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Review

# Liver Transplantation for Hemangioendothelioma

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**Abstract**

Epithelioid hemangioendothelioma is a rare vascular endothelial cell-derived tumor that occurs in one in a million cases, and one of the most common organs affected is the liver. Clinically, it can range from benign to aggressive. Due to its rarity, clinical management has not been standardized. For this reason, diagnosis is difficult, and it is often confused with other liver tumors. The prognosis is better than that of other liver malignancies. Laboratory findings are nonspecific, and tumor markers may also be elevated but are nonspecific. Imaging methods, particularly computed tomography and magnetic resonance imaging, are used. For a definitive diagnosis, a biopsy and immunohistochemical staining must be performed to demonstrate the staining of various endothelial cell antigens. Here, it is important to determine the hemangioma and sarcoma patterns with the help of genetic markers, as this will closely affect the course of the disease. Treatment is divided into two main categories: surgical and non-surgical. If possible, surgical treatment is the first recommended curative option. Surgical treatment includes liver resection and liver transplantation. Liver resection may be preferred in unilobar and unifocal disease. However, liver transplantation may be more appropriate in patients with late diagnosis and multilobar and multifocal disease at the time of diagnosis. Extrahepatic metastasis is not considered a contraindication for curative surgery. Lung metastasis is the most common type of metastasis. The success rates of both surgical methods are similar, but it should be noted that studies have shown that patients who undergo resection are in earlier stages of the disease, while those who undergo transplantation are in later and more advanced stages. Being over 60 years of age, Asian ethnicity, male gender, tumors larger than 10 centimeters, symptomatic disease, and involvement of serosal surfaces in the body are poor prognostic factors. The success rate after transplantation is over 90% in the first year, while the 5-year results are around 80%. The presence of macrovascular invasion reduces the 5-year survival rate by half. The rate of complications after transplantation is also around 20%. Non-surgical treatments include chemotherapy, radiotherapy, immunotherapy, radiofrequency ablation, hormone therapy, chemoembolization, radioembolization, and arterial embolization. These treatments are more commonly used as a bridge to surgical treatment rather than as a curative first step. With chemotherapy alone, the 5-year survival rate is below 30%. Due to the vascular origin of the tumor, commonly used chemotherapeutic agents include anti-VEGF agents and interferon alpha-2B. It has been observed that this rate is much lower when no treatment is administered. New studies will also help to better understand tumor biology and improve neo- and adjuvant treatment protocols.

**Keywords:** Epithelioid hemangioendothelioma, hepatectomy, liver transplantation, transplant oncology

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Epithelioid hemangioendothelioma (EHE) is a rare vascular endothelial cell tumor composed of epithelioid and histiocyte-like vascular endothelial cells in a mucus or fibrotic matrix.[1] It can occur in multiple parts of the including the liver, lungs, soft tissue, head and neck, pleura, spleen, bones and many other organs.[1] The incidence of hepatic hemangioendothelioma (HEHE) is 0.1 per 100.000 population.[1] The malignancy potential changes between

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hemangioma and hemangiosarcoma.[2] Due to its rarity and protean behavior, the optimal clinical management of HEHE has not been standardized.[3] This study aims to review the clinical characteristics of HEHE and evaluate the outcomes of liver transplantation as a treatment strategy.

## Pathology and Genetic basis of HEHE

The disease is more prevalent in women and is most commonly seen in the 30 to 50 age group.[1] The mean age of patients who underwent LT because of HEHE are changing between 32 and 43 years in previous reports (Table 1).[4-11] Females more frequently underwent LT, although two studies reported a higher proportion of males.[6,9] No definitive cause has been identified for the disease, but various risk factors have been suggested. These include oral contraceptive (OC) use, alcoholic hepatitis, viral hepatitis, primary biliary cholangitis, and exposure to toxic substances such as vinyl chloride, asbestos, polyurethane, chloroethylene, and silica.[12] Among patients who underwent LT, the incidence of alcohol abuse, nonalcoholic steatohepatitis (NASH), cirrhosis and Budd-Chiari syndrome is 16%, 4.7%, 2%, and 4%, respectively.[10] Most HEHE patients undergoing LT do not have significant underlying liver disease. Patients generally do not suffer from underlying liver disease or portal hypertension-related symptoms. The Model End-Stage Liver Disease (MELD) scores of patients who underwent LT are between 6 and 10 in most of the studies.[4, 9, 10] The patients with higher MELD scores have suffered from portal hypertension due to portal vein thrombosis or huge tumors that decrease the functional liver parenchyma. In a study by Rodrigue et al. nearly 20% of patients were followed intensive care unit before liver transplantation and the mean MELD score was 27 (Range between 6 and 40).

