating the tumor, and also has the advantage of detecting pulmonary metastases. As is the case with US, HB may appear in many forms on CT. HB tumors typically enhance heterogeneously and overall enhance less than surrounding liver [74]. Peripheral enhancement during arterial phase may also be present.

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MRI/MRA is usually the preferred method for delineating tumor margins and vascular anatomy. Appearance on MRI can vary depending on histologic subtype. Epithelial derived tumors can appear homogenous where as mixed epithelial-mesenchymal tumors are typically heterogenous [74]. MRA is excellent at defining vascular anatomy and invasion, which is vital for surgical planning.

Staging

There are two complementary staging systems currently in use for patients with HB. The PRETEXT staging system as developed by the SIOPEL trial is used to stage the tumor before any treatment is initiated [75]. This staging system is outlined in the figure below (Figure 1). The Children's Oncology Group (COG) staging system is utilized after surgical resection. Stage I signifies negative surgical margins, stage II has residual microscopic disease at the margins, stage III represents grossly positive margins or regional lymph node involvement, and stage IV indicates metastatic disease.

Treatment & Outcomes

History

Survival rates for hepatoblastoma (HB) has significantly increased over the past several decades to upwards of 80% due to innovative medical advances and combined multidisciplinary efforts. Although surgical resection alone was once thought to be curative therapy, more than half of the patients have unresectable tumors at time of diagnosis.

Chemotherapeutic strategies depend on surgical resectability, stage and the presence of metastatic disease. Pretreatment extent of disease (PRETEXT) developed by the International Childhood Liver Tumor Strategy Group (SIOPEL) served to guide therapy for their first trial, and was revised in 2007 for the SIOPEL 3 trial.

Various chemotherapeutic agents have been utilized for the treatment of HB, with the most common being platinum based agents. The introduction of cisplatin and doxorubicin in the 1980's revolutionized the treatment of HB and was noted to have a profound impact on survival. Nearly 30 years later, cisplatin continues to remain one of the most effective chemotherapeutic agents. It is usually administered in doses of 80-100mg/m^2 over 24 hours every 14, 21, or 28 days for 4-8 cycles. Doxorubicin is the second most common agent administered after cisplatin. It is typically dosed at 30mg/m^2/dose for 2-4 days. According to the 1990 SIOPEL-1 trial, patients who received PLADO (4 courses pre operative cisplatin and doxorubicin) had a 5 year survival of 75% and event free survival of 66%. Other non-platinum based chemotherapeutic agents include flurouracil, vincristine, and irinotecan.

PRETEXT/POST-TEXT	Definition
I	One section involved
	Three adjoining sections are tumor free
II	One or two sections involved
	Two adjoining sections are tumor free
III	Two or three sections involved
	One adjoining section is tumor free
IV	Four sections involved
Annotation:	
V	Venous involvement, V, denotes vascular involvement of the retrohepatic vena cava or involvement of all three major hepatic veins (right, middle, and left)
P	Portal involvement, P, denotes vascular involvement of the main portal vein and/or both right and left portal veins
E	Extrahepatic involvement of a contiguous structure such as the diaphragm, abdominal wall, stomach, colon, and so on.
M	Distant metastatic disease (usually lungs, very rarely bone, or brain)
C	Caudate lobe
F	Multifocal tumor nodules
R	Tumor rupture prior to diagnosis

POST-TEXT, posttreatment extent of disease; PRETEXT, pretreatment extent of disease.

Figure 1: POST-TEXT and PRETEXT diseases.

Current Treatment

For patients with PRETEXT 1, 2 or 3 without vascular involvement or extrahepatic disease, the SIOPEL 3 trials recommend cisplatin monotherapy as standard of care (Table 2). Four cycles of neo adjuvant chemotherapy are administered, followed by surgical resection and 2 cycles of adjuvant chemotherapy [76]. Doxorubicin is not required as part of therapy in patients with low risk hepatoblastoma according to COG and SIOPEL trials [77].

Patients with PRETEXT 4 with extrahepatic disease, low alfa-fetoprotein (AFP <100 ng/mL) fall into the category of high risk tumors. These patients pose a particular challenge to treatment. Although Doxorubicin can be safely omitted in children with standard risk hepatoblastoma, this subset of patients should receive treatment with Doxorubicin. Based on the SIOPEL-4 protocol, this includes weekly PLADO therapy. Given the high dose of chemotherapy, particular attention should be given to assess for potential drug induced toxicity [77,78]. Platinum based chemotherapeutic agents pose a potential risk for the development of ototoxicity. The role of amifostine was recently studied in a randomized control trial. The authors concluded that amifostine failed to significantly reduce the incidence of platinum-induced toxicities in patients with HB [79].

Indications for Surgical Therapy

Despite novel chemotherapeutic agents, surgery still remains at the forefront for achieving definitive cure especially in patients with advanced disease. The general principles of liver resection are applied based on segmental anatomy, and all involved

Table 2: Therapy Guidelines.
Major venous involvement: invasion of inferior vena cava, hepatic or portal venous system.

