Hepatic Epithelioid Hemangioendothelioma and Adult Liver Transplantation: Proposal for a Prognostic Score Based on the Analysis of the ELTR-ELITA Registry

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Background. Hepatic epithelioid hemangioendothelioma (HEHE) is a rare vascular tumor which has an intermediate aggressive behavior. Although the value of liver transplantation (LT) is well established, its place in the management of HEHE is still unclear. The aim of this study is to confirm, based on a very large patient cohort, the value of LT in the management of HEHE and to identify risk factors for post-LT recurrence. **Methods.** The outcome of 149 transplant recipients with HEHE recorded in the European Liver Transplant Registry during the period November 1984 to May 2014 was analyzed. Median post-LT follow-up was 7.6 years (interquartile range, 2.8-14.4). **Results.** Cox regression analysis showed that macrovascular invasion (hazard ratio [HR], 4.8; $P < 0.001$), pre-LT waiting time of 120 days or less (HR, 2.6; $P = 0.01$) and hilar lymph node invasion (HR = 2.2; $P = 0.03$), but not pre-LT extrahepatic disease, were significant risk factors for recurrence. These findings, which were also confirmed in a propensity score analysis, allowed the development of a HEHE-LT score enabling stratification of patients in relation to their risk of tumor recurrence. Patients with a score of 2 or less had a much better 5-year disease-free survival compared to those having a score of 6 or higher (93.9% vs 38.5%; $P < 0.001$). **Conclusions.** The analysis of this (largest in the world) HEHE adult liver recipient cohort clearly confirms the value of LT in the treatment of this rare disorder and also permits identification of patients at risk of posttransplant recurrence. Posttransplant follow-up should take the HEHE-LT score into account. Extrahepatic disease localization is reconfirmed not to be a contraindication for LT.

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Hepatic epithelioid hemangioendothelioma (HEHE) is a rare vascular tumor which has an aggressiveness graded between hemangioma and hepatic hemangiosarcoma (HHS).[1] The disease has been documented in infants (0-3 years), children and adolescents (4-18 years), and adults (>18 years). Adult patients have a clinical and pathologic presentation distinct from younger patients.[2-4] Due to its rarity and protean behavior, the optimal clinical management of HEHE has not yet been standardized.[5] In rare cases of unilobar

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disease, partial hepatectomy has been advocated, despite the fact that aggressive recurrences have been reported after both minor and major hepatectomies.[6,7] In cases of advanced liver involvement and/or extrahepatic disease (EHD), liver transplantation (LT) has been performed successfully.[8-10] About 200 transplants have been reported, most of them part of 3 multicenter studies, originating from the United States (110 patients), Europe (59 patients), and Canada (11 patients).[4,11,12]

The present study, which presents149 recipients reported to the European Liver Transplant Registry (ELTR), represents the worldwide largest HEHE patient as well as HEHE transplant series. The authors decided to update the original 2007 "HEHE-ELTR" analysis for the following reasons. (a) to further confirm the value of LT in the current management of HEHE in a cohort that was almost triple the original study group; (b) to verify if the attitude of the transplant community had evolved since the 2007 report;(c) to identify risk factors for posttransplant recurrence; (d) to create a propensity score to confirm the marginal role of EHD as risk factor for transplantable HEHE patients and finally (e) to develop a predictive score to standardize a therapeutic algorithm for these patients.

MATERIALS AND METHODS

A detailed questionnaire, comprising 216 items, was sent to the 52 ELTR centres who had transplanted the 149 HEHE patients between November 1984 and May 2014.

The questionnaire consisted of 3 parts: (a) pretransplant period (recipient data, biochemistry, clinical and radiologic presentation, neoadjuvant treatments); (b) peritransplant period (donor and transplant data, histologic examination); and c) posttransplant period (outcomes, recurrence, adjuvant treatments).

All patients had a complete follow-up, with a median period of 10.5 years (interquartile ranges [IQR], 4.1-17.1) from diagnosis and of 7.6 years (IQR, 2.8-14.4) from LT. One hundred eight (72.5%) and 77 (51.7%) patients had a follow-up of 5 and 10 years from time of tumor diagnosis. Ninety-seven (65.1%) and 65 (43.6%) patients had a posttransplant follow-up of 5 and 10 years.

