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Hepatoblastoma: Is it really un-resectable?

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Abstract

Aim: This study aims to evaluate the results of the patients with hepatoblastoma who underwent resection or liver transplantation.

Material and Methods: The patients referred to our clinic for liver transplantation due to un-resectable hepatoblastoma were included in the study. They were evaluated according to demographic findings, alpha feto-protein level, the surgery type, and clinical results.

Results: Between 2006 and 2020, 32 patients with hepatoblastoma were investigated among all liver transplant patients. All patients have been referred to us because of un-resectable hepatoblastoma. Twenty-five patients underwent liver transplantation, and the other seven underwent hepatic resection without transplantation. The donor preparation has been done for all patients, including the resection group. The overall survival rate was 76% for transplant patients and 71.4% for resection patients.

Conclusions: LT is an important surgical solution in patients with unresectable hepatoblastoma. In the state of requiring extended resection, preparing a donor simultaneously provides surgical options during the surgery.

Introduction

Hepatoblastoma (HB) is a malignant tumor that is characterized as a large painless mass in the abdomen, accompanying high alpha-fetoprotein protein (aFP) levels, and constituting 90% of childhood liver cancers, especially seen among children under 5 years of age [1, 2]. Its frequency is 1.2/1,000,000, and 100 new cases are detected in the United States (US) every year [2]. It is found to be 1.5 times more common among boys than girls [3].

Before 1980, when chemotherapy was still not used to treat the disease, surgical resection seemed to be the only treatment, however survival rates were reported as low as 20–30% [4]. After the year 1980, it was reported that the 5-year-survival rate increased to 75% with the increase in platinum-based chemotherapy protocols pre and post-surgical resection [5-6]. Current treatment approaches include combining the preoperative and postoperative systemic chemotherapy with mass liver resection. To brief the process, it can be defined as the autologous peripheral blood stem cell transplantation (APBSCT) combined with local high-dose chemotherapy by interventional radiology; and liver transplantation (LT) with preoperative and postoperative systemic chemotherapy [1, 7].

Although the malignancy generally responds well to systemic chemotherapy, complete removal of the primary tumor seems to be the most important key in the treatment of HB [8]. Improvements in the surgical technics and technology have led to extensive liver resection metastasectomy surgeries. In recent decades, LT has constituted as a great surgical option in HB surgery [9].

In this study, the preparations, surgeries, and surgical results of HB patients referred to our clinic for LT are shared, furthermore the importance and advantages of living donor liver transplantation (LDLT) are emphasized. In addition, it is concluded that the patients who have undergone tumor-free surgical resection without LT after being prepared for their live donors are an advantage of LDLT.

Material and Methods

Patients referred to our clinic for LT with an non-resectable HB and who underwent resection or LT were included in the study. Ethics committee approval was issued by Memorial Hospital local Ethics Committee, dated on 29.04.2020 with the decision no:2. The study was conducted and completed according to the principles of the Helsinki Declaration of 2008.

Information about the preoperative preparation protocols was given to the patients and their donors. The study includes the evaluation of the demographic data of all pa-

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tients and the donors, the type of surgery performed, surgical complications encountered, mortality/survival rates obtained, and inpatient services. Postoperative follow-up and immunosuppression protocols of transplant patients were presented. Since liver transplant and hepatic resection patients were two different groups, a comparative study was not performed.

Liver Transplant Recipient Preparation: All of the patients who underwent LT or resection were referred to our clinic from the Department of Pediatrics Oncology with HB diagnosis. All recipient patients were prepared according to the routine" LT preparation program" applied in our clinic. Complete blood count, coagulation tests, comprehensive biochemistry analysis, tumour markers, viral serology, blood and urine cultures, were performed in addition to whole abdomen Ultrasound-Doppler, contrast-enhanced thorax-abdominal tomography (CT)/magnetic resonance (MR) examination and hepatic vascular reconstruction, lung function tests, and cardiac examinations. Pediatric gastroenterology and cardiology, chest diseases, and infectious diseases consultations were also performed.

