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Journal

Journal of Pediatric Surgery, 57(10)

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Publication Date

2022-10-01

DOI

10.1016/j.jpedsurg.2022.05.022

Peer reviewed

HHS Public Access

Author manuscript

J Pediatr Surg. Author manuscript; available in PMC 2023 October 01.

Published in final edited form as:

J Pediatr Surg. 2022 October ; 57(10): 251–256. doi:10.1016/j.jpedsurg.2022.05.022.

Outcomes of Children with Well-Differentiated Fetal Hepatoblastoma Treated with Surgery Only: Report from Children's Oncology Group Trial, AHEP0731

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Abstract

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ClinicalTrials.gov **Identifier:** NCT00980460

Level of Evidence: Prognosis Study, Level I evidence

Background: Hepatoblastoma (HB) requires surgical resection for cure, but only 20–30% of patients have resectable disease at diagnosis. Patients who undergo partial hepatectomy at diagnosis have historically received 4–6 cycles of adjuvant chemotherapy; however, those with 100% well-differentiated fetal histology (WDF) have been observed to have excellent outcomes when treated with surgery alone.

Patients and methods: Patients on the Children's Oncology Group non-randomized, multicenter phase III study, AHEP0731, were stratified based on Evan's stage, tumor histology, and serum alpha-fetoprotein level at diagnosis. Patients were eligible for the very low-risk stratum of surgery and observation if they had a complete resection at diagnosis and rapid central histologic review demonstrated HB with 100% WDF histology.

Results: A total of 8 eligible patients were enrolled on study between September 14, 2009 and May 28, 2014. Outcome current to 06/30/2020 was used in this analysis. The median age at enrollment was 22.5 months (range: 8–84 months) and the median AFP at enrollment was 714 ng/ml (range: 18–77,747 ng/mL). With a median follow-up of 6.6 years (range: 3.6–9.8 years), the 5-year event-free (EFS) and overall survival (OS) were both 100%.

Conclusion: This report supports that HB with 100% WDF histology completely resected at diagnosis is curable with surgery only. The development of evidence-based surgical guidelines utilizing criteria based on PRETEXT group, vascular involvement (annotation factors), tumor-specific histology and corresponding biology will be crucial for optimizing which patients are candidates for resection at diagnosis followed by observation.

Keywords

Hepatoblastoma; Resection; Well-differentiated; Fetal

1. Introduction

Hepatoblastoma (HB) is the most common pediatric liver malignancy and surgical resection remains the foundation of curative therapy [1,2]. Reports have shown that among children with tumors amenable to resection at diagnosis, also referred to as upfront resection, those with 100% pure fetal histology (PFH) have better outcomes than patients with other tumor histologies [3,4]. The Children's Oncology Group (COG) evaluated this concept in two consecutive clinical trials [5,6]. Intergroup HB study INT-0098 treated 9 patients with PFH tumors resected at diagnosis with adjuvant doxorubicin as single-agent therapy [5] while study P9645 (NCT00003994) was the first study that completely omitted chemotherapy following surgery in 16 patients with PFH tumors [6]. Survival in both studies was 100%. This approach, previously unique to COG, demonstrated that upfront surgical resection without adjuvant chemotherapy is curative in children with tumors with 100% PFH. This histology is now internationally classified as well-differentiated fetal (WDF) histology. WDF is defined as a tumor composed of uniform epithelial tumor cells that resemble fetal hepatocytes with centrally placed, round nuclei and cytoplasm that may contain variable amounts of glycogen or lipid, and minimal mitotic activity (< 2 mitoses per 10 high-powered fields × 400 microscopic fields) [7].

While this cohort of patients represents only 3–6% of children with newly diagnosed HB, its recognition spares patients the potentially significant acute and long-term toxicities associated with cisplatin-based HB chemotherapy including hearing loss, renal toxicity, immune suppression, as well as nausea, vomiting, and malnutrition [8–11]. The most recent COG trial, AHEP0731, for the treatment of children with all stages of HB, continued the validation of this strategy of foregoing postoperative adjuvant chemotherapy in a specific, very low-risk stratum whereby surgery was the only treatment provided to children with 100% WDF histology. Within this trial, surgical guidelines were recommended to determine if patients were eligible for partial hepatectomy at diagnosis in order to minimize intra- and post-operative complications. The outcomes of these patients and adherence to the surgical guidelines for determining appropriate candidates for resection at diagnosis were analyzed.

