MINI-REVIEW

Hepatoblastoma in children

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Summary Hepatoblastoma (HB) is the most common malignant tumor of the liver in children in countries where hepatitis B is not endemic, and this has also been the case in Taiwan since nationwide hepatitis B vaccinations were implemented in 1984. The outcome of HB has become much better in the past two decades because of improved imaging modalities, adjuvant and neoadjuvant chemotherapy, and technical improvements in liver resection and liver transplantation. In this mini-review, the current strategy of HB treatment as reported in the literature will be described.

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1. Introduction

Hepatoblastoma (HB) is the most common malignant liver tumor in children, with an incidence of 0.7 to 1 per million children under 15 years of age in Western countries.1 In Taiwan, the incidence of HB is higher than that of hepatocellular carcinoma, and it has become the most common malignant tumor in children in the past two decades after nationwide hepatitis B vaccinations were implemented in 1984.2

Although the outcome of HB was poor three decades ago, the long-term survival rates today have improved, reaching 75–80%, largely because of advances in chemotherapy and better surgical decision-making.3 However, whereas complete surgical resection remains the most important intervention required to achieve long-term cure, tumors are resectable when they are diagnosed in only 60% of patients that present with tumors.4 For those patients with initially unresectable tumors, adjuvant chemotherapy and liver transplantation have expanded the scope of treatment alternatives to achieve the goal of curative therapy.5

2. Epidemiology and incidence

HB is the most common hepatic malignancy in children, accounting for nearly 80% of all malignant liver tumors, and...
typically presents itself before the child is 3 years of age with an abdominal mass, failure to thrive, and anemia. Boys are affected more commonly than girls, with a male:female ratio ranging from 1.2:1 to 3.6:1. In one study, the mean age at diagnosis was 19 months, and the median age was 16 months.

3. Histology

HB is mainly divided into two histologic types: epithelial, accounting for 56% of cases, and mixed epithelial/mesenchymal. The epithelial type can be further divided into fetal (31%), embryonal (19%), macrotrabecular (3%), and small-cell undifferentiated subtypes (3%). It has been observed that the subtypes have an effect on the prognosis, with the pure fetal type having the most favorable outcome and the small-cell undifferentiated type having the worst.

4. Associated risk factors

Although most cases of HB are sporadic without any associated anomalies, some associated risk factors have been reported, such as parental smoking, Beckwith–Wiedemann syndrome, familial adenomatous polyposis, and low birthweight. In our own experience, twins seem to have a higher incidence of HB in one of the twins than in the other (not yet reported).

5. Clinical picture

Patients with HB often present with an asymptomatic abdominal bulging mass found incidentally. Anorexia, weight loss, abdominal pain, and emesis are other presenting symptoms that indicate more advanced disease. The right lobe of the liver is affected more commonly than the left, and in 35% of patients there is bilateral involvement. Around 20% of patients present with metastasis, most in the lung at the time of diagnosis.

Laboratory findings typically show a mild elevation of liver enzymes. Very high levels of serum alpha-fetoprotein (AFP) are noted in over 90% of patients, the level often being higher than 1×10⁵ μg/L. AFP is an excellent tumor marker that not only reflects the extent of the disease, but also is very useful for monitoring both the effect of ongoing therapy and tumor recurrence at an early stage.

6. Staging

Two staging systems are commonly used. A decision to use the old system (the Children’s Cancer Group or Pediatric Oncology Group system) is based on the findings at surgery or after surgery, and thus greatly depends on the surgeon’s surgical technique. In this system, Stage I refers to complete resection with negative margins, Stage II to gross resection with microscopically positive margins, Stage III to gross residual disease after attempted resection or biopsy only, and rupture of the capsule, and Stage IV to distant metastasis.

The other system is the PRETEXT (Pretreatment Extension) system, designed by the International Childhood Liver Tumor Strategy Group (SIOP-EL) and with good interobserver reproducibility and good prognostic value. The PRETEXT system has been made more accurate by advanced imaging facilities such as computed tomographic angiography and magnetic resonance imaging. This system has been evolving for 20 years, and the updated PRETEXT staging is described in the 2005 report.

The PRETEXT staging system is based on Couinaud’s system of segmentation of the liver, which groups the liver into four sections: Segments 2 and 3 (left lateral section), Segments 4a and 4b (left medial section), Segments 5 and 8 (right anterior section), and Segments 6 and 7 (right posterior section). The term “section” is used here (where other authors use “segment” or “sector”) to avoid terminologic confusion. In the original system, the caudate lobe (Segment 1) was ignored. Determination of the PRETEXT stage takes into consideration the involved sections not only prior to, but also after resection. For example, if the tumor involves only the left medial section, the PRETEXT is Stage II rather than Stage I because hepatectomy will also resect the left lateral section. This number roughly estimates the difficulty of the surgical resection.