Donor Preparation: Preparations were initiated by the search of donors among adults aged between 18-65 and with blood type compatibility. Ethics Committee approval was obtained from the 4th degree distant relative donor candidates. The examinations included complete blood count, coagulation tests, coagulation genetic tests [Factor V Leiden and Prothrombin (factor II) Gene mutation], comprehensive biochemistry analysis, tumour markers, viral serology, and blood and urine cultures. Parenchyma structure and vascular anatomy were visualized by liver tri-phasic CT angiography. The biliary anatomy was evaluated with MRCP. The estimated weight of the graft to be used was calculated by tomography. The age and weight of the recipient patient were used as the determiners for the graft to be used. In donor preparation; fatty liver greater than 10%, homozygous Factor II and/or Factor V Leiden mutations, and any systemic comorbidities were considered as contraindications.

Preparation of liver resection

This patient group was also referred to our clinic for LT. Patients who were thought to undergo primarily hepatic resection were taken into surgery by making donor preparations due to the possibility of liver failure or residue tumor after extended liver resection. All surgical preparations were done in order that the donors could be operated any time, and they were kept ready in the inpatient ward.

Immunosuppression protocol

Calcineurin inhibitors (tacrolimus or cyclosporine) and prednisolone-based protocol were used as post-transplant immunosuppressive therapy. Mycophenolate mofetil (MMF) was added to immunosuppression on need. Calcineurin inhibitor doses were adjusted according to the daily plasma levels.

Follow-up: In the post-discharge period, the patients were referred to the Pediatric Oncology team. LT was followed up in the outpatient clinic for at least every month during the first year and then every 3 to 6 months in the following years if needed. In addition to routine biochemical parameters, aFP levels were also measured at follow-up. HB recurrence control with abdominal MRI/CT and thorax CT was performed according to the clinical examination and aFP values.

Table 1. Demographic finding of LT and liver resection cases

	Hepatoblastoma	Liver Resection
Gender	Male: 14 (56%) Female: 11 (44%)	Male: 5 (71.4%) Female: 2 (28.6%)
Age	3.9 ± 3.5 years (R: 0.5–14.5)	2.0 ± 0.9 years (R:8 ay-3.5 yıl)
Body weight	15.6 ± 11. 9 kg (R: 7. 1–65)	13.0 ± 3.2 kg (R: 8–18)
Follow-up	4.2 ± 3.0 years	3.0 ± 1.7 years
Overall survival	76%	71.4%

Statistical analysis

According to the descriptive nature of the study, no comparisons were performed between LT and Resection groups.

Statistical analyses were performed using the IBM Corp. released in 2019. (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Descriptive statistics will be presented using mean, standard deviation, median, minimum, maximum for continuous variables, frequencies (n) and percentages (%) for categorical variables. Kaplan Meier survival graph is used to indicate the survival rates.

Results

In our clinic, 1246 LTs were performed for 1203 patients between the years 2006 and 2020. Patients who were transplanted due to HB or referred for LT and had resection without LT were included in the study.

LT patients:

The demographic information of the 25 patients who underwent LT is summarized in Table 1.

It was remarkable that two female patients in the group were identical twins.

In the preoperative MRI/CT imaging of the patients, it was observed that all patients were PRETEX 3 and 4, and the mean aFP level was 41,495 ± 119,658 IU/ml (R: 5–450,800). All patients were followed by pediatric oncology before LT and entered LT process after two to six cycles of chemotherapy. As preoperative chemotherapy, Cisplatin-based treatment was used in varying doses and number of times depending on the patient.

Twenty-two patients were referred to us without surgical intervention after chemotherapy due to a non-resectable mass, and LT was performed. Among these 22, one patient had a single focal metastasis in the right lung. The other three patients had a history of previous liver mass resection. Two of these three patients had undergone LT; the former due to liver failure after wide resection and the latter local liver tumor recurrence.

