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Liver transplantation for hepatoblastoma

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Abstract

Liver transplantation is the only potentially curative option for unresectable hepatoblastoma. The introduction of platinum-based chemotherapy drastically improved the survival outcomes of patients with hepatoblastoma. However, the use of neoadjuvant chemotherapy and the optimal number of cycles required in patients listed for liver transplantation, as well as the potential use of adjuvant chemotherapy, remain unclear. Additionally, the shortage of donor liver grafts, along with the lack of clear consensus on the management of metastatic hepatoblastoma, makes the decision on whether to proceed to liver transplantation even more complex and challenging. Technological advances may optimize intraoperative imaging of both the primary tumor and metastatic sites, thus facilitating complete resection. Such improvements, along with the wider use of social media platforms to increase public awareness, could potentially pave the way for more optimal implementation of liver transplantation for the treatment of patients with unresectable hepatoblastoma.

Keywords: Hepatoblastoma, liver transplantation, chemotherapy, liver tumors, pediatric

INTRODUCTION

Hepatoblastoma is a rare tumor that accounts for the majority of liver tumors in children and typically presents in children less than three years of age[1,2]. The annual incidence of the tumor is 0.05-0.15 per 100,000[3]. This tumor can be sporadic in nature or occur in the context of another more complex genetic disease such as familial adenomatous polyposis (FAP) or Beckwith-Wiedemann syndrome[4,5]. The occurrence of the tumor has been associated with multiple gestational risk factors such as low birth weight, very low birth weight, and paternal or maternal smoking[6].

Approximately 20% of hepatoblastomas present with metastatic disease, and the most common sites of metastases are the lungs[7]. However, hepatoblastoma can remain asymptomatic even in advanced stages. When symptomatic, patients may present with abdominal mass or distention. Usually, liver function is preserved until very late in the disease process. Hepatoblastoma cases may require urgent care in the case of spontaneous tumor rupture or hemorrhage that may lead to the patients presenting with signs of acute abdomen or hemorrhagic shock[2,8].

The very first liver transplantation was performed in Denver, Colorado, by the pioneering surgeon Thomas Starzl[9]. In the early years of liver transplantation, the outcomes of the operation were poor; as such, it was considered only as a salvage option[10]. However, the first analysis of the outcomes of unresectable liver hepatoblastomas after liver transplantation performed by Otte *et al.* demonstrated favorable results[11]. They demonstrated that patients who had undergone primary liver transplantation for unresectable hepatoblastoma had a 10-year post-transplant survival of 85%, and patients who had undergone the same operation as a "rescue procedure" after a previous partial hepatectomy had a 10-year post-transplant survival of 40%. Additionally, a report on the world experience of liver transplantation for unresectable hepatoblastoma showed that patients undergoing primary liver transplantation had a survival of 82%, while patients undergoing rescue liver transplantation had a survival of 30%. These unexpected data made liver transplantation a progressively acceptable option for the treatment of advanced stage hepatoblastoma among pediatric surgeons and oncologists. Once the patient selection criteria became stricter, outcomes started to improve even more[10,12]. These changes, along with the increased availability of deceased donor liver grafts, which can be attributed to modifications of the organ allocation system, have made liver transplantation considered a feasible treatment option for advanced stage hepatoblastoma[13-15]. Despite the many steps forward that have been taken, controversies still exist. To this day, no consensus has been reached on the implementation of neoadjuvant and adjuvant chemotherapy on transplant patients[16]. Additionally, the optimal timing of the operations and the type of graft to be used are yet to be clarified[16]. En bloc resection of the tumor and metastases remain the cornerstone of treatment; thus, in the current era, multiple imaging modalities are being developed that could potentially help surgeons identify tumor cells and metastases and facilitate the complete resection[17-20].

The aim of this review is to assess the role of chemotherapy and surgery in the treatment of unresectable hepatoblastoma, the changes in the outcomes of liver transplantation as a curative option for hepatoblastoma, the different types of grafts that may be implemented, the advances in the management of metastatic disease, and the possible implementation of biomarkers as prognostic factors for outcomes.

HISTOPATHOLOGY

Hepatoblastoma is derived from the embryonal cells of the liver, called hepatoblasts. These primitive liver cells are arrested in different phases of their development, and it is this arrest that provides a diversity of histologic subtypes. Mesenchymal, epithelial, and undifferentiated cells are combined in different ways and produce these different subtypes, which are very difficult to classify even by very experienced pathologists,

because of the rare nature of the tumor[2,8]. A growing number of studies have attempted to identify associations between the histopathologic subtype of the tumor and prognosis, with limited success. Only two histologic subtypes have been associated with prognosis to date. Patients with well-differentiated pure fetal hepatoblastomas have a great prognosis with surgical treatment alone, while patients with small cell undifferentiated hepatoblastomas tend to have a more dismal prognosis[2,8].