Statistical Analysis

Categorical variables were reported as number of cases and percentages; continuous variables as medians and IQRs. A univariate Cox regression analysis was performed including 11 different variables, with the intent to identify risk factors for posttransplant recurrence. The tested variables were LT performed between 1984 and 1999, waiting time (WT) of 120 days or less, pathological invasion of hilar lymph nodes (LN), pathological microvascular (MiVi) and macrovascular invasion (MaVi), recipient female gender, neoadjuvant therapy, EHD at radiology, time between diagnosis and LT, recipient age and additive surgery during LT. All these variables were selected according to their clear clinical connection with the risk of tumor recurrence. All variables showing a *P* value less than 0.2 were used for constructing a multivariate Cox regression model; a stepwise backward conditional method was adopted. Standard errors, 95% confidence intervals and hazard ratios (HR) were reported. A *P* value less than 0.05 was considered statistically significant. Based on the results obtained from the multivariate analysis, an HEHE score was developed; the weight of each risk factor was calibrated according to the obtained HR.

Patient-free and disease-free survival (DFS) rates were analyzed using the Kaplan-Meier method; patient survival was calculated both from the time of HEHE diagnosis and of LT. Log-rank test was used for comparison of survivals.

A propensity score match (PSM) was calculated to investigate the HEHE patients presenting with EHD. This analysis was restricted to those patients transplanted after 1999 with the intent to exclude the historical series (1984-1999) from this specific analysis. A multivariate logistic regression model was constructed with the EHD status considered as the independent variable and 9 different possible confounding variables for the risk of post-LT recurrence as covariates (WT ≤120 days, pathological invasion of hilar LN, MiVi, MaVi, recipient female gender, neoadjuvant therapy, time between diagnosis and LT, recipient age and additive surgery during LT). PSM was performed using a "nearest neighbor matching" algorithm, attempting to match to each patient in the EHD group a patient from the no-EHD group with the closest propensity score (maximal difference <0.30 times the standard deviation of the scores). Each pair was used once. Unpaired patients were discarded from analysis. A final 1:1 match was generated. Statistical analyses and plots were performed using SPSS 23.0 (IBM SPSS Statistics for Windows, Armonk, NY).

RESULTS

Clinical and biochemical presentations of HEHE are displayed in Tables 1 and 2. Median ages at time of diagnosis and LT were 40 years (IQR, 31-48) and 43 years (IQR = 36-51). Median time from diagnosis to LT was 1 year (IQR, 0-3). Male-female ratio was 33.6/66.4%. An underlying liver disease was present in 10 (6.7%) patients.

The most frequent symptoms were upper abdominal discomfort (n = 85; 57.0%) and pain (n = 77; 51.7%). Thirty-five (23.5%) patients were asymptomatic.

Pre-LT imaging revealed bilobar liver involvement in 136 (91.3%) patients. Liver lesions were solitary, confluent and peripheral in 51 (34.2%), 85 (57.0%), and 13 (8.8%) patients. Portal and hepatic vein thrombosis were documented on imaging in 55 (36.9%) and 35 (23.5%) cases; 5 (3.4%) patients presented both the conditions simultaneously. Pre-LT imaging revealed EHD in 40 (26.8%) patients. The most common EHD localizations were pulmonary (n = 23; 15.4%), abdominal, and/or thoracic LNs (n = 8; 5.4%) and diaphragm (n = 6, 4.0%). Peritoneum, brain, adrenal glands, spleen, bones, vessels, and skin were other localizations.

One hundred thirty (87.2%) patients had a pre-LT percutaneous (n = 96; 64.4%) and/or surgical (n = 52; 34.9%) biopsy; 18 (12.1%) patients had undergone both procedures. In 30 (20.1%) cases, biopsy of EHD had been done. Final HEHE diagnosis was confirmed by pathologic examination of the total hepatectomy specimen or of the EHD tissue removed during additive surgery.

Neoadjuvant Treatment

Forty-two (28.2%) patients had a surgical or medical neoadjuvant treatment. Twenty-one (14.1%) patients had undergone surgery. Eight (5.4%) and 5 (3.4%) patients had received interferon and steroid therapy. Six (4.0%) patients had received transarterial chemoembolization and 1 (0.7%) patient had local radiotherapy. Twelve (8.1%) patients had received systemic chemotherapy (CHTH) (Table 3).

