Childhood Cancers: Hepatoblastoma

CYNTHIA E. HERZOG, RICHARD J. ANDRASSY, FARZIN EFTEKHARI

University of Texas M.D. Anderson Cancer Center, University of Texas-Houston Medical School, Houston, Texas, USA

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ABSTRACT

Hepatoblastoma is the most common primary liver tumor in children, accounting for just over 1% of pediatric cancers. The etiology is unknown, but it has been associated with Beckwith-Weidemann syndrome, familial adenomatosis polypi, and low birth weight. The primary treatment is surgical resection, however, chemotherapy plays an important role by increasing the number of tumors that are resectable. The prognosis for patients with resectable tumors is fairly good, however, the outcome for those with non-resectable or recurrent disease is poor. The Oncologist 2000;5:445-453

INTRODUCTION

Hepatoblastoma is the most common malignant tumor of the liver in children. Surgery remains the primary means of curative therapy, but the role of chemotherapy in both the adjuvant and neoadjuvant setting has become increasingly important over the past three decades. New insight has also been gained into the molecular biology of hepatoblastoma.

EPIDEMIOLOGY

The Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute has published data for the 21-year period from 1975 to 1995 showing that hepatoblastoma accounts for 79% of liver cancer in children under the age of 15. However, since liver cancers account for only a little more than 1% of childhood cancer, this results in about 100 cases of hepatoblastoma a year in the U.S. The incidence of hepatoblastoma is highest in infants (11.2 per million) and falls off rapidly, with most cases occurring prior to age 5. During this 21-year period, the incidence of hepatoblastoma has almost doubled from 0.8 per million (1975-1979) to 1.5 per million (1990-1995) [1]. SEER reports a male:female ratio of 1.2, however, data from group trials in the U.S. and Europe show a higher male:female ratio, ranging from 1.6 to 3.3 [2-5]. Population-based data for hepatoblastoma from Taiwan show an age distribution similar to the SEER data, but a higher male:female ratio of 2.9 [6].

An increased incidence of hepatoblastoma has been reported in Beckwith-Weidemann syndrome (BWS), hemihypertrophy and familial adenomatosis polypi (FAP). However, the extent of risk is difficult to determine due to the rarity of hepatoblastoma. Evaluation of the risk of hepatoblastoma in BWS revealed a relative risk of 2,280 (95% confidence intervals 928-1,165) during the first four years of life [7]. The only clinical feature of BWS associated with an increased risk of cancer was limb hypertrophy. In FAP the relative risk for hepatoblastoma in the first four years of life is 1,220 (95% confidence intervals 230-2,168) [8].

Recent studies in Japan have shown low birth weight to be associated with the development of hepatoblastoma [9, 10]. The relative risk for developing hepatoblastoma is 15.64 for patients weighing less than 1,000 gm compared to those weighing 2,500 gm or more. These data have been supported by the high percentage of premature and extremely low birth weight infants diagnosed with hepatoblastoma on the latest Children’s Cancer Group (CCG) trial and in single institution populations [11-13]. The increased survival of low birth weight infants and their increased risk of hepatoblastoma may account for the increased incidence of hepatoblastoma seen in the SEER data.

CLINICAL PRESENTATION

Most patients present with an enlarging abdominal mass. The right lobe is involved three times more commonly than...
the left, with bilobar involvement seen in 20%-30%, and multilobar involvement in 15% [14, 15]. Less common symptoms are anorexia, weight loss, and pain [15]. Association with precocious puberty has been reported [14].

Serum alpha-fetoprotein (AFP) level is almost always elevated. Bilirubin and liver enzymes are usually normal. Anemia and platelet abnormalities have been reported [15]. Although low platelet counts can occur in hepatoblastoma, thrombocytosis is commonly reported [16, 17]. The etiology of this finding is unclear, however, the liver is a source of thrombopoietin production and increased thrombopoietin has been reported in hepatoblasoma [16, 18].

There is no clear correlation between AFP and outcome, however, persistence or recurrence of elevated AFP is a sensitive marker of disease. There is a correlation between AFP and extent of disease for all stages [2], and the rate of decline in AFP with treatment is prognostic [19, 20]. Low AFP levels are associated with anaplastic histology and poor outcome. On the German Cooperative Group HB89 study, only one of four patients with AFP less than 100 ng/ml survived. Two of these patients, with normal AFP and anaplastic histology, had no response to treatment [19]. On the CCG 823F trial, two of two patients with AFP less than 100 ng/ml died [20].