IMAGING AND STAGING

Radiological imaging is of vital importance as excellent quality imaging is needed for the determination of preoperative staging. The imaging modalities of preference include contrast computed tomography (CT) scan and magnetic resonance imaging (MRI), whereas some radiologists prefer magnetic resonance angiography (MRA) with the use of specific contrast agents, such as gadoxetate disodium, which may be useful in the localization of multifocal disease[21].

The rarity of the tumor led to the formation of a multitude of international collaborations for the optimization of the multimodal management of hepatoblastoma. These groups include SIOPEL (Societe Internationale d'Oncologie Pediatrique)[22-26], COG (Children's Oncology Group)[26-31], JPLT (Japanese Study Group for Pediatric Liver Tumor)[32-35], and GPOH (German Society for Pediatric Oncology and Hematology)[36,37].

Throughout the years, the different study groups have been implementing different staging systems. Children's Oncology Group used the Evans staging system (Stage I, resected at diagnosis; Stage II, attempted resection at diagnosis; Stage III, preoperative chemotherapy; Stage IV, metastatic at diagnosis). On the contrary, the SIOPEL group, which has always supported the need for neoadjuvant chemotherapy prior to any surgical intervention, formulated a pretreatment staging system [Pretreatment Extent of Disease (PRETEXT)] that is based on imaging, is non-invasive, and is performed prior to the initiation of any treatment modality. According to the PRETEXT classification, the liver is divided into four different segments, a right anterior, a right posterior, a left lateral, and a left medial[26]. Depending on the percentage of the liver parenchyma that is affected, the patients are assigned to different groups. If only one segment of the liver is affected, then these patients are assigned to PRETEXT I group; if two adjacent segments are affected, then the patients are considered PRETEXT II; if only one segment of the liver is tumor-free, then the patients are considered PRETEXT III; and, if the whole liver parenchyma is affected, then these patients are classified as PRETEXT IV[38]. The PRETEXT staging system also takes into consideration the extent of extrahepatic disease through the use of the various annotation factors (V, hepatic veins or retrohepatic vena cava; P, main portal bifurcation; E, contiguous organ such as diaphragm, abdominal wall, bowel, *etc.*; F, multifocal tumor nodules; R, tumor rupture at diagnosis; N, lymph nodes; C, caudate lobe; M, distant metastasis). Restaging is performed once chemotherapy has been completed, and the post-treatment extent of disease (POSTTEXT) classification - similar to PRETEXT has four groups and the same annotation factors - is used at that point[38]. Currently, all different study groups have adopted the PRETEXT staging system[39].

Given the decreased annual incidence of the tumor, the small number of patients that are included in each study group, and the various staging systems that each group implemented, the Children Hepatic tumor International Collaboration (CHIC) was formulated with the aim of creating a universal risk stratification system for hepatoblastoma[40]. CHIC created an international database based on the patients who were reported in eight multicenter studies and eventually formulated five groups that are based on the known prognostic factors: (1) PRETEXT I/II; (2) PRETEXT III; (3) PRETEXT IV; (4) metastatic disease; and (5) α-fetoprotein (AFP) level of ≤ 100 ng/mL at diagnosis. The authors performed a multivariable analysis and

came up with a new risk stratification system, which was the first to ever include age and VPFR as important determinants of outcome. The same risk stratification system is being used in the Paediatric Hepatic International Tumor Trial (PHITT)[41].

THE ROLE OF CHEMOTHERAPY AND SURGERY

As shown in a recent analysis by the National Cancer Database[42], chemotherapy and surgery are the cornerstones in the management of hepatoblastoma. The introduction of cisplatin-based chemotherapy improved the survival rates of patients with hepatoblastoma. The initial survival rates of patients diagnosed with this specific tumor were around 30%. Currently, the survival rates exceed 80%; this great increase is the result of a combination of factors[16]. The introduction and formation of multiple international collaborations are two of the most important contributing factors to this improvement of the overall survival rates[2]. The use of cisplatin as monotherapy has demonstrated great results in standard risk tumors, whereas either carboplatin or doxorubicin and intensive weekly doses of cisplatin have demonstrated great results for tumor shrinkage in high-risk and very high-risk patients[23,43].