2. Patients and methods

2.1 Study design and participants

AHEP0731 was activated September 14, 2009 and closed permanently on July 20, 2018. Patients less than 21 years of age with newly diagnosed, previously untreated HB were eligible for study if they had primary resection and if rapid central histological review of the tumor had been performed (MJF, SR) within 14 days of surgery. The cohort was limited to patients with Evan's surgical stage I resections (complete resection with microscopically negative margins) [8]. Patients who had stage I tumors with 100% WDF histology and low mitotic activity (< 2 mitoses per 10 high-powered fields × 400 microscopic fields), were classified as very low-risk patients and received no post-operative chemotherapy. Outcome current to June 30, 2020 was used in this analysis.

2.2 Study oversight

The National Cancer Institute, the Pediatric Central Institutional Review Board (IRB), and the IRBs of the participating institutions approved the protocol. Informed consent was obtained for all patients according to Department of Health and Human Services guidelines.

2.3 Study procedures:

Baseline physical exams, organ function, alpha-fetoprotein (AFP) levels, and imaging studies were performed at diagnosis. Computed tomography (CT) or magnetic resonance imaging (MRI) of the primary tumor and a chest CT to evaluate for metastatic disease were required at diagnosis. Assignment of the PRETEXT group (I, II, III, or IV) was performed by the treating institution for all patients at diagnosis. PRETEXT group and PRETEXT Annotation Factors (VPEFRCNM) (V=vena cava, hepatic veins; P=portal veins; E=extrahepatic disease; F=multifocal disease; R=rupture at diagnosis; C=caudate lobe involvement; N=lymph node involvement; and M=metastatic disease) were also assigned by central radiographic review (Fig. 1) [12]. The V and P status were further defined as shown in Fig. 1 legend. PRETEXT was not to be used for risk classification but was to guide the surgical approach, in particular, to assess if patients should be considered resectable at diagnosis. All radiologic imaging was centrally reviewed for reporting accuracy by a study committee of 2 radiologists and 6 surgeons, but not for real-time institutional decision making.

The study provided permissive surgical guidelines that were not protocol-mandated and recommended resection at diagnosis for all PRETEXT I and II tumors with a ≥ 1 cm radiographic margin from the middle hepatic vein, inferior vena cava (IVC, intrahepatic), and the portal vein bifurcation. These tumors were also coded as hepatic vein / IVC (V) and portal vein (P) negative (no vascular involvement) on the study central radiographic review. The surgical guidelines further emphasized that patients outside of these criteria should undergo biopsy and neoadjuvant chemotherapy. Surgical details were prospectively collected including surgery-associated complications from individual operative notes and case report forms (CRF). A complete response (CR) was considered as the resolution of all lesions and a normal AFP level, according to institutional normal ranges.

2.4 Statistical analysis:

The target accrual for the very low-risk strata was 9 patients. The primary outcome measure, event-free survival (EFS) was defined as the time from enrollment to disease progression, diagnosis of a second malignant neoplasm, death from any cause, or last follow-up, whichever came first. Overall survival (OS) was defined as the time from enrollment to death or last follow-up, whichever came first. The proportion of patients who were event-free or alive as a function of time since enrollment was estimated using the Kaplan-Meier Method and 95% confidence intervals were estimated by the complementary log-log transformation.[13]. Median follow-up time was estimated by the method of Schemper and Smith [14]. If 2 or more analytic events were observed during the first year of follow-up, the strategy of surgery alone without adjuvant chemotherapy was to be considered as demonstrating insufficient disease control. If this strategy was associated with event-free survival of 65%, the probability of accepting it was 0.12. If this strategy was associated with a long-term event-free survival of 93%, the probability of accepting it was 0.89. Analyses were conducted in SAS version 9.4 (Cary, NC) and STATA version 15 (College Station, TX).

When the study was permanently closed, this stratum was one short of the planned accrual of 9 patients and the decision was made to close the study as the addition of one patient would not provide data that would change the protocol outcome, specifically not meeting the criteria for protocol failure.

3. Results

3.1 Study Population and Outcome

A total of 236 children were enrolled on study (Supplementary Figure 1). Eight children who underwent resection at diagnosis were confirmed by rapid central review to have WDF histology HB and were treated with surgery followed by observation without adjuvant treatment.