Metastases at diagnosis occur in 10%-20% of patients [3, 4, 15, 21], with the lung being the predominant site of metastases both at presentation and relapse. Other sites of distant metastases, including brain and bone, are rare and usually occur in the setting of relapsed disease [3, 15, 22, 23]. A higher incidence of non-pulmonary metastases has also been reported in congenital hepatoblastoma [5]. Although pulmonary metastases are usually accompanied by an increase in AFP, recurrence of pulmonary metastases has been reported to occur without such an increase [24, 25].

**Imaging Studies**

Hepatoblastoma usually appears as a focal or multifocal solid tumor. Stippled or chunky calcifications can be detected in 40%-50% of patients, which is significantly higher than in patients with benign lesions such as hemangiomas and hemangiendotheliomas [26, 27]. Intralesional calcification closely correlates to histologically detected osteoid matrix. While magnetic resonance (MR) is not as sensitive as computed tomography (CT) for the detection of calcification, the presence of calcification is not essential for diagnosis.

Traditional imaging modalities (conventional radiography, excretory urography, and hepatic arteriography) have largely been replaced by ultrasonography, spiral CT...
and MR (Figs. 1-5). These newer modalities with their capabilities for multiplanar image reconstruction have virtually eliminated the need for conventional arteriography. These newer modalities elegantly display the extent of hepatic involvement by tumor and its proximity to the portal vein, and thus help to determine its resectability. The role of arteriography now is probably limited to rare instances where transarterial chemoembolization is a therapeutic consideration.

Ultrasound in conjunction with color Doppler, a noninvasive modality, is especially useful in young infants. It can assign the tumor to the liver and define its relationship to the portal vein. For the purpose of percutaneous biopsy, either ultrasound or CT guidance can be used to obtain tissue samples for histological analysis. Ultrasound, however, may not be as sensitive in the evaluation of the postoperative bed due to the presence of either omental flap or gas-filled loops of bowel.

The imaging work-up used at our institution begins with spiral CT for initial staging of the tumor and for assessing its resectability. It is also used to monitor tumor response to preoperative chemotherapy and search for tumor recurrence. A single-phase spiral CT is obtained prior to and following intravenous administration of an iodinated contrast material (2 ml/kg body weight). Using an automatic injector, and allowing a 60-sec delay after commencement of the injection, the CT images are obtained. This technique allows optimal visualization of the tumor during the late arterial/early portal phases. In our experience hepatoblastomas are not as hypervascular as adult hepatocellular carcinomas. Therefore, a dual or triple-phase spiral CT will not provide any additional information. Performing MR requires sedation and is reserved for instances of allergy to iodine or to document a recurrent tumor.

Because pulmonary metastases occur in about 10% of hepatoblastomas, but nonpulmonary metastases are rare, further imaging evaluation recommended at diagnosis should include chest radiography and chest CT to determine if pulmonary metastases are present.

**PATHOLOGY/MOLECULAR BIOLOGY**

Hepatoblastoma is classified by histology as epithelial (56%) or mixed epithelial/mesenchymal (44%) [28]. Epithelial hepatoblastoma is further broken down to pure fetal (31%), embryonal (19%), macrotrabecular (3%) and small-cell undifferentiated (3%) (Fig. 6). The most common mesenchymal elements are osteoid and cartilage (Fig. 7). In one study, osteoid made up a small component of 36% of untreated hepatoblastoma, but was increased in treated hepatoblastoma to 82% and composed up to 90% of the tumor area [14]. The presence of mesenchymal elements has been associated with improved prognosis in patients with advanced disease [29]. In completely resected tumors, pure fetal histology confers a better prognosis, while small-cell undifferentiated histology is associated with a poor prognosis [29].

Multiple cytogenetic abnormalities have been noted in hepatoblastoma with gain of chromosome 20 being the most common, followed by gain of chromosome 2 or 8 [30, 31].
Hepatoblastoma is also associated with FAP, and trisomy 20 is a common finding in colon adenomas [32]. Schneider et al. reported a recurring chromosomal aberration, der(4)t(1q;4q), in four hepatoblastoma patients [33], and two subsequent cases have been reported [30, 34]. Four of the six cases have the same abnormality, der(4)t(1;4)(q12;q34). Structural abnormalities resulting in a gain of material on 1q are also common. The frequency of these abnormalities suggests that they contribute to the etiology of hepatoblastoma.