Although many children with hepatoblastoma present with resectable disease, identifying the optimal surgical management for patients with unresectable hepatoblastoma is particularly challenging. Some patients may initially present with unresectable tumors, but neoadjuvant chemotherapy can lead to downstaging and eventually resection, while others may not respond well to chemotherapy and remain unresectable. These tumors usually distort a large percentage of the liver parenchyma, are multifocal, or demonstrate extensive involvement of the hepatic vascularity, as they may infiltrate the hepatic or portal vein[12]. Such tumors may be treated with either extreme liver resection or liver transplantation.

On the one hand, by performing an extreme liver resection, patients are spared the long-term immunosuppression that is required after liver transplantation, but performing an extreme resection requires excellent surgical technique, and even in the skilled hands of an experienced surgeon, it can lead to a very small and non-functional liver remnant. Some of these patients may eventually require salvage liver transplantation, a procedure that has inferior outcomes compared to primary liver transplantation[44]. On the other hand, liver transplantation offers the possibility of complete removal of any visible tumor as well as any other non-visible tumor deposits, but it is a complex procedure that necessitates proper multidisciplinary care, a supportive system, and the use of lifelong immunosuppression[45].

In general, patients with PRETEXT IV multifocal lesions, a POSTTEXT IV lesion, or a central or extensive lesion that may infiltrate the IVC, the portal vein (P+), or all three hepatic veins should be considered as having unresectable hepatoblastoma and be referred early on for liver transplant evaluation in specialized centers[44,46].

Although the importance of chemotherapy overall has been documented in patients requiring liver transplants for hepatoblastoma, the most optimal setting of administration (neoadjuvant only *vs.* adjuvant only *vs.* both neoadjuvant and adjuvant) has yet to be determined. Currently, there is no clear consensus as to whether chemotherapy should be used after liver transplantation in the adjuvant setting. It seems that there is a tendency in transplant centers to use post-transplant chemotherapy[47]. Moon *et al.* suggested excellent results in patients who undergo both liver transplantation and adjuvant chemotherapy[48], with survival rates over 80%. However, data from Pediatric Liver Unresectable Tumor Observatory (PLUTO), an international database that collects liver transplantation data from 134 reporting centers, did not show any benefit of the use of adjuvant chemotherapy[15]. This study group failed to show the benefit of chemotherapy after assenting 110 patients who underwent liver transplantation, including 85 who received chemotherapy

and 25 who did not[15]. Additionally, Ziogas *et al.* in their recent analysis demonstrated that the use of chemotherapy is associated with superior outcomes[16], and the timing of the administration of the chemotherapy (neoadjuvant *vs.* adjuvant *vs.* neoadjuvant and adjuvant) did not influence the outcomes in surgically treated children with hepatoblastoma.

OUTCOMES OF LIVER TRANSPLANTATION FOR HEPATOBLASTOMA

In a recent analysis of the United Network for Organ Sharing database, Ezekian *et al.* demonstrated the improved outcomes of patients undergoing liver transplantation for hepatoblastoma in the current era[10]. They divided the patient cohort into two subgroups based on the timing of their transplant: patients who underwent liver transplantation after 2010 were categorized in the contemporary group, whereas patients who underwent liver transplantation prior to 2010 were categorized in the historic group. When comparing the two groups in terms of survival, the contemporary group demonstrated superior one- and five-year survival rates (one-year, historic 84.6% *vs.* contemporary 89.1%; five-year, historic 75.1% *vs.* contemporary 82.6%; $P < 0.001$).

This temporal improvement in outcomes could be attributed to an increase in the utilization of deceased donor segmental allografts. This increase in the utilization of deceased donor allografts might be due to changes that have occurred over the past years that make deceased donor grafts more accessible to patients with hepatoblastoma. In an attempt to implement a "sickest first" approach to organ allocation, Model for End-stage Liver Disease/Pediatric End-stage Liver Disease scores is used in the USA to prioritize deceased donor liver allocation[49]. However, these scores do not reflect the real burden of hepatoblastoma. In 2010, patients with hepatoblastoma were granted a Pediatric End-stage Liver Disease score of 30 for 30 days, and after that timeframe, they were listed as Status 1B[13]. Since 2011, patients with hepatoblastoma have been immediately listed as Status 1B without having to wait for 30 days[14], facilitating their to deceased donor grafts and decreasing waitlist times and, thus, waitlist-related mortality.

