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Hepatoblastoma: Transplant Versus Resection Experience in a Latin American Transplant Center

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Background. Hepatoblastoma is the most common primary malignant liver tumor in children and is usually diagnosed during the first 3 years of life. Overall survival has increased 50% due to chemotherapeutic schemes, expertise surgery centers, and liver transplantation. **Methods.** A retrospective collection of data was performed from pediatric patients with diagnosis of hepatoblastoma. Variables included demographic, diagnostic tools and histological classification; chemotherapy and surgical treatment; and outcomes and patient survival. The PRETEXT classification was applied, which included the risk evaluation, and according to the medical criterion in an individualized way, underwent resection or transplant. The morbidity of patients was evaluated by the Clavien-Dindo classification. Statistical analysis was performed according to the distribution of data and the survival analysis was carried out using the Kaplan-Meier method. **Results.** The patients (n = 16) were divided in a resection group (n = 8) and a transplant group (n = 8). The median age at the time of diagnosis was 13.5 months. The motive for the initial consultation was the discovery of a mass; all patients had high levels of α-fetoprotein and an imaging study. Ten of 16 patients required chemotherapy before the surgical procedure. In the resection group, 5 of 8 patients were classified as Clavien I and 4 of 8 patients of the transplant group were classified as Clavien II. Patient survival at 30 months was 100% in the resection group and 65% in the liver transplantation group. **Conclusions.** To our knowledge, this is the first case report of pediatric patients with hepatoblastoma and liver resection or transplant in Colombia and Latin America. Our results are comparable with the series worldwide, showing that resection and transplant increase the survival of the pediatric patients with hepatoblastoma. It is important to advocate for an increase of reporting in the scientific literature in Latin America.

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The hepatoblastoma (HB) is an embryonal tumor that originates from the precursor of hepatocytes (hepatoblast cells).[1] Several genetic syndromes, such as trisomy 18 (Edward Syndrome), Beckwith-Wiedemann syndrome, and familial adenomatous polyposis, have been associated with this pathology.[2,3]

The HB is the most common primary malignant liver tumor in children and is usually diagnosed during the first 3 years of life.[4] The incidence is twice as high in boys compared to girls[4] and has a range between 0.5% and 2% for the pediatric population (age, 0-14 years).[5,6]

Regarding the diagnosis of HB, the only biomarker that is widely used for the diagnosis, stratification and monitoring of the response to therapy is the α-fetoprotein (AFP). Previous studies have investigated the prognostic value of AFP, finding that levels <100 ng/ml, as well as levels greater than 1.2× 106 ng/mL, are related with a poor outcome.[7] From the histopathological point of view, the 2 predominant histologic types are: epithelial (56-67%) and mixed (epithelial and mesenchymal differentiation).[8]

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Several imaging studies have been used in the diagnosis and staging of HB, such as Doppler ultrasound, due to its low cost and safety. Other imaging tests are generally requested to provide greater detail, such as computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance with dissemination by weight, which is used to differentiate between benign and malignant lesions to avoid a biopsy.[9]

Currently, the risk stratification protocols take into account the PRETEXT classification, which evaluates the extent of the tumor before treatment, based on the system of Couinaud segmentation, vascular involvement, and metastasis, as evidenced in CT or MRI.[10] Also, the risk stratification accounts for the histology of a tumor, that is, whether there is metastatic disease and the levels of AFP to achieve an adequate therapeutic conduct.[7,11-13]

Thanks to the evolution in the treatment of HB during the past 4 decades, the overall survival has increased from 30% to 80%, mainly as a result of advances in chemotherapy, the introduction of the agent cisplatin, and the ability to perform a complete surgical resection.[4] The agent cisplatin allows tumor regression facilitating resection in those patients with surgically unresectable HB.[9] The standard regimen of chemotherapy consists of cisplatin, 5-fluorouracil, and vincristine (C5V).[14] Czauderna et al, recommend C5V for low-risk HB or C5V and doxorubicin for patients with intermediate and high-risk HB.[4]