In FAP, decreased expression of the adenomatous polyposis coli (APC) gene is associated with increased expression of β-catenin. The increased incidence of hepatoblastoma in FAP has led to the evaluation of sporadic hepatoblastoma for alteration in APC and β-catenin. Kurahashi et al. [35] evaluated the mutation cluster region of the APC gene and found mutations in only 1 of 11 samples evaluated. Another study by Oda et al. [36] reports genetic alterations in the APC gene in 8 of 13 samples. Koch et al. [37] studied 52 hepatoblastoma samples and found no mutations in the mutation cluster region of the APC gene, but detected mutations in the gene encoding β-catenin in 48% of samples. Two further reports by Wei et al. [38] and Jeng et al. [39] have shown β-catenin mutations in 12 of 18 (67%) and 8 of 9 (89%) hepatoblastoma samples. These studies suggest that alterations in the APC/β-catenin pathway contribute to the pathogenesis of hepatoblastoma.

Changes in the expression of H19 and IGF2 have also been implicated in the etiology of hepatoblastoma. Both of these genes are imprinted, with the maternal allele of H19 and the paternal allele of IGF2 generally expressed in human tissue. However, the human liver has monoallelic expression of IGF2 at birth, with a switch to biallelic expression during the first year of life. Ross et al. [40] have recently studied 30 hepatoblastoma samples and found that H19 remains imprinted with monoallelic expression in the 13 evaluable samples.

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However, monoallelic expression was also seen in 10 of 13 samples evaluable for IGF2. Whether this represents dysregulation of IGF2 or greater variability of the timing of the switch from monoallelic to biallelic expression will require study of a larger number of samples from both hepatoblastoma and normal liver.

**STAGING**

The lack of a uniformly accepted staging system for malignant hepatic tumors in childhood has been an ongoing problem for international comparison. The staging system used in the U.S. for the Intergroup Hepatoma Studies is based on surgical exploration with the completeness of resection and spread of tumor key to staging (Table 1). Therefore, staging laparotomy and biopsy are essential. The resectability of the primary tumor has no bearing on the staging of hepatoblastomas when distant metastases are present [41]. This staging system is also currently used by the German Cooperative Study Group [42, 43]. The Japanese Society for Pediatric Surgery attempted a classification based on the TNM (tumor, node, metastases), with clinical stage determined by imaging studies prior to surgery. Tumor size, number of involved lobes, regional lymph node involvement, and distant metastases determine stage [44]. The number of liver segments involved and distant metastases were of prognostic significance. The International Society of Pediatric Oncology (SIOP) has used the number of involved sectors to determine stage (Table 1) [45]. A recent report from SIOP shows that grouping based on the pretreatment extent of disease (PRETEXT) has prognostic significance for both overall survival (OS) and event-free survival (EFS), even when all tumors considered are surgically resectable [21].

**TREATMENT**

**Surgery**

Historically, only complete surgical excision of the primary tumor was felt to correlate with cure. Complete resection of the tumor remains the best hope for long-term survival; however, the advent of effective chemotherapy may permit cure in the presence of initially unresectable or metastatic disease. If at initial laparotomy the tumor appears resectable, reasonably safe attempts should be made to remove the tumor. If the tumor is deemed unresectable and the patient is at high risk for complications, a biopsy is taken and preresection chemotherapy is indicated [46–48]. Whether a tumor is resectable may be somewhat subjective, since what one surgeon may consider unresectable may be resectable to another. The classic reasons for a tumor to be deemed unresectable include an extremely large tumor that may lead to excessive bleeding, involvement of both the right and left lobes, involvement of major hepatic veins or the inferior vena cava (IVC) and diffuse multifocal disease. After initial chemotherapy, tumor shrinkage allows for easier resection with less blood loss and morbidity. Prior to the use of preoperative chemotherapy, about half of newly diagnosed hepatoblastomas were considered resectable [15]. In more recent reports only about 30% have been considered resectable at diagnosis, since tumors that are likely to result in significant surgical morbidity with resection are now considered unresectable [45, 48]. Chemotherapy has been proven to be effective both in an adjuvant as well as neoadjuvant setting. The use of neoadjuvant chemotherapy has resulted in most nonmetastatic hepatoblastomas being resectable [45, 48].