Like the etiology, the pathological mechanism of the disease has not been fully elucidated. Genetic mapping has revealed changes in two genes, WWTR1-CAMTA1 and YAP1-TFE3, that contribute to in the development of the disease.[13] These gene mutations are oncogenic in nature and activate tumor formation.[13] As the underlying genetic mutation exists throughout the liver, there might be several tumor origins in the liver. As in the early phase of HEHE, there’re several nodular lesions among the parenchyma. It has been suggested that hepatotrophic, regenerative cellular signalling after hepatic resection may lead to rapid hyperproliferation of residual malignant disease in some patients.[14] After nodular formation, diffuse pattern is seen in whole liver and invasion of vessels are seen.

In addition to this genetic mapping, the downregulation and upregulation of microRNA (miRNA) have also been shown to play a role in the etiology of the disease.[15] Although our current knowledge suggests that mapping has limited prognostic and therapeutic effects in HEHE, we believe that it has significant impacts in such rare diseases and will become more effective in the future.

## Diagnosis

Due to the lack of specific clinical features and rarity of HEHE, it is often misdiagnosed or overlooked at first.[16] It is most commonly misdiagnosed with cholangiocarcinoma, angiosarcoma, hepatocellular carcinoma (HCC), or metastatic carcinomas.[1] More than a quarter of cases are asymptomatic, and approximately 40% are diagnosed incidentally.[16] In the previous studies, the incidence of asymptomatic patients who underwent LT for HEHE was between 19% and 36%.[7,10,17] As the tumor grows slowly and a significant number of patients are asymptomatic, the patients are mostly diagnosed in late phases, such as bilobar involvement. The most common symptom is right upper quadrant pain; however, hepatomegaly, weight loss, jaundice, nausea, and anorexia may also be present. The

**Table1.** Summary of previous studies about Liver Transplantation for Hemangioendothelioma

| Study | n | Male (%) | Mean Age (years) | Mean MELD score | Ratio of LDLT (%) | Re-Transplantation rate (%) | Survival | | | Recurrence (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 1-year survial | 3-year survial | 5-year survival | |
| Brahmbhatt et al.[1] | 31 | 29 | 43 | 7 | 5 | 22 | 88.6 | 78.9 | 77,2 | 6.8 |
| Rodrigue et al.[6] | 10 | 20 | 40.5 | NA | 0 | 0 | NA | 87.6 | NA | NA |
| Lerut et al.[2] | 59 | 27 | 42 | NA | 5 | NA | 93 | 85 | 83 | 23.7 |
| Krasnodebski et al.[3] | 18 | 16 | 39 | 7 | 0 | 0 | 94 | | 82 | 0 |
| Nudo et al.[4] | 11 | 27 | 38.7 | NA | 0 | NA | NA | NA | 82 | 36.4 |
| Na et al.[11] | 4 | 25 | 41.3 | 10 | 100 | 0 | 75 | 75 | 75 | 25 |
| Larson et al.[5] | 121 | 56 | 43 | 7 | 11 | NA | NA | NA | 72 | 4.9 |
| Lai et al.[6] | 149 | 33 | 43 | 9 | 3.4 | NA | NA | NA | 80 | 24.8 |

LDLT: Living Donor Liver Transplantation; MELD: Model for End Stage Liver Disease; NA: Not Avaliable; n: Number of patients.

incidence of right upper quadrant discomfort or pain is 57%-62% among patients with LT.[7,10,17] The severity of disease symptoms increases as the disease progresses, with an increase in the number and size of lesions. Rarely, an association with Kasabach-Merritt syndrome or Budd-Chiari syndrome has been reported.[10,16,18] Portal vein thrombosis or hepatic vein thrombosis may occur due to compression from liver lesions. These compressions might lead portal hypertension and Budd-Chiari symptoms. In the study of Agrawal et al, one patient waiting for LT died due to liver failure accompanied by jaundice, ascites, and abnormal liver function tests.[19]