Regarding the surgical resection of HB, the following techniques are included: segmentectomy, sectionectomy, and/or hemihepatectomy for the PRETEXT I and II; trisectomy for PRETEXT III and IV or transplant for tumors with invasion of the bilobar portal vein or the hepatic vein and the inferior vena cava or extensive loss of normal parenchyma.[3,4] The technical challenges of the surgery include: bleeding, wound infection, liver failure, postoperative biliary stricture, and sequelae for obstruction of the entry or exit of fluids during surgery.[9]

The objective of this article is to present the experience in the management of a series of pediatric patients with HB diagnosis, which had been made by the multidisciplinary group of the Transplant Unit of the Clinic Fundación Valle del Lili (Cali, Colombia).

MATERIALS AND METHODS

A retrospective collection of data was performed from the medical records of pediatric patients with diagnosis of HB in the Transplant Unit of the Fundación Valle del Lili (FVL) in Cali, Colombia. The variables that were included, were divided in 4 modules of study: demographic; diagnostic tools, and histological classification; chemotherapy and surgical treatment; outcomes and patient survival.

Within the first module, the following variables were registered: sex, age in months at the time of diagnosis, and the date of the procedure.

For the second module on diagnostic tools and histological classification, signs and symptoms that had been reported before diagnosis were recorded. Furthermore, the initial studies were noted, which included: type of imaging study performed (ultrasound, MRI, and/or CT), size of the lesion registered (the largest diameter of the tumor mass), which liver lobe was affected, and the PRETEXT classification. The histological variety and report of the levels of AFP in blood (μg/mL) at the time of diagnosis were also included.

The PRETEXT classification was applied for each case, which included the risk evaluation for HB. This classification is based on the extension of the tumor tissue in 4 major regions of the liver: right-hand zone (Couinaud 6, 7); front right area (Couinaud 5, 8); central left zone (Couinaud 4a, 4b); left side area.[2,3] Each anatomical status was assigned to a group (PRETEXT I, II, III, or IV) determined by the number of adjacent zones affected. According to this classification, the patient identified as PRETEXT I-II underwent resection and the patient classified as PRETEXT III-IV underwent liver transplantation, except in 1 case that required transplant due to a relapse of the disease, according to the medical criterion in an individualized way.

The third module included the number of cycles, the chemotherapeutic scheme used before and after the intervention, and the surgical procedure performed, whether it was resection or transplantation. As concerns, the surgical procedure, the duration of the surgery, the amount of intraoperative bleeding, and the transfusion requirement were recorded.

Finally, for the fourth module, the following variables were included: time of stay in the intensive care unit (ICU) and hospitalization (in days); complications; immunosuppressive scheme indicated, which was individualized according to each patient, using tacrolimus, steroids, and mycophenolate mofetil in different combinations; follow-up time in months; and patient survival.

The morbidity of patients who underwent surgery was evaluated by the Clavien-Dindo classification,[15] which catalogues patients to 1 of 5 possibilities, depending on the severity of the type of therapy needed to correct the complication.[16]

Statistical Analysis

The variables were analyzed descriptively with continuous variables summarized as median and interquartile ranges (IQR) and mean ± standard deviation (SD) according to the distribution of the data evaluated using the Shapiro-Wilk test, the categorical variables were summarized in percentages. Survival analysis was carried out using the Kaplan-Meier method. Data were censored at the date of the last follow-up or date of death. Values of P less than 0.05 were considered significant. All analyses were performed with STATA 12.

RESULTS

Module 1, Demographic Data

A series of 16 patients was obtained (Table 1 shows the demographic variables). The median age of the patients at the time of diagnosis was 13.5 months (IQR, 8-35 months). The patients were divided according to the surgical procedure performed, resection and transplant groups. In general, the demographics of the groups were similar. Regarding the surgical intervention, the median of age at the time of the procedure was 15.5 months (IQR, 12-42 months).