One of the liver transplants performed was a full-size graft from a deceased donor, and the others were four right lobes, and 20 left lateral segment transplants from living donors. The graft to be used in living donors was determined according to the age and weight of the patient and the liver anatomy of the living donor. The mean weight of the grafts used was 347 ± 195 g, and the mean graft-body ratio (GBR) was 2.6 ± 0.8%. End-to-end bile duct anastomosis was performed in the right lobe and cadaveric transplantations (five patients) as bile duct reconstruction, and Roux-Y bile anastomosis technique was used in the other 20 patients who gave left lateral grafts.

A total of six patients among 25 LTs died in the early and late periods. Two (8 %) patients were lost in the perioperative period; one died due to sepsis and the other due to cardiogenic shock. The other four patients were lost due to disease recurrence in the pediatric oncology clinics, where their treatment was in the 1st, 2nd, 4th and 8th years after LT.

Major complications were seen in the early and late periods in a total of five (20%) patients. Re-laparotomy + bridectomy was performed in one patient due to mechanical bowel obstruction in the perioperative period. One patient required laparotomy drainage due to biliary leakage. The endoscopic intervention was needed in one patient due to gastrointestinal system bleeding. Pleural drainage was carried out in one patient due to massive pleural effusion. Percutaneous catheterization and dilatation were performed in one patient due to late biliary stricture.

The patient who had a metastatic lung lesion before LT underwent resection of the lung tumor metastasis 1 month after LT. The patient is still under follow-up, and he has no recurrence or metastasis in his 3rd year of LT.

All surviving patients were referred to pediatric oncology clinics to continue chemotherapy after discharge, and their chemotherapy continued. In the oncological follow-up of the patients, one patient had multiple lung metastases in the 3rd month postoperatively, and her chemotherapy is going on. This patient with early lung lesions is a 14.5-year-old patient who underwent LT with above 50,000 ng/ml of aFP level without any benefit from three cycles of chemotherapy before surgery.

LT patients were discharged in a mean of 15.5 ± 5.9 days, and the mean follow-up period was 4.2 ± 3.0 years. Overall survival in all patients was 76%, and the 1-year, 3-year, 5-year, and 10-year survival rates were 87.6%, 83.2%, 76.8%, and 64%, respectively (Figure 1).

Donors

Of the 24 donors, who 14 were male and 10 females, 23 were close relatives up to the 4th degree. One donor was a distant relative and needed to be approved by the ethics committee. The mean age was 35.2 ± 10 years, and the mean BMI was 26 ± 5. Right lobe hepatectomy was performed in four of these donors, and left lateral segmentectomy was performed in 20. In the postoperative period, minor complications that did not require intervention developed in five donors. Gastric ulcer bleeding requiring endoscopic sclerotherapy was observed in one of the donors. The donors were discharged in an average of 7.4 ± 2.5 days.

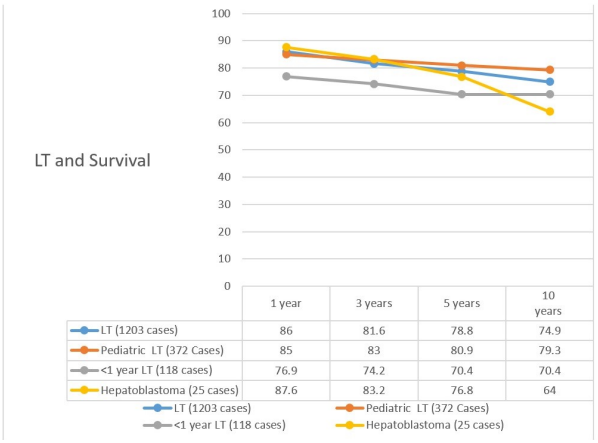

Figure 1. Survival of LT cases.

Liver resection patients

Primarily hepatic resection was decided for seven of 32 patients who were referred for LT preoperatively. Demographic information of patients who received three to five sessions of chemotherapy before surgery is summarized in the table. All patients underwent resection after the donor preparation. In the medical history of one patient, the first diagnosis was made with intra-abdominal tumor rupture.

