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REVIEW

# Liver transplantation and vascular tumours

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## Summary

Based on analysis of the literature and of the audited ELITA (European Liver Intestinal Transplant Association)–ELTR (European Liver Transplant Registry) data, the place of liver transplantation (LT) in the treatment of vascular tumours is discussed. Hepatic epithelioid haemangioendothelioma has currently become a good indication for LT with 5- and 10-year post-LT patient survival rates of 83% and 74% respectively and 5- and 10-year recurrence-free survival rates of 82% and 64% respectively. In contrast, the results of LT for haemangiosarcoma (HAS) are disastrous with an universal tumour recurrence within 6 months and no single patient survival after 2 years. Therefore, HAS remains an absolute contraindication to LT. The value of LT in the treatment of infantile haemangioendothelioma is more difficult to evaluate because of the very reduced number of reported cases and because of the often difficult differential diagnosis with angiosarcoma. LT should be reserved to those children not responding to medical treatment on the condition that sarcomatous modifications are excluded by expert pathologists to avoid a futile transplant procedure.

## Introduction

The value of liver transplantation (LT) in the treatment of hepato- and cholangiocellular cancers has been clearly delineated during the last two decades. In contrast, the place of LT in the treatment of vascular liver tumours remains controversial; this is the main reason why many patients are denied the chance to undergo a possibly curative transplant procedure. This paper deals with the most recent information in relation to the actual place of LT in the treatment of primary vascular liver tumours through an updated literature search via Medline (using keywords: vascular tumour, liver, transplantation, sarcoma, haemangioendothelioma) and a concise review of the European transplant experience in this field reported by the European Liver Intestinal Transplant Association (ELITA) and European Liver Transplant Registry (ELTR) during the period 1989–2004. The results of the ELITA–ELTR data have already been published extensively previously [1,2].

## Hepatic epithelioid haemangioendothelioma

Hepatic epithelioid haemangioendothelioma (HEHE) is a rare (<1 per million population), low-grade malignancy, which has a behaviour intermediate between haemangioma and haemangiosarcoma (HAS) [3,4]. This tumour, which became only recognized since 1982 in soft tissues, is more frequent in adult women in their forties. Liver involvement occurs most often as a primary tumour. No definitive aetiological factor has been identified. The clinical course of HEHE can be extremely variable from prolonged spontaneous survival (up to 28 years!) to rapidly progressing disease with fatal outcome [3,4].

The clinical manifestation of HEHE may vary from an asymptomatic state (20% of patients) to hepatic failure.



 

The most frequent symptoms are upper abdominal or epigastric discomfort or pain, weakness, impaired general condition and jaundice. About 10% of patients present with pulmonary symptoms. Hepatosplenomegaly and weight loss are the most frequent clinical signs. Portal hypertension may be caused by vascular compression or infiltration [1–4].

Anicteric cholestasis and cytolytic activity are present in 60% and 40% of patients. Serum tumour markers are normal in the absence of accompanying liver disease.

Radiological investigation identifies an early peripheral and nodular, usually bilobar, type (peripheral pattern) and a later confluent type (diffuse pattern) with eventual invasion of the greater vessels. Calcifications are present in 20% of tumours. Complete assessment of these patients is mandatory to exclude other, especially thoracic and osseous, disease localisation. FDG-PET imaging plays a role in the staging of the disease and in early detection of recurrent disease [5].

Macroscopically, HEHE appears as multifocal fibrous masses; microscopically, HEHE contains pleiomorphic epithelioid cells that spread within sinusoids and small veins at the periphery of the lesion, whereas the centre is fibrous and filled with tumour cells (Fig. 1a). In contrast to HAS, the hepatic landmarks are usually preserved. The endothelial origin of HEHE explains positive immunohistochemistry (IHC) for FVIII-related antigen and endothelial markers CD31 and CD34 (Fig. 1b).

The definitive diagnosis is frequently based on a high degree of suspicion combining both radiological and clinical features such as the occurrence of numerous intra-hepatic tumours in a young 'healthy' (female) adult having a long standing clinical and/or radiological history. The diagnosis can only be confirmed by pathological examination of appropriate biopsy specimen [3].