Module 2, Diagnostic Tools and Histologic Classification

The main reason for the initial consultation, before the diagnosis of HB, was the discovery of a mass (n = 6), followed by abdominal distension (n = 2) and an incidental finding (n = 2). The median of the levels of AFP was of 3211 μg/mL (IQR, 643–30 305 μg/mL), and the difference between the levels of AFP between the 2 groups was not statistically significant (P = 0.29).

TABLE 1.
Clinical and demographic characteristics

Characteristics	Total (n = 16)	Resection (n = 8)	Transplant (n = 8)	*P*
Age at diagnosis time, mo				
Median (IQR)	13.5 (8-35)	13.5 (8-23)	21.5 (8-36)	0.5984
Range	7-43	7-42	7-43	
Age at the procedure, mo				
Median (IQR)	15.5 (12-42)	13.5 (10-23)	30 (12-46)	0.1149
Range	8-66	8-45	12-66	
Sex male, n (%)	10 (63)	5 (63)	5 (63)	1.000
AFP, µg/mL				
Median (IQR)	3211 (643-30 305)	21 175 (602-139 626)	2298 (643-3335)	0.2936
Range	143-202000	143-202 000	475-15 173	
Size of the tumor, cm				
Mean ± SD	9.2 ± 3.7	9.2 ± 3.6	9.2 ± 4	0.9846
Range	4-17	4-14	4.4-17	
Pretext, n (%)				
I	2 (12.5)	2 (25)	0	
II	6 (37.5)	5 (63)	1 (12.5)	0.024
III	6 (37.5)	1 (12)	5 (62.5)	
IV	2 (12.5)	0	2 (25)	
Chemotherapy before intervention, n (%)	10 (62.5)	2 (25)	8 (100)	0.007

The mean of the size of the tumor was 9.2 ± 3.7 cm. According to the results of the images, 53% of patients had the right liver lobe compromised and in 24% of patients, the left lobe had been affected. Further on, it was classified with the PRETEXT classification (Table 1), showing a greater number in the transplant group than the patients that underwent resection (P = 0.024). The histological type with the highest prevalence was the epithelial (n = 12).

Module 3, Surgical Treatment and/or Chemotherapy

From 16 patients, 10 (62.5%) required chemotherapy before the surgical procedure. From these, 8 were transplanted and 2 underwent resection (P = 0.007) (Table 1).

Eight (50%) of the patients underwent surgical resection and the other half hepatic transplant. In patients that underwent surgical resection, 6 (75%) required a right hemihepatectomy, 1 (12.5%) a left hemihepatectomy with metastasectomy of the segments V-VIII, and 1 (12.5%) required segmentectomy of the segments VII-VIII. As to the transplants, 5 (62.5%) were from cadaveric donors (segments II and III) and 3 (37.5%) from related living donors (segments II and III).

The mean duration of surgical procedure in liver transplantation was 275 ± 27 minutes versus the mean time of the surgical resection 168 ± 52 minutes. The average intraoperative hemorrhage was 265 ± 205 mL, with requirement of transfusion in 14 (87.5%) of the cases.

For the cases of liver transplantation, the most common immunosuppressive scheme was tacrolimus plus prednisone (n = 3).

Module 4, Outcome and Survival

The mean duration of the hospitalization (including ICU and in-patient) from the day of the procedure was of 32.5 days (IQR, 18-45 days) until discharge. Complications were presented in 11 (68.7%) of the patients and classified according to the modified Clavien classification (Table 2). The complications were due to portal vein thrombosis stenosis of biliary duct, biliary fistula, sepsis, and pneumonia.

In the resection group, 5 (62.5%) where classified I by the Clavien scale (any deviation from the normal postoperative course without need of intervention beyond pharmacological therapy). On the other hand, in the transplant group, 4 (50%) had a score greater than II in the Clavien, including a patient with Clavien V who died in postoperative hospitalization due to pneumonia with high suspicion of infection by Aspergillus. The difference of the complications that the patients presented with in the 2 groups according to the Clavien was statistically significant (P = 0.036).