	Indications	Contraindications
Chemotherapy	Cisplatin monotherapy: PRETEXT I-III Cisplatin + Doxorubicin: PRETEXT IV or extrahepatic disease	well differentiated fetal type tumor
Partial Liver Resection	PRETEXT I, II PRETEXT III after neoadjuvant chemotherapy POST TEXT I-III (without major venous involvement)	see transplant indications
Transplant	PRETEXT IV POST TEXT III with major venous involvement POST TEXT IV	lung metastases at presentation persistent extrahepatic disease following neoadjuvant chemotherapy

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segments involving tumor must be resected en bloc to achieve an R0 resection. POST-TEXT evaluation based on contrast enhanced computed tomography (CT), ultrasound and/or magnetic resonance imaging (MRI) allows for appropriate pre op planning, ensuring the optimal surgical procedure is carried out.

PRETEXT I and II tumors are resected via a segmentectomy or lobectomy per the ongoing AHEP-0731 trials [80,81]. POST-TEXT I or II tumors, sectionectomy and hemihepatectomy are applied. POST-TEXT III tumors are typically treated with trisectionectomy often referred to as hemihepatectomy. These radical resections have expanded the surgeon's ability to perform resections without a total hepatectomy. In one series of 14 children with POST III and IV tumors who underwent aggressive resection resulted in 88% 5 year survival and 75% event free survival therefore precluding liver transplantation.

POST-TEXT IV tumors usually indicated advanced disease with 4 sections of the liver involved. These patients are good candidates for total hepatectomy and liver transplant (LTX) [80,81]. However, in one series of 14 children with POST III and IV tumors who underwent aggressive resection resulted in 88% 5 year survival and 75% event free survival [82].

Of note, microscopic residual disease following resection is not indicative of overall survival [83].

Indications for Liver Transplant (TXP)

The utilization of orthotopic liver transplant has markedly improved outcomes for those with unresectable disease following chemotherapy. Patients undergoing liver transplant will require lifelong immunosuppression, therefore candidates must be evaluated with prudence. The SIOPEL-4 guidelines have outlined basic principles and indications for liver transplant. Patients with large as well as multifocal PRETEXT-IV tumors tend to fare the best when treated with transplant. Those with multifocal disease benefit the most from a total hepatectomy followed by liver transplant in order to remove all remaining gross and microscopic disease. However, much is to be said regarding the use of liver transplant in patients with PRE-TEXT IV multifocal disease, because some authors believe this subset of patients can be down staged successfully with neoadjuvant chemotherapy [84]. Centrally located unifocal tumors involving the hilar structures or main hepatic veins will still remain unresectable despite a favorable response to chemotherapy therefore deeming them suitable candidates for transplantation. Under no circumstance should neoadjuvant chemotherapy be prolonged to obviate the need for transplant. Candidates should be referred to a liver transplant center no later than 2 cycles following chemotherapy. Based on the current COG guidelines, pulmonary metastesectomy must be peformed for residual nodules prior to transplantation to clear all extrahepatic disease.

Relapsed Hepatoblastoma

Children with relapsed or progressive HB should be treated with combination of chemotherapy and surgery. Generally speaking, the same chemotherapy agents used as first line treatment should not be used when treating recurrent disease. Although many agents exist for the treatment of progressive HB, only cisplatin, doxorubicin and carboplatin have been tested as single agents [85]. Doxorubicin can be safely omitted when treating standard risk HB according to SIOPEL and COG trials; however it plays a pivotal role in the treatment of high-risk HB [86]. Although the incidence of carboplatin associated nephrotoxicity and ototoxicity is lower than cisplatin, its efficacy in terms of rescue is diminished when compared to patients treated with cisplatin.

According to SIOPEL 2 and 3 protocols, of the 17 patients treated with cyclophosphamide monotherapy, only one patient showed an appropriate response, making single agent cyclophosphamide ineffective in the treatment of recurrent disease.

High dose chemotherapy (HD-CT) is a feasible option for patients with relapsed disease. Multiple trials have been conducted utilizing HDCT, however to date no consensus on an optimal regimen has been defined. Its role in the treatment of relapsed disease remains unknown and its efficacy yet has to be proven [87].

Complete surgical resection is imperative for cure. However, previous surgeries for resection of their primary tumor can become challenging as scar tissue formation can distort tissue planes for appropriate dissection. It may present as isolated lung or concurrent relapse in lungs, liver and other organs. Pulmonary lesions may be unilateral, bilateral or multiple. As discussed previously, the role of neoadjuvant chemotherapy and isolated pulmonary metastectomy is well defined. However its role is unclear in the setting of recurrence [88]. Prior to liver transplantation, all extrapulmonary and extrahpeatic lesions must be resolved. Studies have shown a higher overall survival in patients undergoing primary liver TXP than those who undergo the so called 'rescue' liver TXP with post op survival 82 percent and 30% respectively. According the SIOPEL-1, the 10 year overall survival for the 7 patients who underwent primary liver TXP was 85% when compared to the 5 patients who underwent liver TXP following primary resection had a 10 year overall survival of only 40% [89].

Despite advances in medical research outcomes for children with relapsed disease remains poor. The development of novel chemotherapeutic agents has shown potential to improve treatment; however its role in the treatment of this type of cancer remains unknown.

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