TABLE 1.

HEHE recipient characteristics

Parameters	Median (IQR) or N (%)
Sex (M/F)	50/99 (33.6/66.4)
Age at diagnosis, y	40 (31-48)
Age at transplant, y	43 (36-51)
Time diagnosis-LT, y	1 (0-3)
WT, mo	3 (1-7)
<120 d	80 (53.7)
Recipient MELD at LT	9 (6-17)
Alcohol abuse	24 (16.1)
NASH	7 (4.7)
Cirrhosis	3 (2.0)
Budd-Chiari disease	6 (4.0)
History of pregnancy	35 (23.5)
Symptoms	
Upper abdominal discomfort	85 (57.0)
Upper abdominal pain	77 (51.7)
Asymptomatic	35 (23.5)
Weakness	33 (22.1)
Fatigue	32 (21.5)
Nausea	16 (10.7)
Dyspnea	7 (4.7)
Signs[a]	
Hepatosplenomegaly	48 (32.2)
Weight loss	27 (18.1)
Anorexia	17 (11.4)
Ascites	17 (11.4)
Portal hypertension	11 (7.4)
Hemangioma	10 (6.7)
Jaundice	7 (4.7)

[a] Less commonly observed signs: acute liver failure, encephalopathy and hepato-pulmonary syndrome = 2 cases (1.3%); hepatorenal syndrome = 1 case (0.7%).
N, number; UNOS, United Network for Organ Sharing; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; DM, diabetes mellitus.

Peritransplant and Adjuvant Treatment

LT characteristics are reported in Table 4. Complementary surgery at the time of LT was performed in 60 (40.3%) patients. One patient each with pre-LT diagnosed bilateral pulmonary lesions underwent segmental pulmonary resection and double lung transplantation 29 and 21 months post-LT. One patient, needing diaphragmatic resection at LT, received post-LT systemic CHTH because of peritoneal seeding.

Thirty-seven (24.8%) patients experienced tumor recurrence: 21 (14.1% of the total cohort and 56.8% of the recurring patients) were treated. Surgery was performed in seven (4.7%) of them. Of note is the 7 years DFS of the patient who was retransplanted after 11.5 years due to HEHE recurrence. Seventeen (11.4%) patients had medical treatment: CHTH (13 patients), local radiotherapy (5 patients), and hormonal therapy (one patient). Radiofrequency was used in 1 case (0.7%). Four (2.7%) patients had a multimodal approach (Table 3).

Pathology

Median weight of the total hepatectomy specimen was 1595 g (IQR, 1250-2303); the biggest tumor weighed 11.1 kg. HEHE was always multinodular; only 16 (10.7%) patients had fewer than 6 lesions and tumors were nearly always bilobar (92.7%). HEHE was confirmed by routine hematoxylin-eosin (H&E) staining and/or immunohistochemical (IH) staining for Factor VIII-related antigen (FVIIIRA). IH was found positive in 93 (62.4%) liver specimens. MaVi and MiVi were observed in 20 (13.4%) and 71 (47.7%) livers. Hilar LN invasion, based on routine H&E and/or IH staining, was present in 40 (26.8%) patients. In seventeen (11.4%) patients LN invasion was based on H&E only, in 15 (10.0%) patients on both H&E and FVIIIRA IH staining and in eight (5.4%) patients only on positive IH staining in the absence of H&E positivity. In five (3.4%) patients foci of HHS were suspected; their DFS of 11.3, 13.4, 15.9, 20.7, and 24.5 years, however, contradict this diagnosis.

TABLE 2.