The mean time of follow-up after the surgical intervention was 27.3 months (4.7-38 months) (Table 2). One of the transplant patients had a relapse, confirmed by pathology, and unfortunately, there was a lack of follow-up. Patient survival at 30 months was 100% in the resection group and 64% in the liver transplantation group (P = 0.3232) (Figure 1).

DISCUSSION

This report includes 16 pediatric patients referred to the Transplant and Surgery Unit of the FVL (Cali), due to a diagnosis of HB, during the period 2011 to 2014. It is noted that the epidemiological behaviour regarding the biological characteristics and risk factors of the cases in this series is consistent with what is reported in the literature for HB.[17-19]

The diagnosis of HB usually occurs when the patient is taken to a medical consult due to the presence of an asymptomatic abdominal mass, which was observed in 6 (37%) of our patients. In 2 (12.5%), the diagnosis was done by a incidental finding, which is consistent with what is reported

TABLE 2.
Outcome and patient survival

Characteristics	Total (n = 16)	Resection (n = 8)	Transplant (n = 8)	*P*
Surgical time, min				
Mean ± SD	221 ± 68	168 ± 52	275 ± 27	0.0002
Range	75-330	75-220	240-330	
Intraoperative hemorrhage, mL				
Mean ± SD	265 ± 205	175 ± 139	355 ± 228	0.0782
Range	0-800	0-450	110-800	
Clavien-Dindo, n (%)				
I	5 (31.2)	5 (62.5)	0	
II	6 (37.5)	2 (25)	4 (50)	
IIIb	3 (18.8)	1 (12.5)	2 (25)	0.036
IVa	1 (6.2)	0	1 (12.5)	
V	1 (6.2)	0	1 (12.5)	
Hospitalization time, d				
Median (IQR)	32.5 (18-45)	18 (17-29)	41.5 (32-53)	
Range	16-55	16-37	31-55	0.0073
Follow-up time, mo				
Median (IQR)	27.3 (4.7-38)	33 (27-43)	7 (2-24)	0.0929
Range	0.6-50.6	0.6-50.3	1-50.6	
Death, n (%)	2 (12)	0	2 (25)	0.467

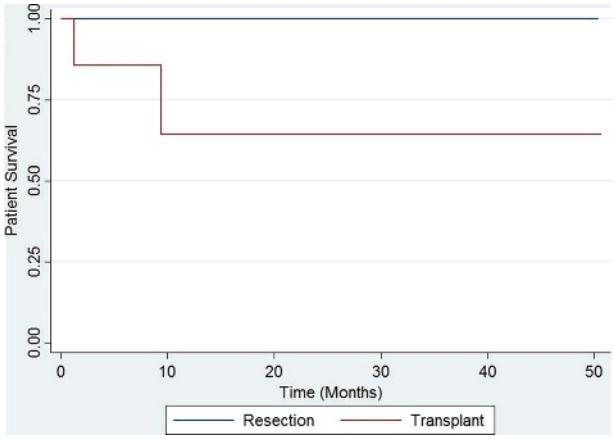

FIGURE 1. Survival analysis.

in the literature, 10% of cases are a incidental finding of hemihyperplasia during a physical examination.[20]

According to current guidelines, all patients undergo ultrasound and then a CT scan and/or MRI. Further on, a biopsy of the tumor mass is taken,[21] and an adequate sample for histology is obtained via open biopsy, laparoscopic, or percutaneous procedure. These procedures allow the visualization and capture of the tissue from a visible lesion and also offers an immediate and effective control of bleeding; reducing the mortality associated to hemorrhage during liver biopsy.[21] According to the literature, 85% of all cases of HB belong to the epithelial type,[1] which is the most common type of HB found in the study.