However, the utilization of deceased donor liver grafts comes with a price. Patients and surgeons can never be certain when the graft will be available, and therefore the predetermined cycles of chemotherapy may be interrupted and resumed after the operation is performed[15]. The lack of timing is the main drawback of deceased donor liver grafts. It has been reported that, in the USA, around 7% of patients who are on the waiting list are removed because of medical deterioration or death[50]. Similar findings were reported by Wu *et al.*[51], who reported on a cohort of 763 children with hepatoblastoma. They noted that 3.5% of patients experienced waitlist mortality, 8.5% remained on the list or were removed from the list for another reason, and 87.9% underwent liver transplantation[51].

LIVING DONATION

Candidates for liver transplants may alternatively receive a graft from a living donor. Several studies have reported on the trends of the implementation of different types of grafts based on the availability of each graft type in different parts of the world (eastern *vs.* western countries)[52]. Zhang *et al.* recently reported that using grafts from living donors is preferred for pediatric liver transplantation[53]. This trend towards living donor liver transplantation (LDLT) in Asia can be justified by the decreased numbers of deceased donor grafts that are available, mainly due to cultural reasons, which has led to great improvements and advancements in the technical aspects of the operation and survival outcomes[54].

The use of a liver graft coming from a living donor is very useful for the management of hepatoblastoma, as the transplant procedure becomes elective, which can allow for optimal timing between chemotherapy and surgery, and thus it prevents the clinical deterioration of patients[55]. To increase the availability and supply

of living donor liver grafts, paired liver exchanges (PLE) and non-directed liver transplantations (NDLT) are increasing in popularity.

PLE is a procedure in which two or more living recipient and donor pairs swap for a compatible transplant[56]. PLE as an option assists in the shortening of the waitlist and, thus, helps to reduce waitlist-related mortality. Indications for PLE include ABO incompatibility, suboptimal hepatic mass, or anatomical considerations[57]. Another interesting option that may increase the availability of living donor liver grafts in pediatric patients is NDLT. NDLT, also called altruistic donation, is the procedure in which a living donor donates an organ or a part of an organ to an unknown recipient[58]. Even though it is not currently the most popular option for living donor liver grafts, the incidence of implementation has increased over the last few years[59]. It is worth mentioning that, in 2020, 11% of LDLT performed were NDLT[59]. As deceased organ donations have low rates currently, transplant centers and communities have invested in increasing public awareness about living donor transplantations[60,61].

Nevertheless, different studies report conflicting data regarding the survival outcomes by graft type. Austin *et al.* demonstrated better survival in LDLT[62], along with better outcomes in terms of graft failure in the living donor graft group. Khalaf *et al.*[63], on the contrary, demonstrated better results in favor of deceased donor liver transplantation. In their single-center experience, this study group showed that recipients of living donor grafts had an increased incidence of vascular complications, which led to poorer survival outcomes[63]. Zhang *et al.*[53], despite the fact that they also demonstrated that vascular complications were more common in LDLT recipients, failed to prove that there was any significant difference in survival between the two groups. Similar findings were reported by Ziogas *et al.*[64], who analyzed patients with cholestatic liver disease from the Organ Procurement and Transplantation Network database and concluded that survival was similar between patients who received donations from living donors, donations after brain death, and donations after circulatory death.

MANAGEMENT OF METASTATIC HEPATOBLASTOMA

The presence of persistent or unresectable metastasis is an absolute contraindication to liver transplantation[65]. Thus, eradication of metastasis prior to liver transplantation is of paramount importance. Dose-intensechemotherapy or metastasectomy may be performed. The most common sites of hepatoblastoma metastases are the lungs. It has been reported that 40%-60% of patients with metastasis may demonstrate resolution of the metastatic disease with chemotherapy alone[23,24]. Some study groups have also previously implemented the use of thoracotomy for the resection of metastasis[66].

In the current era, indocyanine green (ICG)-guided minimally invasive surgery for the clearance of metastasis seems to have gained popularity among surgeons[17,19,20,67]. ICG is an organic anion that is directly taken up by bile; thus, it does not undergo biotransformation or enterohepatic circulation[68]. ICG is actively taken up by the cells of the hepatoblastoma, but these cells delay the excretion of the molecule in the bile, and this longer retention of ICG in the cancerous tissue facilitates the visualization of the hepatoblastoma in near-infrared mode (NIR)[17]. ICG has been successfully used in the resection of metastases from the lungs, diaphragm, and peritoneum. Kitagawa *et al.* reported how their group implemented ICG in 10 patients and performed a total of 250 fluorescent-positive excisions over 37 operations[19]. Only 29 of them were proven not to be hepatoblastoma metastases, which demonstrates the high specificity of the agent. Similarly, Yamamichi *et al.* demonstrated how their group implemented ICG in the resection of a primary tumor[18], a recurrent tumor, and a metastatic lesion in the lungs. Takahashi *et al.* also used ICG for the resection of hepatoblastoma peritoneal metastases[20].