The treatment algorithm of HEHE was not standardized until recently because of the lack of large patient series with long-term follow-up. Moreover, the place of LT has been questioned in view of spontaneous, long-term survivals, the high incidence of extra-hepatic disease (up to 45%), the lack of predictive clinical or histological criteria and the high incidence (up to 33%) of recurrent allograft disease. The largest single centre series comes from Pittsburgh; 5-year patient (PS) and disease-free survival rates in a series of 16 patients were 71% and 60% respectively [6]. In their recent update dealing with 26 HEHE, 17 liver recipients had a mean survival of 10 years. The authors not only confirmed the role of LT in the treatment of HEHE, but they also underlined the value of TACE as a possible neo-adjuvant treatment to LT in some patients [7]. MEHRABI conducted an extensive literature review on the subject [8]. Total hepatic resection came out as the best treatment option. Five-year survival rates of LT, local or systemic chemo- and radiotherapy and no treatment were 55%, 30% and 0% respectively. Partial liver resection should be abandoned because HEHE is nearly always a multinodular and bilobar disease [1]. Evaluation of nonsurgical treatments, such as radiotherapy, local tumour destruction, hormonotherapy, systemic or locoregional chemotherapy, trans-arterial chemo-embolization was difficult because of the heterogeneity of treatment modalities and follow-up.

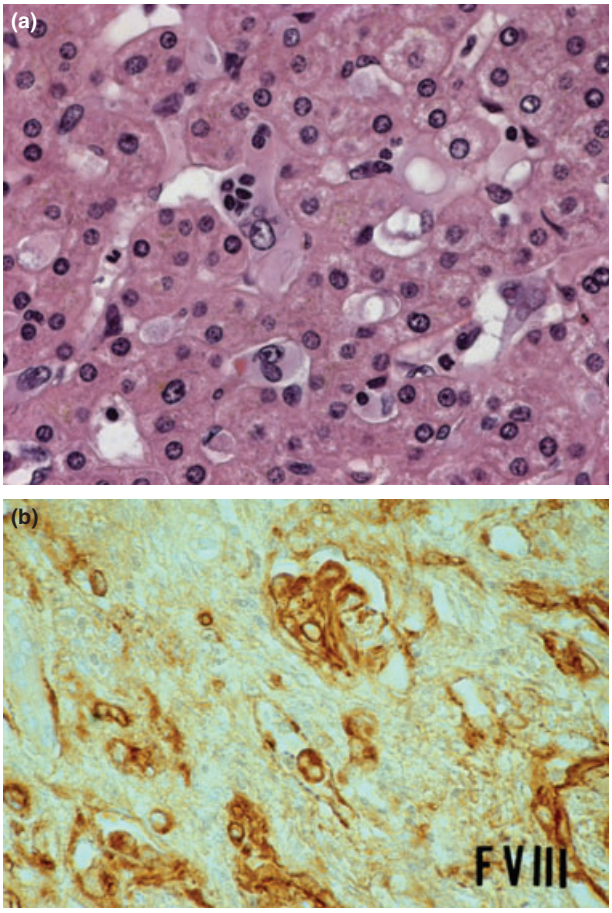


**Figure 1** Microscopic features of HEHE at the periphery of the lesion (a) and immunoreactivity for FVIII antigen (b).

The most complete information was obtained from the audited ELITA–ELTR study considering 59 liver recipients having a complete long-term follow-up from diagnosis to LT (9 years) and from LT (7 years) [1]. Five- and 10-year post-transplant PS rates were 83% and 74% respectively and 5- and 10-year recurrence-free survival rates were 82% and 64% respectively. Medical and/or surgical pre-transplant treatment, invasion of regional lymph nodes and presence of (limited) extra-hepatic disease did not influence survival rates. Combined micro- and macrovascular invasion (present in half of the patients) was the

only parameter, which significantly influenced outcome after LT. Some authors also claim that mitotic index and cellular pleomorphism may reflect a more aggressive tumour behaviour [9,10].The results of the (less detailed) UNOS study including 128 HEHE patients having a median follow-up of 24 months go in the same direction; 1- and 5-year PS rates were 80% and 64% respectively [10].

Recurrent disease after (partial and total) hepatectomy should be treated aggressively as long-term, disease-free survival can be obtained [1,2].