The median age at diagnosis was 22.5 months (range: 8–84 months) (Table 1). There were 1 female and 7 males. The median AFP before surgical resection was 714 ng/ml (range: 18–77,747 ng/mL) and all patients normalized their AFP level following surgery and achieved a

complete response. With a median follow-up of 6.6 years (range: 3.6 to 9.8 years), the 5-year EFS and OS were both 100% (Fig. 2).

3.2 Staging

All patients were Evan's stage I with complete surgical resection and histologically negative margins. PRETEXT central review group assignments were I (n= 2 [25%]), II (n=5 [62.5%]), and III (n=1 [12.5%]) (Table 1). Annotation factors by PRETEXT stage from central review were as following: PRETEXT I (Pneg=2; Vneg=2); PRETEXT II (Pneg=2, P0=1, P2=2; Vneg=3, V2=2) and PRETEXT III (P0=1; Vneg=1). Central and institutional PRETEXT stage were concordant 62.5% of the time.

3.3 Surgical resection and complications:

Resections were all judged grossly complete by the operative surgeon. Operative procedures performed included: right lobectomy (n=4, [50%]), non-anatomic wedge resection (n= 2, [25%]), left lateral sectionectomy (n=1, [12.5%]), and right trisegmentectomy (n=1, [12.5%]) (Table 2). All patients had a negative margin resection with distances ranging from within <1mm to 9mm from the surgical margin. There were no perioperative deaths. One patient (Patient #4) out of the 8 sustained an intraoperative complication with injury to the middle hepatic vein during a right lobectomy for a PRETEXT II tumor. Of the remaining patients, none were reported to have bile leak, repeat laparotomy for complications, liver insufficiency, liver failure, or vascular complications. Based upon central radiographic review of their imaging, 5 patients were treated within the surgical guidelines defined by the trial, and 3 patients were treated outside of these guidelines. Of the patients treated out of the guidelines, one patient had a PRETEXT III tumor (Patient #5) and two patients had tumors that were less than 1cm from central vasculature (PRETEXT annotation positive) which included the patient with the intraoperative complication discussed above (Patient #1, #4).

3.4 Staging and histopathologic inconsistencies:

Three patients were treated as WDF but did not meet the strict definition for the very low-risk group as designated by the trial (Table 2). One patient (Patient #3) with a small PRETEXT I tumor and WDF had an AFP of 18 ng/mL that should have resulted in a high-risk designation due to the AFP < 100 ng/mL. Two other patients had > 2 mitoses per 10 high-powered fields on histologic central review (Patient #7, #8) not meeting the definition of WDF and would have been recommended to receive adjuvant treatment after surgery.

4. Discussion

We report excellent outcomes for children undergoing complete resection of HB with WDF histology treated with surgery alone. This is the third consecutive dose reduction study for HB reported by the COG [5,6,12]. This strategy is applicable for 3–6% of newly diagnosed HB patients [6].

Sixty-six patients from the AHEP0731 study underwent resection at diagnosis among all strata (8 stratum 1, 49 stratum 2, and 9 stratum 3). A recent report of the low-risk cohort stratum 2 demonstrated that HB completely resected at diagnosis, other than WDF histology, is highly curable with minimal adjuvant chemotherapy [12]. That stratum maintained excellent four-year EFS and OS at 92% (95% confidence interval-CI: 79 – 97%) and 95% (95% CI: 82 – 99%) respectively, in patients who received two cycles rather than four cycles of post-operative Cisplatin/5-Flurouracil/Vincristine (C5V) chemotherapy. The results of the low-risk stratum of AHEP0731 provide additional evidence that cisplatin-based chemotherapy can be effectively and safely reduced for carefully selected cohorts of HB patients.

When considering these AHEP0731 very low-risk and low-risk study results together, it is apparent that defined risk stratification can identify children with non-metastatic HB who should be considered for upfront resection at diagnosis. The primary benefit of this strategy is to reduce the acute and long-term toxicities of platinum-based HB chemotherapy while also attempting to minimize surgical complications. These data will continue a paradigm shift in demonstrating the benefits of tumor resection at diagnosis when feasible, diminishing administered chemotherapy with decreased short and long-term morbidity, while maintaining excellent survival.

Overall survival for HB of all stages has improved greatly with platinum-based chemotherapy as shown by cooperative group studies from the US (COG), Europe (SIOPEL), and Japan (JCCG/JPLT) [8–10,15,16]. The SIOPEL group reported excellent outcomes, high resection rates, and low surgical complication rates in children who undergo delayed surgical resection after receiving neo-adjuvant therapy [17], and these results led to a worldwide decrease in patients undergoing HB resection at diagnosis. The upfront resection related complications reported here, and in other COG studies, are very low and similar to those reported by SIOPEL [6,17,18] suggesting that resection at diagnosis is safe, feasible, and ethical.