In the majority of cases, the chemotherapy begun extrainstitutionally and was interrupted until the referral to FVL. In these series of patients, this probably has contributed to the progression of the disease, generating the administration of a greater number of neoadjuvant chemotherapy cycles. In all of the cases, a chemotherapy regimen with C5V and doxorubicin was used for patients with intermediate and high risk, and in some patients, another chemotherapeutic agent was added. A great variability of the schemes and the number of chemotherapy cycles indicated was observed, whereas the therapeutic recommendation is to receive a total of 6 cycles of chemotherapy, performing 4 cycles presurgery and 2 cycles after the surgical intervention.[4]

In one of the cases of the transplant group, the patient had a PRETEXT II; this is because the patient had previous right hepatectomy and chemotherapy after the intervention. Nevertheless, a relapse was confirmed with CT scan where a well-defined mass was evident in the IV and VII segments of the right hepatic lobe, so it was decided to undergo transplant. Concerning the surgical treatment, the liver transplant had a longer operative time and more bleeding compared with the resection procedure (Table 2). This is related to the nature of the surgery and the severely ill patients undergoing this procedure.

Regarding the patients who underwent liver transplant, the percentage of surgical complications registered in our cases is comparable with what is reported in literature: vascular thrombosis was 13%, ranging between 8% and 12%, and bile duct stricture was 38%, occurring between 25% and 35% of the cases.[22] Most of the complications were handled without the need of surgical reintervention. For the cases of bile duct stricture, the treatment consisted of dilation using a balloon and/or the placement of a catheter with interventional radiology, and a small proportion of patients required surgical reconstruction.[23]

In relation to the stay in the ICU and in-patient, the duration was according to the complexity of the surgical procedure and its complications.

Patients who underwent hepatic resection presented a lower morbidity (lower levels in the Clavien et al, classification) compared with those who received a transplant. The foregoing possibly related to a smaller level of PRETEXT at the time of diagnosis.[9]

Within the series of cases reported by the specialized international centers in a period of 10 years, Pittsburgh received 21 patients, London reported 40 cases (in a period of 12 years), and Chile reported 9 cases (over a period of 4 years). It is worth pointing out that, over a 4-year period, 17 cases with diagnosis of HB were referred to our institution. This could probably mean that the prevalence of disease at a national level, within Colombia, may be high.

The number of patients that were determined to have a resectable mass was 8 (50%), which is similar to the reported in international series 44% to 91%.[18] For this group of patients, there was a survival rate of 100% obtained, at 35 months. Although for the transplanted group, survival at 35 and 50 months was found to be 65% (Figure 1). In one of the transplant cases, the patient had a progression of the disease that affected the lung and central nervous system and was therefore referred to palliative care.

We consider that the results previously mentioned are because the patients who required hepatic transplantation had a more advanced state of the disease, at their initial presentation, compared with the group who received a resection.

CONCLUSIONS

FVL is a major referral center aiming to promote a proper diagnosis, record, study, and standardize treatment of the disease, because of the prognosis of the disease changes according to treatment indicated and the experience of the medical groups in specialized centers.[24]

To our knowledge, this is the first case report of HB with liver resection or liver transplant in Colombia and Latin America. Additionally, it is important to advocate for an increase of reporting in the scientific literature regarding rare pathologies, because there are no data on prevalence, or geographical distribution, as is the case of HB at the national level and Latin America.

Being aware of these diseases would allow a better process of diagnosis and intervention and probably lead to more favorable outcomes in pediatric patients who suffer from this pathology. Likewise, it would aid in the assignment of resources to meet the huge economic burden that such diagnosis and treatment mean for families facing this pathology.

REFERENCES

1. Finegold MJ, Lopez-Terrada DH, Bowen J, et al, College of American Pathologists. Protocol for the examination of specimens from pediatric patients with hepatoblastoma. *Arch Pathol Lab Med*. 2007;131:520–529.
2. Kitanovski L, Ovcak Z, Jazbec J. Multifocal hepatoblastoma in a 6-month-old girl with trisomy 18: a case report. *J Med Case Rep*. 2009;3:8319.
3. Meyers RL, Tiao G, de Ville de Goyet J, et al. Hepatoblastoma state of the art: pre-treatment extent of disease, surgical resection guidelines and the role of liver transplantation. *Curr Opin Pediatr*. 2014;26:29–36.

