Liver Transplantation for Malignant Primary Pediatric Hepatic Tumors

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BACKGROUND: Malignant primary pediatric hepatic tumors (MPPHTs) are rare and account for approximately 1% of all childhood malignancies. In recent years, liver transplantation has emerged as a viable treatment options for select patients with MPPHTs.

STUDY DESIGN: We performed a single-center retrospective study using a prospective database to compare outcomes of pediatric liver transplant recipients, with and without cancer, between January 2000 and December 2014.

RESULTS: One hundred fifty-three children underwent 173 liver transplantations during the study period. Of these, 21 (12%) children received 23 (13.3%) transplants for unresectable MPPHTs: 16 hepatoblastomas (HBs), 3 embryonal cell sarcomas (ECS), and 2 hepatocellular carcinomas (HCCs). There was no significant difference in 1-, 3-, and 10-year patient and graft survival rates between MPPHT and non-MPPHT patients (95.2%, 81.2%, 81.2%, and 95.2%, 72,2%, 72.2% for MPPHT vs 92.7%, 89.8%, 87.6% and 85.4%, 81.1%, 75% for the non-MPPHT group, respectively) ($p > 0.05$). Rates of 1-, 5-, and 10-year disease-free survival for MPPHT patients were 76%, 76%, and 76%, respectively. Median age at transplantation for MPPHT patients was 3.1 years (range 58 days to 17 years), median listing time was 81 days, and median wait list time was 15 days. Eight (38%) children had 2 tumors or more and 4 of 16 (25%) HB patients had metastatic disease at presentation. All children received neoadjuvant treatment, with radiographic response in 19 of 21 patients. Presence of metastatic HB at presentation, International Society of Pediatric Oncology Epithelial Liver (SIOPEL) high risk status, and persistently elevated alpha fetoprotein levels after neoadjuvant chemotherapy might be risk factors for tumor recurrence and decreased survival.

CONCLUSIONS: Liver transplantation is an excellent option for select patients with unresectable MPPHTs, with outcomes comparable to those after transplantation for nonmalignant causes. (J Am Coll Surg 2017;225:103−113. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Malignant primary pediatric hepatic tumors (MPPHTs) are rare and account for approximately 1% of all childhood malignancies.[1,2] Hepatoblastoma (HB) is the most common primary childhood liver tumor, with an incidence of about 1 per 1 million children, and it accounts for approximately 80% of all malignant primary pediatric liver tumors. Hepatocellular carcinoma (HCC) is the second most common primary pediatric liver malignancy, with an incidence of <0.5 per 1 million children; undifferentiated embryonal cell sarcomas (ECS), rhabdosarcomas, and germ cell tumors are much more rare.[2-4]

Prospective epidemiologic studies have suggested an increased survival for children with MPPLTs in recent times, mostly due to advancements in oncologic and surgical management.[1,3,5,6] Evolution in treatment of HB, in particular, represents a true success story in pediatric oncology. The SIOPEL (International Society of Pediatric Oncology Epithelial Liver) trials highlighted the chemosensitive nature of HB and showed that that use of

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Abbreviations and Acronyms

AFP = alpha fetoprotein
ECS = embryonal cell sarcoma
HAT = hepatic artery thrombosis
HB = hepatoblastoma
HCC = hepatocellular carcinoma
MPPHT = malignant primary pediatric hepatic tumor
PRETEXT = PRE-Treatment EXT-ension
SIOPEL = International Society of Pediatric Oncology Epithelial Liver
TACE = transarterial chemoembolization
UNOS = United Network for Organ Sharing

cisplatin-based neoadjuvant strategies increased HB survival from approximately 30% at 3 years to 75% at 5 years.[7-10] A similar survival benefit was also noted for select HB patients with metastatic disease at initial presentation and those whose disease remained unresectable after neoadjuvant chemotherapy and who received a liver transplant.[3,7,8,11-14] These results were later replicated in other centers around the world and completely transformed the management of HB.[7,8,11-13] The experience in management of other MPPHTs has similarly evolved over the past 2 to 3 decades, with transplant being routinely offered to select children with unresectable disease.[3,12,15,16]

Hepatoblastoma is staged using the novel PRE-Treatment EXT-ension (PRETEXT) staging system, which has demonstrated superior predictive value for survival compared with other staging methods and is believed to provide better assessment of treatment response and resectability.[7,13] It is based on Couinaud's segmentation of the liver, and the tumor is staged based on the number of involved hepatic sections (Table 1). Additional criteria can be added after the PRETEXT stage to provide more information on the extent of tumor: extrahepatic abdominal disease (E), tumor rupture or intraperitoneal hemorrhage (H), distant metastasis (M), lymph node metastasis (N), portal vein involvement (P), and inferior vena cava or hepatic vein involvement (V). Current recommendations for HB call for neoadjuvant chemotherapy followed by evaluation for surgical resection, with orthotopic liver transplantation reserved for children with unresectable HB (PRETEXT 4 or PRETEXT 2/PRETEXT 3 with major vascular involvement).[3,5,8]

Table 1. PRETEXT Staging System

PRETEXT stage	Definition
I	One section is involved and 3 adjoining sections are free.
II	One or 2 sections are involved, but 2 adjoining sections are free.
III	Two or 3 sections are involved, but no 2 adjoining sections are free.
IV	All 4 sections are involved.

PRETEXT, PRE-Treatment EXT-ension.

This article is a review of a single-center experience with liver transplantation for unresectable MPPHTs over the last 15 years. Outcomes are analyzed and compared with those for children undergoing transplantation during the same period for nonmalignant indications. Our earlier experience with liver transplantation for MPPHTs was previously reported in 2006.[14]

METHODS

This is a single-center retrospective study done using a prospectively collected database. Children (younger than 18 years) with MPPHTs, who underwent liver transplantation between January 2000 and December 2014, were studied. Data on patient demographics, tumor stage and size, neoadjuvant, and adjuvant treatment were collected. Data pertaining to patient and graft survival, disease-free survival, tumor recurrence, and treatment of recurrence were similarly reviewed.

Neoadjuvant therapies and liver transplantation were considered only for tumors not amenable to surgical resection based on multidisciplinary consensus. Presence of at least 1 of the following 4 criteria was required for a tumor to be declared unresectable. These criteria were previously described by Chen and colleagues[14]: underlying significant hepatic parenchymal disease (Child's B or Child's C cirrhosis); bilobar tumor (including central tumors involving both right and left hemi-livers or multifocal tumors with foci on both sides); absence of plane of resection; and involvement of major vasculature.

After completion of neoadjuvant treatment, which included chemotherapy for HB and ECS, and transarterial chemoembolization (TACE) for HCC, all patients were restaged and listed for transplantation with United Network for Organ Sharing (UNOS) if they met criteria. Pediatric End-Stage Liver Disease (PELD) or Model for End-Stage Liver Disease (MELD) exception points were requested and approved for all cases. Living donor evaluations were routinely performed as part of the transplantation workup. However, if a suitable living donor was not available, or if a suitable deceased donor became available before completion of living donor evaluation, then the decision was made to proceed with deceased donor transplantation.

Hepatoblastoma patients were staged using the PRETEXT system; the TNM staging system was used for HCC. Candidacy of HCC patients for transplantation