The limitation to this study is that it is a single-arm, non-randomized trial secondary to the fact that the small number of potential patients does not make a randomized trial feasible. Patients with post-resection microscopic residual disease (Evans stage II) have experienced excellent outcomes with adjuvant chemotherapy [5], while patients with PRETEXT annotation factors such as multifocality (F), contiguous extrahepatic extension (E), tumor rupture (R), or major vascular involvement (V and P) may have a greater risk of recurrence [18]. Second, adherence to surgical guidelines was voluntary. These results raise the question of whether tighter adherence to surgical resection guidelines, such as those recommended in AHEP0731, which counseled against resection at diagnosis in patients with positive PRETEXT annotation factors might further improve outcomes as well as minimize peri-operative complications [12].

Of the three patients treated outside of the surgical guidelines (2 PRETEXT II with positive annotation factors and 1 PREXEXT III), one patient experienced a significant intraoperative complication of vascular injury and hemorrhage. Incidentally, one patient had a low AFP level and was considered for high-risk therapy. However, the resected tumor from this

patient was small and had 100% WDF. Previous reports of tumors with low AFP levels have been associated with either small cell undifferentiated or rhabdoid histology from an earlier era where immunohistochemical and molecular evaluation could not necessarily clarify the diagnosis. Since the opening of the AHEP0731, a handful of such patients with small tumors and low AFP but favorable histologic features have come to the study teams' attention and have not been recommended for high-risk therapy, (personal communication with author [HK]). It will be important to monitor this group of patients in trials going forward to further confirm this observation.

Lastly, the inclusion of two patients who did not meet the strict criteria of WDF with greater than 2 mitotic figures/high-powered fields suggests that this arbitrary definition should be re-evaluated and perhaps any tumor with 100% WDF regardless of high mitotic/crowded fetal histologic areas in the tumor does not need chemotherapy following upfront resection. Sumazin et al. profiled many of the WDF tumors included on this trial and showed very indolent and non-aggressive molecular features of these tumors highlighting the importance of incorporating biology into risk stratification for future trials [19]. Further refinement of guidelines must include a balance of biology/histology with surgical feasibility and safety to ensure the best outcomes for these patients.

To our knowledge, this is the first HB trial that provided specific surgical guidelines, as well as, central radiographic review with study committee surgeons. These guidelines were intended to be permissive rather than restrictive and were not auditable data collection points. As some patients had resections performed outside of the guidelines, an analysis of the surgical procedures and their correlation with outcome from all four AHEP0731 risk groups will be performed elsewhere to attempt to determine to what extent PRETEXT groups and annotation factors are predictive of surgical resectability. It remains critically important that every effort is made to safely perform the correct initial surgical procedure because surgical morbidity can decrease overall survival of patients with HB [20]. This study and the subsequent recently opened international multi-cooperative group (COG, SIOPEL, JCCG) collaborative trial, PHITT/AHEP1531 (Pediatric Hepatic International Tumor Trial) have used surgical guidelines to guide the initial approach to a newly diagnosed patient. These are still guidelines and not requirements in deference to the treating institution making the ultimate decisions for patients based on their best clinical judgement and local capabilities.

PHITT/AHEP1531 will continue validating the data reported in this manuscript. Whether other cohorts of patients might be candidates for a further reduction in therapy and complete omission of chemotherapy as is reported here is a question for a future study and will be further defined by correlating histology to the molecular profiles of these tumors. That concept has been previously considered during the design of the AHEP0731 and AHEP1531 studies but was disregarded as older data suggesting higher rates of relapse in upfront resection of non-WDF tumors who did not receive any chemotherapy. Improved biology-based risk stratification, advancement in radiologic and surgical techniques, and experience from more recent trials may make such a strategy of observation only for all patients who undergo resection at diagnosis according to recommended surgical guidelines safer and feasible.