For reasons of the encouraging results reported in the ELITA–ELTR and UNOS studies, more and more patients are currently referred for LT. Indeed, during the last 5 years, more patients have been transplanted in Europe than during the last 25 years (87 patients during the period 2004–2009, V. Karam, secretary of the ELTRegistry, personal communication). Some patients even underwent simultaneous or sequential hepato-pulmonary transplantation because of diffuse hepatic and pulmonary involvement. New challenges are thus pointing at the horizon…where are the limits of the indication for LT, what about the 'LT first' option followed by pulmonary transplantation in case of simultaneous hepato-pulmonary involvement, which (neo)adjuvant treatment to propose…all these questions need to be addressed from now onwards to improve further the outcome of these mostly young patients. It is conceivable that in view of the high incidences of extra-hepatic disease localisation and of recurrence inside and outside the allograft (22% in the ELITA–ELTR study), anti-angiogenic therapies including alfa-interferon, transarterial intrahepatic chemotherapy, rapamycine and V-EGF-antibodies and even a combined approach consisting of total hepatectomy with eventually simultaneous or sequential lung transplantation could become of interest to improve results further [11–13]. More recently, several patients (also in our own experience) have been transplanted using the m-TOR inhibitor rapamycine taking thereby advantage of both angio-angiogenic and immunosuppressive properties of this potent drug. Until now, follow-up has been too short to draw valid conclusions. The study of molecular and genetic markers of tumour biology will also be of help to monitor efficacy of emerging neo- and adjuvant treatments to recognize aggressive subtypes of HEHE. Looking at the evolution of tumoural V-EGF expression has already been reported [11,12].

## Hepatic infantile haemangioendothelioma

Hepatic infantile haemangioendothelioma (HIHE) is the most common mesenchymal liver tumour in infants (<3 years), which is nearly always diagnosed during the first 6 months of life [14]. HIHE is also more frequent in females and presents with (a)symptomatic hepatosplenomegaly, failure to thrive, congestive cardiac failure (15%), haemangiomas (20–40%), coagulopathy (Kassabach–Merritt syndrome) and hypothyroidism. Although HIHE may regress spontaneously in 5–10% of cases, mortality is as high as 90%. Up to two-thirds of symptomatic patients die of congestive heart failure and liver failure because of the presence of arteriovenous fistulas [15,16].

Hepatic infantile haemangioendothelioma can occur either as a single or as multifocal tumour. The lesions vary from soft, spongy, red-tan to firm grey-white or brown nodules with areas of necrosis and bleeding. HEHE can be differentiated from HIHE based on different, age-related, clinical and pathological characteristics. Microscopic examination of the more frequent type 1 shows intercommunicating small vascular channels lined by a single layer of regular endothelial cells (Fig. 2a) [3,15]. The type 2 presents with nuclear atypia, multi-layering and papillary projections; it is currently considered as a form of HAS (Fig. 2b). IHC examination (looking at e.g. Ki-67 and GLUT1) can be of help to differentiate

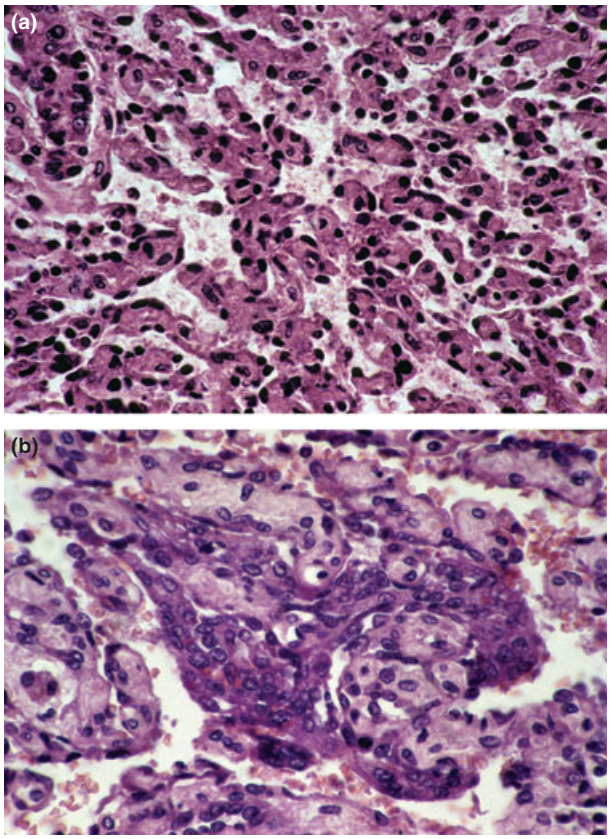


**Figure 2** Microscopic features of HIHE. Type 1 HIHE is made of multiple vascular channels with a single layer of regular endothelial cells (a), whereas in type 2, HIHE more atypia are observed (b).