Biochemical presentation of HEHE

Parameter	Normal values	Median	Patients with abnormal values (%)[a]	
AST	8-35 IU/L	27	>35 IU/L	44/135 (32.6)
ALT	8-40 IU/L	32	>40 IU/L	47/134 (35.1)
Total bilirubin	<1.1 mg/dL	0.8	≥1.1 mg/dL	44/139 (31.7)
GGT	<50 IU/L	55	>50 IU/L	65/125 (52.0)
AP	40-130 IU/L	110	>130 IU/L	38/99 (38.4)
Albumin	3.0-5.0 g/dL	4.0	<3.0 g/dL	9/118 (7.6)
INR	0.8-1.2	1.0	>1.2	9/75 (12.0)
Creatinine	0.8-1.4 mg/dL	0.8	>1.4 mg/dL	1/133 (7.5)
Blood nitrogen	7-35 mg/dL	25	>35 mg/dL	27/127 (21.3)
Hemoglobin	11.5-18.0 g/dL	13.2	<11.5 g/dL	27/132 (20.5)
Platelet count	130-370 × 10^3 cell/mm^3	232	<130 x 10^3 cell/mm^3	11/125 (8.8)
			>370 x 10^3 cell/mm^3	13/125 (10.4)
WBC	4.0-11.0 × 10^3 cell/mm^3	6.1	<4.0 x 10^3 cell/mm^3	18/127 (14.2)
			>11.0 x 10^3 cell/mm^3	11/127 (8.7)
AFP	<9 ng/mL	3.1	≥9 ng/mL	9/104 (8.7)
CEA	<3 ng/mL	1.2	≥3 ng/mL	16/87 (18.4)
CA 19-9	<35 ng/mL	7.2	≥35 ng/mL	6/87 (2.1)

[a] Percentage calculated on the available cases.
AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma glutamyl transferase; AP, alkaline phosphatases; INR, international normalized ratio; WBC, white blood cells; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CA 19-9, cancer-antigen 19-9.

TABLE 3.

Neoadjuvant, peri-LT, adjuvant and neoadjuvant treatments

Parameters	No. cases (%)
Neoadjuvant treatment	
Patients treated	42 (28.2)
Surgery	21 (14.1)
Liver	14 (9.4)
Lungs	5 (3.4)
Other	2 (1.3)
Medical	12 (8.1)
IFN	8 (5.4)
Steroids	5 (3.4)
TACE	6 (4.0)
CHTH	12 (8.1)
RTH	1 (0.7)
Multimodal approach	11 (7.4)[a]
Supplementary surgery during LT	
Patients treated	60 (40.3)
Lymphadenectomy	53 (35.6)
Diaphragm resection	10 (6.7)
Omentectomy	4 (2.7)
Right adrenalectomy	3 (2.0)
Splenectomy	1 (0.7)
Lung transplantation	1 (0.7)
Adjuvant therapy after LT (extrahepatic lesions already known before LT)	
Lung resection	1 (0.7)
Lung transplantation	1 (0.7)
CHTH	1 (0.7)
Adjuvant therapy for tumor recurrence after LT	
Patients treated	21 (14.1)
Surgery	7 (4.7)
Lung resection	3 (2.0)
Hepatic resection	2 (1.3)
Re-LT	1 (0.7)
Breast lesion resection	1 (0.7)
RFA	1 (0.7)
Medical	17 (11.4)
CHTH	13 (8.7)
RTH	5 (3.4)
Hormonal therapy	1 (0.7)
Multimodal approach	4 (2.7)[b]

[a] CHTH + Surgery = 4; Surgery + IFN = 2; Surgery + TACE = 1; Surgery + IFN + Steroids = 1; TACE + RTH = 1; CHTH + IFN = 1; CHTH + Surgery + Steroids = 1.
[b] CHTH + RTH = 2; Surgery + CHTH = 1; CHTH + RTH + RFA = 1.
TACE, transarterial chemoembolization; RTH, radiotherapy; RFA, radio-frequency ablation.

Risk Factors for Recurrence

At multivariate Cox regression analysis, MaVi detected at pathology (HR, 4.9; 95% confidence interval [CI], 2.4-9.9; $P < 0.001$), pre-LT WT ≤120 days (HR, 2.5; 95% CI, 1.2-5.3; $P = 0.01$) and hilar LN invasion, based on both H&E and/or HI staining (HR, 2.2; 95% CI, 1.1-4.5; $P = 0.03$) were independent risk factors for post-LT recurrence.

Importantly, pre-LT EHD was not a risk factor for posttransplant recurrence (Table 5).

Outcome After Transplantation

One-, 5-, and 10-year overall survival rates of the whole patient cohort from the time of diagnosis and of LT were 94.0%, 80.8%, and 77.1% versus 88.6%, 79.5%, and 74.4%, respectively. Early (≤3 months) posttransplant mortality was low (n = 4; 4.7%).