5. Conclusion

HB resected at diagnosis with WDF is curable with no adjuvant chemotherapy. The development of evidence-based surgical guidelines utilizing internationally constructed criteria based on PRETEXT grouping (including annotation factors) and tumor histology will be crucial for the success of this approach and its possible worldwide adoption. Such an approach is currently being evaluated in the accruing PHITT/AHEP1531 trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The study team is indebted to Fran Laurie, Sandy Kessel, Richard Hanusik, Loretta Nelson, and the rest of the staff of the Quality Assurance Review Center for collection of scans, compilation of data, and facilitation of radiographic central review sessions. We would also like to acknowledge clinical research associates from COG institutions for facilitation of study enrollment and data collection.

Funding:

Research is supported by the Chair's Grant U10 CA98543 and the Statistics and Data Center Grant U10 CA98413 of the Children's Oncology Group and the Imaging and Radiation Oncology Core (IROC-RI, formerly QARC) Grant U10 CA29511 from the National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. A complete listing of grant support for research conducted by CCG and POG before initiation of the COG grant in 2003 is available online at-http://www.childrensoncologygroup.org/admin/grantinfo.htm

Abbreviations:

HB	hepatoblastoma
PFH	pure fetal histology
COG	Children's Oncology Group
WDF	well-differentiated fetal histology
PRETEXT	Pretreatment extent of disease
AFP	alpha fetoprotein
V	vena cava, hepatic veins
P	portal veins
E	extrahepatic disease
F	multifocal disease
R	rupture at diagnosis
C	caudate lobe involvement
N	lymph node involvement
M	metastatic disease

CR	complete response
EFS	event-free survival
OS	overall survival

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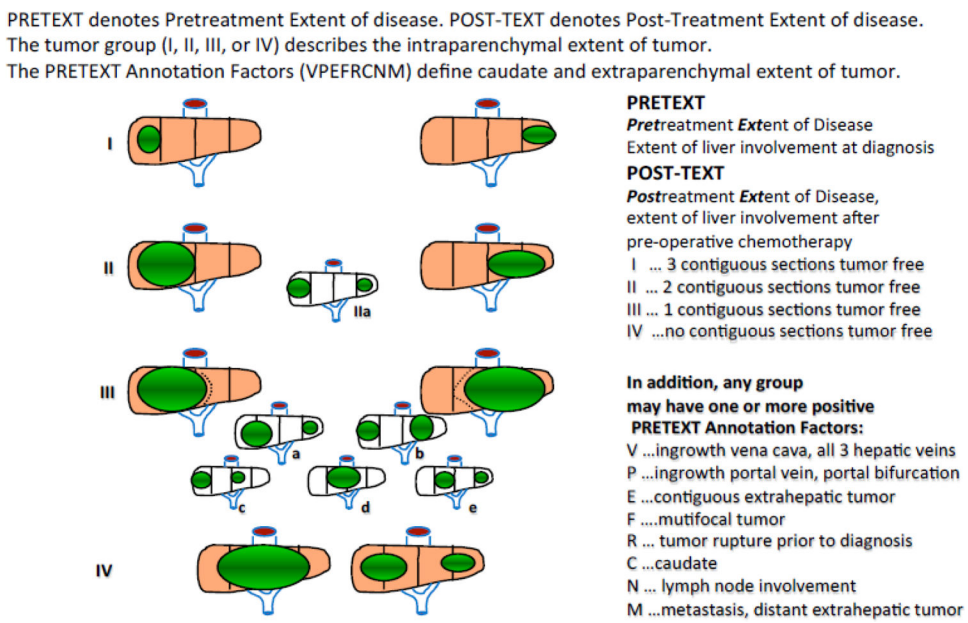

Figure 1. PRETEXT Groups and Annotation Factors.

VPEFRCNM, V=vena cava, hepatic veins; P=portal veins; E=extrahepatic disease; F=multifocal disease; R=rupture at diagnosis; C=caudate lobe involvement; N=lymph node involvement; and M=metastatic disease. The V and P status were further defined as follows: tumors ≥ 1cm distance from the vessel, the coding was Vneg or Pneg; tumors with < 1cm distance from the vessel, the coding was V0 or P0; for tumors touching the vessel, the coding was V1 or P1; and for tumors that compressed or distorted all three hepatic veins and/or IVC, the main portal vein, or right and left portal veins the coding was V2 or P2. For tumors with intravascular tumor thrombus in a hepatic vein, IVC, portal vein (right, left or bifurcation), the coding was V3 or P3.