Although there are no specific laboratory findings, liver function tests (LFTs) may be abnormal, with approximately 15% of patients show no abnormalities. Among LFT's, the incidence of abnormal Aspartate transaminase (AST) and Alanine transaminase (ALT) were found around %35 of patient who underwent LT for HEHE.[7,10,19] The incidence of abnormal gamma glutamyl transferase (GGT) and alkaline phosphatase (AP) was around %50 that is much higher than the incidence of other abnormal LFTs.[5,7,10] The incidence of abnormal international normalized ratio (INR) and albumin was around 2%, which is lower than the incidence of other abnormal values. Increased cholestatic enzymes are related to tumor compression of the biliary system. Deterioration of INR and albumin is mostly related with portal hypertension and liver insufficiency. Patients who underwent LT for HEHE generally have normal tumor marker levels (AFP, CEA, and CA 19-9) and these levels may only be used to rule out primary or metastatic liver tumors.[16] However, some studies have shown that CEA levels may be elevated. In a study by Lai et al., the incidence of abnormal AFP, CEA and CA 19-9 was 8%, 18% and 2%, respectively.[10] In studies by Larson et al. and Remiszewski et al., the tumor marker levels were normal.[5,9]

On ultrasound imaging, lesions are predominantly hypoechoic in appearance, but may also appear hyperechoic or isoechoic in a smaller proportion of cases. Calcifications within the tumor, as well as splenomegaly and capsular retractions, may be observed.[16,20]

Lesions generally appear hypodense on non-contrast computed tomography (CT).[20] Capsular retraction or coarse calcifications within the tumor may be better visualized on non-contrast CT than on contrast-enhanced imaging. Cholangiocarcinomas and metastatic tumors may also cause capsular retraction.[21] A target sign may be seen on contrast-enhanced CT. This is caused by early peripheral arterial filling accompanied by central filling in the portal and delayed phases.[21] The lollipop sign, which is uncommon in other tumors, may also be indicative of HEHE. Here, the image forms as a result of the flow ceasing and the hypodense lesion becoming visible when the lesion protrudes while the flow continues in the portal or hepatic vein branches. The blood flow in the vessel represents the stick, while the lesion represents the sugar part.[21]

Magnetic resonance imaging (MRI) is superior to CT in showing small and subcapsular lesions.[22] In contrast-free T1-weighted sequences, the lesion appears hypointense centrally and hyperintense peripherally, whereas in T2-weighted sequences, it appears hyperintense centrally and hypointense peripherally. This can be explained by central hyposignal intensity due to thrombosis, necrosis, or calcification.[22] In contrast-enhanced MRI scans, images similar to those seen in contrast-enhanced CT are observed. In the arterial phase, homogeneous contrast uptake, ring-like or heterogeneous uptake may be observed. In diffusion imaging, a target sign with hyperintense appearance at the outer edge and centrally may be observed.[21,22]

The patients who underwent LT were mostly evaluated with MRI. In the study of Agrawald et al., all patients were evaluated with MRI and capsule formation was a common finding.[19] In the study of Lerut et al., %86 of patients had bilobar tumors in their livers and more than 15 lesions. The "cocarde image", capsule formation, and calcifications were seen with percentages of 24%, 25% and 13%, respectively.[7] The incidence of portal and hepatic vein thrombosis was 50% and 54%, respectively in the study of Lerut et al., whereas the incidence is portal vein and hepatic vein thrombosis was 36% and 23%, respectively in the study of Lai et al.,[7,10] The bilobar tumor or existence of major vein thrombosis might be higher in transplantation cases as they're mostly selected as inoperable, but on the other hand it should be kept in mind that, cases are mostly presented late. As in the study of all HEHE cases, unilobar disease was seen in only 13% of cases, and only 9% were suitable for resection.[16] In previous studies, the tumor dimensions of patients who underwent LT for HEHE ranged from 3 to 18 cm.[5,8,19] It was suggested that LT is advised for the patients who had multiple lesions (>10 lesions and involvement of >4 segments). Radiological evaluation is performed not only for liver but also for extrahepatic tumor metastasis. Extrahepatic metastasis is not accepted as a contraindication for LT. In the previous studies, incidence of extrahepatic metastasis to lung, brain, peritoneum, spleen and bones were around %16-%26.[5, 7, 10] The most common organ was the lung. As differentiation of lymph node metastasis may not always be possible with radiological evaluation, lymph node metastasis was found in around 20% of the sampled cases.[5, 17, 23] While most of the studies emphasize the lymph node metastasis as a risk factor for recurrence and survival, the study of Cardinal et al. did not show a relationship.[7,10,17]

This may be because not all cases in LT sampled lymph nodes. For this reason, sampling lymph nodes will be beneficial during LT.