In addition to describing the intrahepatic extent of the primary tumor(s), the PRETEXT system includes “additional criteria” that assess the involvement of the inferior vena cava or hepatic veins (designated V), the portal vein (P), extrahepatic abdominal disease (E), and distant metastases (M). The purpose of these criteria, although confusing, was to clarify the criteria for “extrahepatic” disease and to improve our ability to identify prognostic imaging findings and refine risk stratification. Therefore, the original SIOP-EL risk stratification system for HB has been modified in the protocols for current SIOP-EL studies.

7. Treatment

Although complete surgical resection provides the best outcome and is the ultimate goal of therapy, the addition of chemotherapy has changed treatment from surgery alone to a multimodal approach. Chemotherapy alone, and later with a good surgical technique, has improved survival in patients who in the past had unresectable or metastatic disease by reducing the tumor size and permitting complete tumor resection or transplantation. Our own data (part of the data published) showed that the 3-year survival rate for HB increased from zero to 55% and 91% for the periods 1978–1990, 1991–2001, and 2002–2010, respectively.

Chemotherapy is effective as both an adjuvant and a neoadjuvant treatment by separating the tumor from the surrounding vascular structure and thus decreasing the rate of incomplete tumor resection. Cisplatin, vincristine, 5-fluorouracil, cyclophosphamide, and doxorubicin are among the most useful chemotherapeutic agents.

The recommended algorithm in the management of HB, utilizing a combination of conventional resection, chemotherapy, and transplantation proposed by Tiao et al. However, there are several questionable points in this algorithm. First, what is the definition of a so-called resectable tumor? Second, is getting tissue proof necessary for an unresectable tumor before chemotherapy? Third, is chemotherapy better for difficult but resectable tumors before resection? Fourth, should more cycles of
chemotherapy given if the tumor is still considered unresectable after four cycles of chemotherapy? Last, is it necessary to give two more cycles of chemotherapy after liver transplantation?

As to the first controversial point, PRETEXT Stage I tumors are resectable for most surgeons, but resection of Stage II is dependent on the surgeon’s ability. A unifocal, centrally located tumor in Stage II involving the main hilar structures should be considered unresectable. For Stage III/IV disease, chemotherapy is always recommended prior to any trial of resection. Although complete resection is still possible after chemotherapy if the tumor remains in Stage III/IV,20 this depends on the surgeon’s ability, and liver transplantation is recommended for an unresectable Stage III/IV tumor21 because the outcome of rescue liver transplantation is poor.

As regards the second point, although obtaining tissue proof prior to chemotherapy via either a percutaneous route or an open method is safe, it is not always necessary. Patients with a low AFP level, or older children in particular, who are hepatitis B carriers, should have tissue proof prior to chemotherapy.

As for the third point, although some surgeons favor chemotherapy prior to resection even if the tumor is resectable,22 our personal experience leads us to prefer Tiao et al’s protocol,23 although resectability should be very clear. Heroic attempts at partial hepatectomy are discouraged because chemotherapy is effective for downstaging most HBs.

For the fourth point, we prefer two more cycles of chemotherapy for any tumor with equivocal resectability prior to making a decision for resection or liver transplantation if the tumor is susceptible to chemotherapy, as manifested by decreasing AFP levels or a reduction in tumor size. Of course, we should keep the possibility of chemoresistance of tumor in mind when dealing with such cases.

For the final point, most transplant surgeons prefer post-transplant chemotherapy,24 and, in general, this has been tolerated well in most post-transplant patients,25 although the benefit has not yet been proven, and post-transplant chemotherapy should be tailored to the individual child.

Persistence of viable extrahepatic deposits after chemotherapy that are not amenable to surgical resection is the only absolute contraindication for liver transplantation. Macroscopic venous invasion (portal vein, hepatic vein, and vena cava) is not a contraindication if en bloc complete resection can be performed. Patients with incomplete tumor resection after partial hepatectomy or intrahepatic relapse can have so-called rescue liver transplantation, but the survival rate is much lower than in primary liver transplantation.5 Patients with lung metastasis at presentation should not be excluded from liver transplantation if it clears completely after chemotherapy. Complete eradication of metastatic lesions by chemotherapy and surgical resection of any suspicious remnant is a paramount prerequisite for transplantation.21,24,25

In conclusion, excellent results of HB treatment have been achieved in recent decades by a combination of chemotherapy, radical tumor resection, and liver transplantation. In cases without distant metastasis, an overall 5-year survival rate reaches 90% and 75%, respectively. In cases with POSTTEXT III and IV without distant metastasis, liver transplantation should be seriously considered prior to an attempt at liver resection because primary liver transplantation can offer a far better survival than rescue liver transplantation.

References