4. Czauderna P, Lopez-Terrada D, Hiyama E, et al. Hepatoblastoma state of the art: pathology, genetics, risk stratification, and chemotherapy. *Curr Opin Pediatr*. 2014;26:19–28.
5. Spector LG, Birch J. The epidemiology of hepatoblastoma. *Pediatr Blood Cancer*. 2012;59:776–779.
6. Zimmerman A, Saxena R. Hepatoblastoma. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. *WHO classification of tumours of the digestive system*. 4th ed. Lyon, France: IARC; 2010:229.
7. Maibach R, Roebuck D, Brugieres L, et al. Prognostic stratification for children with hepatoblastoma: the SIOPEL experience. *Eur J Cancer*. 2012; 48:1543–1549.
8. Herzog CE, Andrassy RJ, Eftekhari F. Childhood cancers: hepatoblastoma. *Oncologist*. 2000;5:445–453.
9. Kremer N, Walther AE, Tiao GM. Management of hepatoblastoma: an update. *Curr Opin Pediatr*. 2014;26:362–369.
10. Roebuck DJ, Aronson D, Clapuyt P, et al. 2005 PRETEXT: a revised staging system for primary malignant liver tumours of childhood developed by the SIOPEL group. *Pediatr Radiol*. 2007;37:123–132; quiz 249–250.
11. Hishiki T. Current therapeutic strategies for childhood hepatic tumors: surgical and interventional treatments for hepatoblastoma. *Int J Clin Oncol*. 2013;18:962–968.
12. Haeberle B, Schweinitz Dv. Treatment of hepatoblastoma in the German cooperative pediatric liver tumor studies. *Front Biosci (Elite Ed)*. 2012;4: 493–498.
13. Malogolowkin MH, Katzenstein HM, Krailo M, et al. Treatment of hepatoblastoma: the North American cooperative group experience. *Front Biosci (Elite Ed)*. 2012;4:1717–1723.
14. Watanabe K. Current chemotherapeutic approaches for hepatoblastoma. *Int J Clin Oncol*. 2013;18:955–961.
15. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009; 250:187–196.
16. Manterola DC, Moraga CJ, Urrutia VS. Morbilidad postoperatoria en pacientes con hidatidosis hepática no complicada: utilización de una propuesta de clasificación de complicaciones. *Rev Chil Cir*. 2010;62: 362–368.
17. Rodriguez-Galindo C, Krailo M, Frazier L, et al. Children's oncology group's 2013 blueprint for research: rare tumors. *Pediatr Blood Cancer*. 2013;60:1016–1021.
18. Herrera JM, Rossi RF, Harris PD, et al. Progresos en el tratamiento y seguimiento de hepatoblastoma: análisis de una serie de 9 niños. *Rev Chil Pediatr*. 2002;73:43–50.
19. Caicedo L, Sabogal A, Serrano O, et al. Hepatoblastoma: trasplante versus resección. Experiencia en un centro de trasplante latinoamericano. *Rev Mex Traspl*. 2016; Abstract STALYC 2015.
20. Willert JR, Dahl G, Abrams AL, et al. Pediatric hepatoblastoma. Medscape. http://emedicine.medscape.com/article/986802-overview. Updated Novemeber 17, 2014.
21. Ovchinsky N, Moreira RK, Lefkowitch JH, et al. Liver biopsy in modern clinical practice: a pediatric point-of-view. *Adv Anat Pathol*. 2012;19:250–262.
22. Varela-Fascinetto G, Dávila-Pérez R, Hernández-Plata A, et al. Pediatric liver transplantation. *Rev Invest Clin*. 2005;57:273–282.
23. Holguin AJ, Rodriguez-Takeuchi S, Ospina L, et al. Biliary strictures complicating liver transplantation in pediatric patients: experience in a South American transplant center. *Clin Transplant*. 2017;31.
24. Serrano ÓJ, Villegas JI, Echeverri GJ, et al. Trasplante Simultáneo de riñón y páncreas en pacientes con diabetes mellitus de tipo 1, Clínica Fundación Valle de Lili, Cali, 2001-2013. *Rev Colomb Cir*. 2014;29:32–41.