HIHE from other hepatic vascular malformations associated with capillary proliferation [17]. The main problem of HIHE lies in the fact that this tumour is frequently indistinguishable from sarcoma on needle biopsy. This explains why the outcome after surgery is frequently disappointing. The ELITA–ELTR study showed that children with HIHE presenting a rapid deterioration, acute liver failure and/or Budd–Chiari syndrome all presented foci of HAS. They all died after LT because of early tumour recurrence [2].

Treatment of HIHE includes intensive medical therapies (using diuretics, digoxin, high dose steroids, interferon, chemotherapy or radiotherapy, anti-angiogenic drugs) and/or interventional radiology and/or surgery. Symptomatic treatment may raise survival up to 40%; if specific therapy (such as liver resection) can be applied, survival rate can even be higher. Liver resection series are sparse and usually include only some patients [18–20]. The Pittsburgh group reported their experience with 13 patients. Congestive heart failure and huge abdominal mass were predictive factors of 5-month mortality and liver resection generated the best results. Three patients survived for 2, 6 and 20 years after LT; three patients underwent left lobectomy, one patient survived for 5 years. Hepatic artery ligation or embolisation can be proposed as a bridge to partial or total hepatectomy. The recent UNOS report, containing the largest reported series of 35 patients, showed a 5-year survival of 60.6% following LT. The Boston group proposed an algorithm for the treatment based on their large experience with vascular diseases. Partial hepatectomy is indicated if lesions are confined to one liver lobe; children presenting with diffuse HIHE disease, resistant to steroid therapy, should be transplanted [21].

## Hepatic haemangiosarcoma

Haemangiosarcoma (HAS) is the most common primary liver sarcoma, accounting for up to 2% of primary liver tumours [22]. This tumour is predominant in men (male/female ratio 3/1) with a peak incidence in the sixth and seventh decades of life. Seventy per cent of patients present the sporadic form and in 30% of cases environmental carcinogens are associated with HAS. Thorotrast, vinyl chloride monomer, radium, pesticides, external radiation, cyclophosphamid, arsenical compounds, use of androgenic/anabolic steroids and iron overload (in haemochromatosis) all are causative agents.

The diagnosis of HAS can be very difficult despite the introduction of nuclear magnetic imaging [23]. As liver needle biopsy does not many times allow making a correct diagnosis, adequate tissue sampling (using excision biopsy) is of utmost importance to avoid futile surgery. Radiological investigation allows identifying different patterns varying from multiple nodular, large dominant mass to more rarely diffusely infiltrating macro-nodular tumours. Extra-hepatic metastases, mostly located in the lung, spleen, bone and adrenals, are present in 20–40% of patients at the moment of diagnosis.

Macroscopically, HAS appears as ill-defined spongic haemorrhagic nodules that usually involve the whole organ. Microscopic examination reveals sinusoidal growth of malignant endothelial spindle cells on the surface of liver cell plates leading to cellular atrophy, formation of vascular channels and cavernous spaces with papillary intraluminal projections (Fig. 3a). Tumour cells have hyperchromatic nuclei with numerous mitoses (Fig. 3b). IHC is positive for all classical endothelial markers. Differential diagnosis with HEHE is based on the abundance of cellular atypia and on destruction of the normal liver struc-