Detailed surgical principles of hepatic resection are beyond the scope of this review; however, in general a large upper abdominal transverse or bilateral subcostal incision that looks like a bucket handle is used. Rarely in children is it necessary to enter the chest. The liver is completely freed from its attachments and proximal and distal control of the vena cava above and below the liver, as well as control of the porta hepatis, are obtained. Once the resectability is ascertained, the patient is given fluid resuscitation with Ringer’s lactate or blood to maximize intravascular volume. The amount of fluid resuscitation is 10-20 cc/kg, depending on the volume status of the patient at that point in the operation. Total vascular occlusion is then obtained by sequentially and slowly securing the vascular structures above and below the liver as well as the
porta hepatis. Using a combined electric cautery, argon beam, and finger fracture technique, the involved liver segment is removed in a relatively bloodless plane. Ligatures or clips are placed as vessels are identified and blood loss is minimized using total vascular occlusion. The key to reducing complications and providing a successful resection is careful, meticulous dissection of the portal vein, hepatic artery, and hepatic ducts and their branches to assure that the remaining lobes have adequate blood supply and bile drainage.

The most common intraoperative complication is hemorrhage [15, 45]. The risk of bleeding is increased with extended hepatectomy or tumor proximity to the IVC or hepatic vessels [45]. Other complications include air embolus, and damage to the portal vein, hepatic artery, or hepatic duct. Postoperative complications include subphrenic abscess, bile leak, postoperative bleeding, or small bowel obstruction. Seo et al. [48] report fewer complications after preoperative chemotherapy. Complications were higher, however, with second-look surgeries after an open biopsy or hepatic artery cannulation.

At resection, an attempt to obtain clear margins should be made. Due to the regenerative capacity of the liver, up to 85% of the liver can be safely resected. If permanent pathology reports indicate inadequate margins, consideration should be given to re-resection. Elevated AFP levels immediately following surgery are common, however failure of AFP to return to normal or rising levels after stabilization of post-resection AFP levels should prompt aggressive evaluation for local recurrence and/or metastatic disease. Local recurrence can be approached by simple repeated surgical resection. We have had long-term survivors after re-resection and postoperative chemotherapy.

For those tumors that remain unresectable after chemotherapy or local recurrence, liver transplantation can be an option. In a recent review of the literature on transplantation in hepatoblastoma, Dower and Smith [49] reported on 33 stage III and 39 stage IV tumors. In patients transplanted with stage III tumors, disease-free survival (DFS) with minimum follow-up of one year is 72%. For stage IV tumors the DFS was 54% at 4 to 90 months. For both stage III and IV tumors, the two-year DFS was a minimum of 40%. A recent report by Reyes et al. [50] on 12 patients undergoing transplantation for hepatoblastoma demonstrated a one-, three-, and five-year post-transplant survival of 92%, 92%, and 83%. Intravenous invasion, positive hilar nodes, and contiguous spread did not have a significant adverse effect on the outcome. Distant metastasis was responsible for the two deaths. Patients with metastatic disease at diagnosis that resolves with chemotherapy or can be removed surgically can be considered transplant candidates [51].

The most common site of distant metastasis for hepatoblastoma is the lungs. An aggressive approach to excision of pulmonary metastasis can result in long-term survival [23, 52]. Resection of pulmonary metastases was most effective when: A) the primary was resected; B) metastases develop more than six months post-resection; C) metastases had a marked response to chemotherapy and AFP dropped to less than 25 ng/ml; D) resection of metastases occurred soon after the AFP no longer responded to chemotherapy; E) all gross disease was resected [52], and F) there were fewer metastases (personal experience). Thus an aggressive multimodal approach to hepatoblastoma including chemotherapy, resection, re-resection, transplantation, and treatment or resection of metastases can lead to improved DFS.

Chemotherapy

The utility of chemotherapy in the treatment of hepatoblastoma began to emerge in the 1970s. Although surgery remains the predominant mode of therapy, chemotherapy has increased the number of resectable hepatoblastomas and decreased the morbidity of surgery. Initial studies using chemotherapy in hepatoblastoma were disappointing. However, since the reports on single-agent effectiveness in hepatoblastoma for doxorubicin [53] and cisplatin [54], the role of chemotherapy in hepatoblastoma has become established in combination therapies [2, 3, 42, 55]. The most recent Pediatric Intergroup Hepatoma Study [4] compared two regimens: Regimen A, cisplatin 90 mg/m² (day 1), vincristine 1.5 mg/m² (day 3) and 5-fluorouracil 600 mg/m² (day 3) and regimen B, cisplatin 90 mg/m² (day 1) and doxorubicin 20 mg/m²/d (days 1-4). This study randomized 173 hepatoblastoma patients. The EFS and OS were 57% and 69% on regimen A and 69% and 72% on regimen B. EFS and OS by stage is given in Table 2. The OS and EFS were not significantly different on the two arms, however, the toxicity of regimen B was more severe, resulting in a recommendation that regimen A be the treatment of choice.