DEVELOPMENT OF NEW BIOMARKERS AND FUTURE DIRECTIONS

Despite the current advances, there is an increased need for the development of new prognostic markers that could potentially offer a personalized approach to the surgical management of hepatoblastoma[69]. Several research groups have been trying to identify associations that could help predict outcomes and recurrence of the disease. Isono *et al.* noted that a rise in AFP levels after the last chemotherapy session prior to transplant was associated with recurrence[70], whereas Umeda *et al.*[71], in their single-center experience, demonstrated that a decrease in the AFP levels of > 95% led to the absence of disease remission. Triana *et al.*[72], despite their effort to assess multiple factors that could potentially be associated with outcomes of liver transplantation, were unable to find any statistically significant prognostic factor for liver transplantation. Sakamoto *et al.* used multivariate analysis and demonstrated that AFP levels over 500,000 ng/mL at diagnosis[73], donor age less than 39 years, AFP level at LDLT more than 4000 ng/mL, histopathological subtype of hepatoblastoma, and histopathological vascular invasion were all associated with tumor recurrence.

Well-differentiated pure fetal hepatoblastomas are characterized by cells that have very low mitotic activity and resemble fetal hepatocytes. Malogolowkin *et al.* demonstrated, in a study published under the aegis of COG, that patients with this type of histopathology who were treated with surgery only demonstrated a 100% event-free survival[74]. Small cell undifferentiated hepatoblastomas, on the contrary, have been demonstrated to have a very poor response to chemotherapy along with low AFP levels, which is on its own a factor that may demonstrate poor prognosis. Three different reports by three different working groups have demonstrated almost zero survival of patients who have this histological subtype[74-76]. Under this prism, many symposia have been held to create an international consensus for the classification of these tumors[77], and thus future research should also focus on evaluating the outcomes of children with hepatoblastoma by histologic subtype.

On another note, given the limited availability of deceased donor grafts and the organ shortage crisis that the USA currently faces[78], developing new methods of community outreach and raising awareness may be particularly helpful. A strategy that seems promising is the use of social media[79,80]. Henderson *et al.*[79], in their recently published study, handed out a questionnaire to 299 members of the American Society of Transplant Surgeons about their use and perceptions of social media. This study demonstrated that centers that reported monthly or weekly outreach had a higher volume of kidney transplantations compared to those that did not. The impact that social media can have on increasing the number of donations was highlighted by a group of researchers at Johns Hopkins[80]. According to this study, in May 2012, Facebook facilitated the sharing of its users' donor status with their friends and additionally provided them with quick links that could help them officially register as donors. This action led to a 21-fold increase in the number of donors who registered on a single day[80].

CONCLUSION

The management of hepatoblastoma is complex and requires the existence of a multidisciplinary team in a tertiary center that has dedicated tumor boards. This multidisciplinary approach facilitates the accurate diagnosis, staging, and treatment of the condition. History has proven that amazing progress can be achieved during the nearly two decades in the field of liver transplantation for liver malignancies. That progress is shown in the great improvement of outcomes that have been achieved overall and for hepatoblastoma specifically. It is only reasonable to expect that analogous progress will be accomplished in the years to come as we have a better understanding of the role of chemotherapy before or after liver transplantation, better management of patients on the waiting list, and optimal selection of donor grafts. The formation of collaborations between the four collaborative hepatoblastoma groups will pave the way for

the standardization of treatment protocols and optimization of patient care. Improvements in the field of fluorescent-guided surgery could help in the minimally invasive removal of metastatic disease. These initiatives, along with the promotion of awareness and education on donation, could potentially mitigate the hardships faced currently, leading to a wider and safer implementation of liver transplantation. The steps that are currently taken should make surgeons very optimistic about the future implementation of liver transplantation as the only curative option for advanced stage hepatoblastoma.

DECLARATIONS

Authors' contributions

Literature search, data gathering and interpretation, manuscript drafting: Varvoglis DN
Study concept and design, literature search, data gathering and interpretation, critical revision: Ziogas IA
Data interpretation, critical revision: Tsoulfas G

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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