As for the liver resection, two extended right, one right, one extended left, and three non-anatomical segmental tumor resections were performed, and LT was no longer needed. None of these patients had major complications in the postoperative period. One patient was followed up with a biliary leak and regressed spontaneously; another was followed up medically for ileus after surgery.

The mean follow-up period was 3.0 ± 1.7 years. Two patients under chemotherapy treatment were lost due to metastatic disease after 1.5 and 2.5 years following the surgery, and the overall survival rate was 71.4% for hepatic resection.

Discussion

After the first liver transplant for HB was performed by Starzl et al. in 1968, it has become a part of treatment in children considered non-resectable [9].

Although there is no specific gene mutation for HB that has been demonstrated, it may accompany genetic syndromes, such as familial adenomatous polyposis coli, trisomy 18, Prader-Willi or Beckwith-Wiedemann syndrome, suggesting that a genetic predisposition combined with environmental factors causes the disease to occur [10]. The studies of Riikonen et al. on HB in twin boys have been one of the greatest proofs that the disease has a genetic basis, and there are still many gene studies on this subject in the literature review [11]. It is noteworthy that two of the patients who underwent LT in our series were identical twin girls.

Another interesting issue in this case series was LT in a patient with concurrent lung metastases. During the preparation period, a 1.5-cm lesion was detected in the patient's right lung, and the main tumor focus was decided to be removed by performing LT. The mass in his lung was also removed in the first month after LT. The

patient, whose chemotherapy was continued by oncology after surgery, was doing well at the 3-year follow-up, and no recurrence was found in his controls. Concerning this situation, in a study published in 2021, it was observed that especially single lesion lung spread before LT did not affect long-term survival, and lung metastases after liver transplantation had a little worse effect on survival compared to other distant organ metastases [12].

In 2002, Pimpalwar et al. reported that the survival rate in patients who underwent LT because of local recurrence following resection was 30% less than that of patients who underwent direct LT [13]. Another study claimed that this situation could be considered as a relative contraindication due to the poor results of patients who relapse after resection [14]. In contrast to these studies, 525 liver resections and 103 LT operations were compared in the US HB database, and no significant difference was found in survival and disease-free survival between resection and LT [15]. In the same study, although the metastatic disease was detected on an average of 17% at the time of diagnosis, it did not affect survival. In the study from Japan, no significant difference was found in terms of survival between patients who developed recurrence after resection and underwent LT and those who underwent primary LP without resection [12]. In both studies, the importance of neoadjuvant and adjuvant chemotherapy and its effect on survival is noted.

Considering all current literature, the most important point in HB surgery is surgical resection without leaving any residual tumor [8]. In addition to resection, LT has been added to the surgical interventions performed to avoid residual tumors. With LT, it offers the opportunity to remove the organ that is the source of the disease, even in PRETEX 3-4 tumors, without leaving any residue. Despite its great advantages (the mortality rate of LT, the biliary or vascular complications of LT, the need for lifelong immunosuppression, and the presence of complications related to immunosuppression, and most importantly, the presence of donor complications and mortality), in countries such as Turkey where the use of living donors predominates, LT should be prioritized only in patients who cannot undergo safe resection.

In our clinical experience, LT also provides an advantage in terms of extended liver resections. It is an important surgical advantage that liver transplantation can be performed in case of a possible post-resection complication by keeping the living donor ready in patients who are thought to have safe tumor resections that will lead to very large resections.

In our clinic, routine donor preparation has become a rule in patients who are planning extensive liver resection. On the day of surgery, unlike other LT groups, the recipient's operation is started first. If safe resection is possible, extended resection is performed, but if safe resection is not possible, LT is switched by including the donor in the surgery. In this manner, seven patients underwent resection, and the surgeries were completed without LT.

Conclusion

Chemotherapy before and after surgery plays an important role in the survival for HB patients. Removing the main tumor mass by surgical resection with a safe tumor margin is the most important step of treatment, even in metastatic patients. LT is an important surgical solution in patients who are not suitable for surgical resection. In patients requiring extended resection, preparing the patient's donor and acting together with a liver transplant center provides important advantages for both the surgeon's comfort and the patient's safety.

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