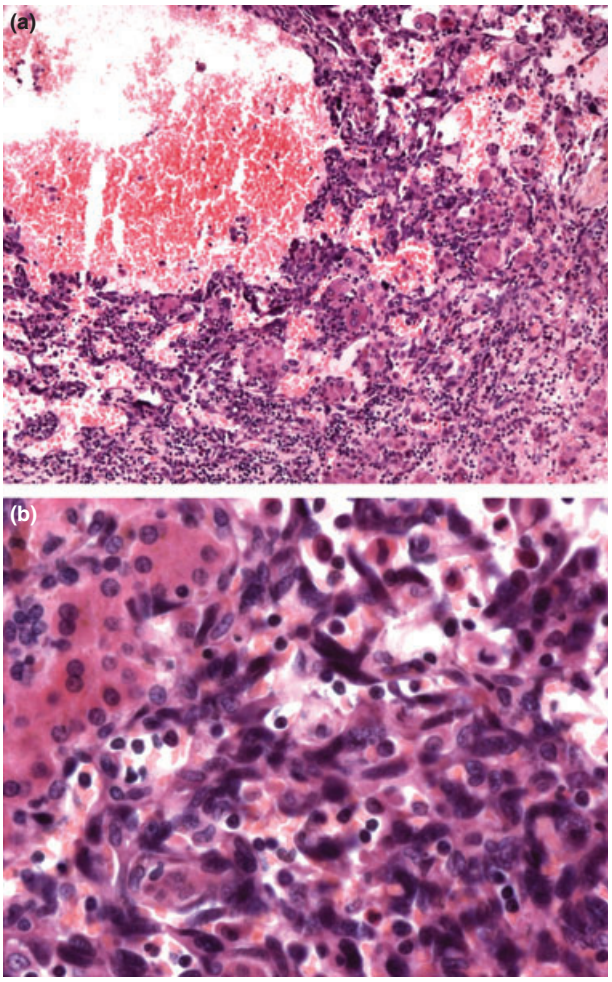


**Figure 3** Microscopy of HAS shows the development of a cavitary space (a); because of the sinusoidal progressive growing of tumoural cells, the liver cell plates are destroyed (b).

 

tures. The difficulty to make a correct diagnosis is exemplified in the ELITA–ELTR study; HAS was diagnosed in only six of 16 biopsied patients.

Biochemical expression of HAS is aspecific; cholestatic enzymes are elevated in 70% of patients; tumour markers are also negative in the absence of accompanying liver disease. HAS may present with hepatosplenomegaly, ascites, jaundice, signs of portal hypertension, weight loss and muscle waist; in the later stadium pain, peripheral oedema, acute Budd–Chiari syndrome, acute abdomen caused by tumour rupture and thrombocytopaenia may follow.

Evolution of HAS patients after liver surgery is dramatic. Long-term survival after partial liver resection has not been reported and all liver recipients in the ELITA–ELTR study developed tumour recurrence after a median of 6 months; no patient survived for more than 2 years. The Cincinnati Transplant Tumor Registry (six patients) and the Memorial Sloan Kettering group (five patients) reported similar bad results [24,25]. These experiences confirm that HAS is an absolute contra-indication to transplantation. We therefore recommend, on the basis of survival data from the ELITA–ELTR study, in case of unclear differentiation between HIHE or HEHE and HAS, to respect an observation period of 6 months from the moment of tumour diagnosis onwards. This precise time lapse has the advantages that it does not interfere with the outcome of HEHE after LT and that it allows observing an eventual progression of the disease confirming the sarcomatous nature of the vascular tumour(s) avoiding thereby the waist of a scarce organ resource. It is clear that this aggressive disease merits a more effective interdisciplinary oncological approach to improve patient outcome.

## Conclusion

Since the successful implementation of LT in clinical practice in 1963 by STARZL, medical and surgical indications for LT have continuously been widened and refined. Although the results of LT for benign and malignant liver diseases improved dramatically during the last two decades, no major advances have been made in the field of the vascular hepatic tumours. Following the reports of the ELITA–ELTR and UNOS, the place of LT in the therapeutic algorithm of these vascular tumours has become more clear.

Liver transplantation is currently a valid option in the treatment of epithelioid haemangioendothelioma; in contrast, it has no place at all in the treatment of HAS. Its place in the treatment of infantile haemangioendothelioma must be seen in the light of responsiveness to medical therapies. In nonresponders, results of transplantation are good on the condition that the liver specimen does not contain sarcomatous foci. Detailed, expert pathological examination of adequate liver tissue samples is of utmost importance. The study of molecular and genetic markers of these vascular tumours and of (neo-)adjuvant therapies is necessary to recognize aggressive subtypes of hamangioendothelioma and to refine the diagnostic procedure. Clinical trials with new pharmacological agents and detailed long-term analyses as well in larger transplant as nontransplant patient cohorts are necessary to optimize further the use of a scarce organ resource in this particular field of hepatic oncology. Living liver donation will undoubtedly play a major role in the extension of transplant indications in these patients that will never benefit from prioritization in the MELD allocation system.

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