Unfortunately, both doxorubicin and cisplatin are associated with the potential for significant side effects, cardiac toxicity with doxorubicin and nephro- and ototoxicity with cisplatin. The current Intergroup trial, in an attempt to reduce toxicity, is comparing cisplatin, vincristine and 5-fluorouracil to cisplatin alternating with carboplatin. Each regimen is

<table>
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<tr>
<th>Stage</th>
<th>Intergroup [4]</th>
<th>German Study [42]</th>
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<tbody>
<tr>
<td>I</td>
<td>91% (n = 43)*</td>
<td>100% (n = 21)</td>
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<tr>
<td>II</td>
<td>100% (n = 7)</td>
<td>50% (n = 6)</td>
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<tr>
<td>III</td>
<td>64% (n = 83)</td>
<td>74% (n = 38)</td>
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<tr>
<td>IV</td>
<td>25% (n = 40)</td>
<td>29% (n = 7)</td>
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*Patients with pure fetal histology excluded.
given with or without the addition of Amifostine in an attempt to decrease the toxicity. In addition all patients will receive G-CSF and bactrim to reduce toxicity. Patients with stage I pure fetal histology will be treated with surgery alone, with monitoring of scans and AFP.

The Cooperative German Paediatric Liver Tumour Study HB 89 [42] treated patients with IPA, ifosfamide 3.5 gm/m² over 72 h (days 1-3), cisplatin 20 mg/m²/d for 5 days (days 4-9), and doxorubicin 60 mg/m² over 48 h (days 9-10). EFS and OS by stage are given in Table 2. More recently the German group has given carboplatin and etoposide to patients who have failed IPA and seen responses in 6 of 14. One patient with multiple lung metastases had a complete response (CR), while three patients with a partial response and one with stable disease were disease-free following surgery [43].

Due to the rarity of this disease there are limited data on the effectiveness of newer agents in the treatment of hepatoblastoma. Fuchs et al. have reported responses to paclitaxel in xenograft models [56], but no responses were seen on a phase II trial [57]. Eight patients with hepatoblastoma were treated on a phase II study of topotecan, with stable disease seen in two for seven and 10 cycles [58]. Topotecan may prove useful in preparative regimens for autologous stem cell transplant in the treatment of hepatoblastoma. Stem cell transplant following thiotepa, melphalan and busulfan has been used in the treatment of microscopic residual disease with good results [59]. A CR to ifosfamide, cisplatin, etoposide has been reported [60]. In addition, we have treated a patient with multiple liver relapses using ifosfamide, carboplatin, and etoposide and achieved a very good partial response prior to liver transplant.

Other Treatments
Transcatheter arterial chemoembolization or hepatic arterial chemoembolization involves giving chemotherapy and vascular occlusive agents via catheter into the artery supplying the tumor. This offers the advantage of higher tumor concentrations of chemotherapeutic drugs with lower systemic exposure. Occlusion of the artery supplying the tumor resulting in tumor ischemia can be done since tumors receive most of their blood supply from the hepatic artery, while the blood supply to normal liver parenchyma comes primarily from the portal vein. This approach has been used in adults with primary or metastatic liver tumors. Several small series include 20 children treated for hepatoblastoma [61-64]. Although all had a response, complete resection was achieved in 12 of 12 treated early in their course of therapy, but only two of eight treated after poor response to initial therapy or after relapse. The potential benefit of chemoembolization over systemic chemotherapy as initial therapy for unresectable tumors has not been determined, although response rate has been high. Cryoablation, and more recently radiofrequency ablation, have also been used in the treatment of liver tumors in adults with little experience in children.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis for hepatoblastoma is impacted by the age of the patient. In infants hemangiomas, heman-gioendotheliomas and hamartomas are common liver tumors. However, a liver tumor in an adolescent is likely to be a hepatocellular carcinoma (HCC) [65]. In patients under age five, hepatoblastoma is 23 times more common in the U.S. [1], while in Taiwan the incidence of HCC in this age group was only slightly less than that of hepatoblastoma [6]. This is probably a reflection of the fact that hepatitis B, which is associated with an increased risk of HCC, is endemic in Taiwan. HCC is less likely than hepatoblastoma to be resectable at diagnosis (10%-30%) and less responsive to chemotherapy.

CONCLUSIONS
Hepatoblastoma is the most common primary liver tumor in children. The primary treatment is surgical resection, and the use of preresection chemotherapy can increase the number of tumors that are resectable. The prognosis for patients with resectable tumors is fairly good in combination with chemotherapy. However, the outcome for those with nonresectable or recurrent disease remains poor and new therapies are needed.

REFERENCES
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