FDG metabolism, uptake, and excretion show considerable variation in HEHE cells. Therefore, PET-CT scans performed at different times may be useful for detecting lesions.[24] A study showed that FDG uptake is associated with tumor cellularity and may shed light on the histopathology of the lesion.[24] Approximately one-third of cases show uptake similar to that of normal liver parenchyma. Central fibrosis and peripheral FDG uptake caused by peripheral neoangiogenesis are present in the images, but this pattern is also present in diseases such as peripheral cholangiocarcinoma. The fact that FDG uptake is lower in HEHE cells than in other hepatic malignancies such as peripheral cholangiocarcinoma, which may be helpful in differential diagnosis.

The most reliable method for diagnosis is biopsy followed by a histopathological examination.[25] However, the false-negative rate after biopsy can reach 10%. Among patients who underwent LT for HEHE, percutaneous liver biopsy has mostly been performed with an incidence of 87%-100%.[10, 17, 19] In one of the studies, biopsies were obtained by diagnostic laparoscopy before LT.[5] Only one case of seeding during the biopsy has been reported.[7] Histopathological examination reveals dendritic and epithelioid cells showing vascular differentiation.[25] Immunohistochemical examination reveals CD31, CD34, cytokeratins, and Factor VIII-related (FVIII-RAg) antigens in endothelial cells.[26] Factor VIII-RAg positivity is 98% in HEHE. Histological features of HEHE might resemble with sclerosing hemangioma, angiosarcoma, or cholangiocarcinoma; an immunohistochemical examination is needed. However, there is no histopathological feature that can predict the prognosis of the tumor. With increasing experience about HEHE, more molecular findings are accepted as prognostic factors and the nature of tumor. WWTR1 and CAMTA1 genetic markers for HEHE can be used for dominancy of hemangioma or sarcoma like patterns of HEHE.[27] Also, new genetic markers will help us for monoclonal nature of the disease. By this way, approach to multiple liver lesions or extrahepatic lesions might be changed.

## Treatment

Due to the rarity of the disease and the lack of homogeneity in its clinical course, there is no definitive treatment guideline. The prognosis is better when compared to other liver malignancies. It has been reported that 25% of patients with HEHE did not receive any treatment have 1-year survival rate less than 50%, 5-year survival rate is around 5%-30%.[16,28] Treatment modalities are divided into surgical and non-surgical treatments. Only 19% of patients present with unilobular disease, and of those, only 9% are candidates for liver resection.[16] Grotz et al. suggest liver resection only for patients with solitary lesions.[28] Negative surgical margins are considered sufficient for surgical treatment. Extrahepatic lesions are not contraindication for liver resection. The respectability rate is low and the 5-year survival rate following liver resection is around 75%.[16,28,29] This is probably due to hepatotropic, regenerative cellular signaling after liver resection or an underlying genetically defective liver. Additionally, after radical or palliative resection, aggressive disease recurrence or fulminant hepatic failure have been reported.[30] Although there is no underlying liver disease with HEHE, patients with multiple HEHE lesions have died from hepatic failure while waiting for a LT[19] HEHE lesions probably deteriorate liver function in addition to occupying mass. The presence of extrahepatic metastases, the patient being over 60 years of age, Asian ethnicity, male gender, a tumor larger than 10 cm, symptomatic disease, and serous effusion have been shown to be poor prognostic factors.[31] Also, in liver diseases such as underlying liver cirrhosis, multifocal diseases, and cases where radical resection is not possible. In the study of Lai et al., the incidence of underlying liver diseases (Budd-Chiari, cirrhosis, portal hypertension) is 13.4%.

Non-surgical treatments such as radiotherapy, radiofrequency ablation, hormone therapy, arterial embolization, chemoembolization, and irreversible electroporation have been performed in a limited number of cases and without uniform treatment modalities.[16, 32, 33] It is unclear whether these treatments are performed for a limited number of lesions or for advanced diseases. However, the 5- year survival for chemoradiotherapy is less than 30%.[16, 28] These treatment modalities may be preferable for bridging treatment before LT. In a study of Cardinal et al., 2 patients underwent LT after Transarterial Chemoembolization (TACE) and achieved survival of more than 100 months.[17] In non-surgical treatments, anti-VEGF agents have been emphasized, considering that the tumor is of vascular origin. Thalidomide, sorafenib, bevacizumab, and paclitaxel are among the agents used. In addition to these agents, interferon alpha-2B (IFN-a 2b) has begun to be used to reduce post-transplant recurrence and metastatic lesions.[34] Other studies have shown that IFN-a 2b therapy provides partial response, complete response, and disease stabilization. The proposed mechanism involves hepatic NK cell activation, inhibition of COX-2 and VEGF expression.[35] Sirolimus is an immunogenic agent that exerts its effect by inhibiting endothelial growth factor and can be used in treatment. However, in previous studies, everolimus has not been mentioned as part of an immunsuppressive protocol. Everolimus may be preferred as an immunosuppressive agent after LT. It has been shown that chemotherapy is more useful for stabilization than radical treatment. In patients awaiting transplantation or those who are not candidates for surgery, the combination of capecitabine and bevacizumab has been shown to significantly reduce tumor size. Chemotherapy treatment has been shown to have a negative impact on survival in localized tumors. If distant metastasis is present, no difference in survival has been observed between the surgical and non-surgical groups. Adjuvant therapies after transplantation are recommended to prevent graft loss and recurrence. In a randomized, multicenter study conducted in China demonstrated that Huaier granule, a substance that inhibits angiogenesis, reduces the risk of recurrence in the postoperative period.[35]