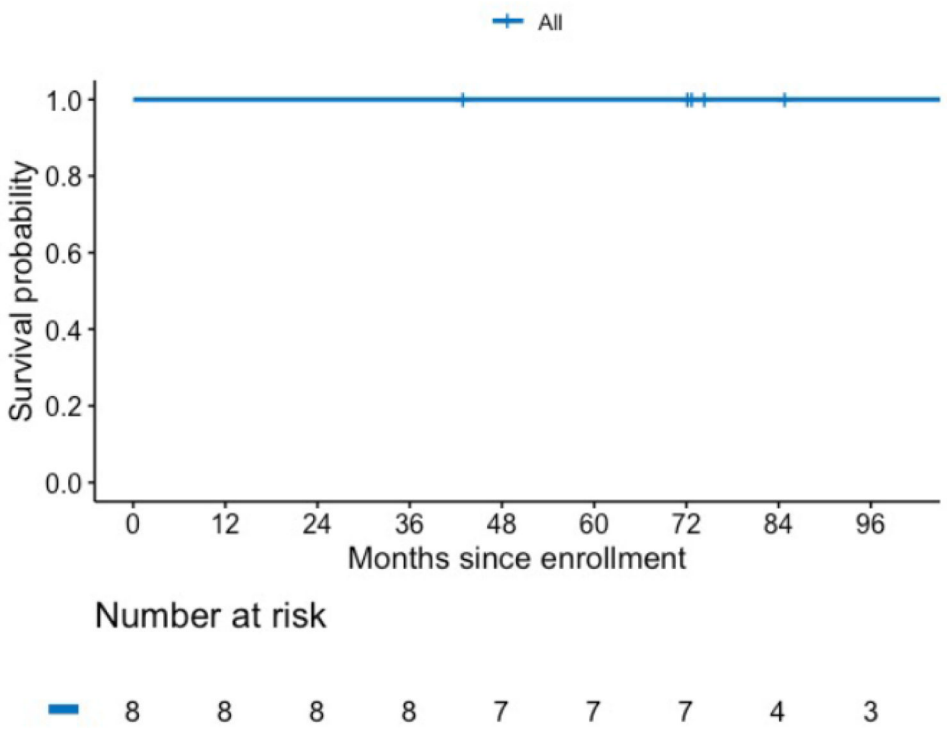

Figure 2. Event-free Survival and Overall Survival of Patients with Very Low-Risk Hepatoblastoma Resected at Diagnosis.

Kaplan-Meier curves and at-risk tables of EFS and OS for very low-risk hepatoblastoma. As there were not events, the curves for EFS and OS were the same.

Table 1.

Patient Characteristics for Children with Very Low-Risk Hepatoblastoma.

	Number (percent)
Age at enrollment	
< 12 months	2 (25)
1 – 3 years	3 (37.5)
4 – 8 years	3 (37.5)
Sex	
Male	7 (87.5)
Female	1 (2.5)
PRETEXT	
I	2 (25)
II	5 (62.5)
III	1 (12.5)
IV	0
P annotation	
Pneg	4 (50)
P0	2 (25)
P1	0
P2	2 (25)
P3	0
V annotation	
Vneg	6 (75)
V0	0
V1	0
V2	2 (25)
V3	0
Stage	
I	8 (100)
II	0
AFP prior to surgery	
< 100 ng/ml	1 (12.5)
100 – 999 ng/ml	4 (50)
≥ 1,000 – 999,999 ng/ml	3 (37.5)

Table 2.

Clinical and Surgical Traits for Children with Very Low-Risk Hepatoblastoma

Patient	Age (months)	AFP at diagnosis (ng/ml)	Central Pathology	PRETEXT Stage from central review	V	P	Couinaud Segments from central review	Resection
1	25	4,410	WDF	II	V2	P2	2, 3, 4B*	Left lateral sectionectomy*
2	61	2,868	WDF	I	-	-	6	Right lobectomy
3	20	18	WDF	I	-	-	6	Non anatomic wedge
4	84	379	WDF	II	V2	P2	5, 6, 7, 8	Right lobectomy
5	10	211	WD,	III	-	P0	4B, 5, 8	Right trisegmentectomy
6	49	518	WDF	II	-	-	5, 6	Right lobectomy
7	17	910	WDF- hi mit	II	-	P0	5, 8	Right lobectomy
8	8	77,747	WDF- hi mit	II	-	-	5	Non anatomic wedge

*segment 4B involvement was described in the central review; however the operative note indicated only a resection of segment 2 and 3 without involvement of 4B.

(-) refers to Vneg or Pneg.