As HEHE is usually multifocal and therefore not suitable for partial resection, LT appears to be an acceptable treatment method. In a recent analysis, the 5-year survival rates for HEHE recipients and non-HEHE recipients were 72% and 77%, respectively.[9] Similarly several recent studies have found the 5-year survival rates to be around 80% in HEHE recipients[4, 7, 8, 10] (Table 1). The 1-year survival rates are also around 90% in previous studies.[4,7] However, in Rodriguez et al.'s study, the one-, three-, and five-year survival rates were 80%, 68%, and 64%, respectively, which are lower than in other reports.[6] This is probably due to the high percentage of pediatric HEHE cases in this study (38%). It should also be kept in mind that patients who underwent LT had more advanced liver lesions than patients who underwent liver resection. For this reason, a comparison of LT and liver resection with similar tumor features has not been performed. Compared to liver resection, LT is thought to have fewer advantages due to the need for immunosuppression and the complexity of the procedure. However, the multifocal nature of HEHE makes LT a better therapeutic option. However, nearly 20% of cases have extrahepatic metastasis, which raises concerns about high-risk recurrence after LT. In the study by Cardinal et al., the existence of extrahepatic disease beyond the regional portal nodes was a negative predictor of the outcome after liver transplantation (LT). However, several other studies have shown that patients with extrahepatic metastases can have long survival rates after LT. In the study by Lerut et al., one patient underwent mediastinal tumor resection before LT. In the study by Lai et al., 4.7% of patients underwent surgery due to extrahepatic metastasis.[7,10] Some studies have also shown that pulmonary resections, splenectomies, peritoneal resections, omentectomies, and diaphragmatic peritonectomies were performed during LT.[7,8,10,34] In the study of Lai et al, %18 patients underwent organ resections during LT and %53 underwent lymphadenectomy during LT.[10] Lymphadenectomy is advised during LT. Among these studies, the localization of extrahepatic disease is reconfirmed not to be a contraindication for LT. As presented in a previous study, patients can die from rapidly progressive disease while on the waiting list, and most cases are unresectable. In countries where deceased donor liver transplantation (DDLT) is performed, patients with HEHE receive exceptional points on the liver transplantation waiting list.[4, 10, 19] In the study by Larson et al., it was shown that the exception point rate is 74% for HEHE patients.[9] This high rate of exceptional points shows how severe the tumors are. However, of the 131 candidates with HEHE who were waitlisted for LT, only 67% underwent LT, and 10% were removed due to death or illness. The study in which exceptional points were given showed that the median waiting time for LT for patients with HEHE was 78.5 days.[4] In Agrawal et al.'s study, the mean waiting time for LT for three out of four patients with HEHE was 80 days; however, one patient with HEHE died while on the waiting list.[19] Previous studies have shown that the LDLT rate is limited (Table 1). Only in the study by Na et al. did all patients undergo LDLT.[11] The rate of domino liver transplantation for HEHE in the study by Lai et al. was 2%. For these reasons, living donor liver transplantation, which has no waiting period, is strongly suggested.[4] Increased post-transplant survival was achieved with LDLT.[9] In countries in which extra points are not given for HEHE should wait longer period for LT. In these countries LDLT is a better option for patients with HEHE.[11] On the other hand, the Lai study found that a waiting period of less than 120 days was associated with an increased risk of post-LT recurrence.[10] Waiting time is a tool for observer tumor behavior and aggressiveness and a means to permit the delivery of neoadjuvant therapy. Lai et al. suggested observing patients under neoadjuvant treatment to select patients based on tumor aggressiveness. They also stated that recurrence after LT for hepatic hemangiosarcoma (HHS), which is difficult to differentiate from HEHE, is mostly seen within the first six months.[10] However, HHS is a completely different and aggressive disease and a comment is not possible regarding difficult differentiation. Additionally, this registry did not provide waiting drop-out rates.[10] For these reasons, longer waiting period might risk the loss of chance for LT for patients with HEHE.

In countries where DDLT mostly performed, the patients with HEHE in waiting list are taken into neoadjuvant treatments. In the study of Lerut et al., 15% of patients underwent systemic or locoregional chemotherapies before the LT.[7] Liver TACE treatment was performed in the 4% of patients in the study of Lai, and two patients in the study of Cardinal et al.[10,17] The rate of neoadjuvant treatment is

42% in previous studies.[10] No study has compared patients with HEHE who underwent LT with or without neoadjuvant treatment; but Lai et al. describe some of the potential mechanisms for neo- and adjuvant treatments.[10] In the study of Lerut et al., survival was not affected by lymph node metastases, prior treatment, or the presence of extra-hepatic disease.[7]

The recurrence rate after LT for HEHE is between 4-32% in previous studies.[6,7,9,10] In the study of Lerut et al., the mean recurrence time is 49 months (range 6-98 months).[7] The most common metastatic sites are the liver and lungs. Lung resection, lung transplantation, radiotherapy and chemotherapy have been used for the treatment of metastasis.[7] The 1-, 5- and 10-year disease free survival rates are 90%, 82%, and 64%, respectively.[7] The estimated recurrence related mortality rate is 15.3%.[7] In the study of Rodriguez et al., the rate of mortality due to HEHE metastasis is 16%.[6] In the study of Lai et al., the recurrence rate was 24%, and nearly half of the recurrent cases were treated with surgery, chemotherapy, radiotherapy, or hormonal therapy.[10] The median time for recurrence is 18 months (range, 8-65 months).[10] The 1-, 5- and 10-year disease free survival rates are 88%, 79.4% and 72.8%, respectively.[10] In a study with limited number of cases, the recurrence rate was 36%, with a median recurrence time of 25 months.[23] The reports indicate that recurrences occur soon after LT and are treated with other options. Lymph node invasion, macro- and microvascular invasion were shown as risk factors for recurrence after LT.[7,10] The 5-year DFS rate were 84.7% versus 44% in patients without or with macrovascular invasion.[10] The 5-year DFS rate were 84.2% versus 65.4% in patients without or with LN invasion.[10] On the other hand, in another study with a limited number of cases, the rate microvascular invasion was 11%, and the rate of macrovascular invasion was 0%. However, the recurrence rate was much higher 36%.[23] In the study of Cardinal et al., angiolymphatic invasion or positive LN involvement was not a prognostic factor for recurrence.[17] These conflicting results show that the tumor biology and features should be defined in detail. There is no standard treatment modality for LT patients with HEHE.

The complication rate after LT in patients with HEHE were between 18% and 24%.[7,17] Complication rates after LT for HEHE are not significantly different than the LT for non-HEHE cases.[9] The immunosuppressive protocols are not mentioned in the literature for LT for HEHE.

At the Acibadem Atakent Organ Transplantation Unit, two female patients who initially presented with right upper abdominal pain underwent LT. In their first MRI evaluation, there were bilobar multiple nodular lesions without vascular invasion. The largest lesions measured 5 and 6 cm. The lesions were suspected to be metastases, but the the pathological diagnosis was HEHE. One of the patients underwent domino liver transplantation from a Criggler-Najar child. The second one underwent LDLT from her brother. They are 25 and 53 years old. They have survived for 20 and 86 months without recurrence. The immunosuppressive changed from Tacrolimus to Everolimus 6 months after the LT.

## Conclusion

LT remains the most effective treatment for HEHE. The biological behavior of HEHE mostly depends on its molecular markers. Defining the molecular background may affect its hemangioma or hemangiosarcoma like growth or metastasis. New studies on biology and structure of tumors may help us devedlop neo- and adjuvant treatment options for LT. Further research is needed to establish the efficacy of LDLT in patients with HEHE.

### Disclosures

**Authorship Contributions:** Concept –T.U.Y.; Design – T.U.Y.; Materials – A.A.S. Data collection &/or processing – A.A.S.; Analysis and/ or interpretation – T.U.Y.; Literature search –A.A.S.; Writing – T.U.Y., A.A.S.

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