DFS at 1, 5, and 10 years were 88.7%, 79.4%, and 72.8%. Thirty-seven (24.8%) patients developed a recurrence after a median time of 18 months (IQR, 8-65).

Patients having 1 or more risk factor(s) for HEHE recurrence, all had lower DFS compared with patients without risk factors (Figure 1).

One-, 5-, and 10-year DFS rates were: 91.8% versus 68.4%, 84.7% versus 44.0%, and 78.4% versus 36.7% in patients without or with MaVi ($P < 0.001$); 93.8% versus 84.2%, 86.7% versus 73.3%, and 84.4% versus 63.0%, in patients with WT longer than or 120 days or less ($P = 0.02$); 91.5% versus 80.6%, 84.2% versus 65.4%, and 77.9% versus 57.4% in patients with or without hilar LN invasion ($P = 0.01$).

Pre-LT EHD was not significant in relation to post-LT DFS survival (1-, 5-, and 10-year: 89.4 vs 86.5%, 82.2 vs 71.6%, and 76.5 vs 61.4%, in patients with or without pre-LT EHD) ($P = 0.25$).

Of note is the fact that the results obtained during the second period (2000-2014) of the survey were markedly improved compared to those obtained during the first period (1894-1999) (1-, 5-, and 10-year DFS of 93.5%, 86.5%, and 85% vs 79.8%, 73.6%, and 69.5% $P = 0.002$).

The HEHE-LT Score

According to the results obtained from the multivariate analysis, a score was developed based on the following formula:

$$5 \times (\text{pathological MaVi}) + 3 \times (\text{WT} \leq 120\,\text{days}) + 2 \times (\text{pathological invasion hilar LN})$$

The proposed HEHE-LT score successfully stratified the patients according to their risk of post-LT recurrence. Five-year DFS were excellent (93.9%) in cases with a low score (score, 0-2; n = 58) still very good (76.9%) but significantly lower ($P < 0.006$) in those with an intermediate score (score,

TABLE 4.

Transplant-related variables

Parameters	Median (IQR) or N (%)
Donor	
Sex (M/F)	97/52 (65.1/34.9)
Age, y	38 (23-49)
Transplantation	
Split liver	13 (8.7)
Domino LT	2 (1.3)
LDLT	5 (3.4)
Open time, h	6.2 (4.5-8.2)
CIT, min	7.2 (5.5-9.7)
WIT, min	48 (33-62)
Postoperative course	
ICU stay, d	3 (2-7)
Total hospital stay, d	21 (14-30)
Recurrence	37 (24.8)
Time from LT to recurrence, mo	18 (8-65)

LDLT, living-donor liver transplantation; CIT, cold ischemia time; WIT, warm ischemia time; ICU, intensive care unit.

TABLE 5.

Risk factors for HEHE recurrence after LT (multivariate Cox regression analysis, backward conditional method)

Variables	B	SE	*P*	HR	95% CI for Exp (B)	
					Lower	Upper
Univariate analysis						
Pathological MaVi	1.5	0.4	<0.001	4.3	2.2	8.6
LT performed during period 1984-1999	1.0	0.3	0.003	2.8	1.4	5.5
WT ≤ 120 days	0.8	0.4	0.02	2.3	1.1	4.6
Pathological invasion hilar LN	0.8	0.3	0.02	2.3	1.2	4.4
Pathological MaVi	0.8	0.3	0.02	2.2	1.1	4.3
Recipient gender (M/F)	–0.5	0.3	0.1	0.6	0.3	1.2
Neoadjuvant therapy	0.4	0.3	0.2	1.6	0.8	3.1
EHD at radiology	0.4	0.4	0.2	1.5	0.8	3.0
Time between diagnosis and LT (x month)	–0.04	0.04	0.3	1.0	0.9	1.0
Recipient age, y	–0.01	0.01	0.5	1.0	1.0	1.0
Additive surgery during LT	0.04	0.3	1.0	1.0	0.5	1.9
Multivariate analysis (backward conditional method)						
Pathological MaVi	1.6	0.4	<0.001	4.9	2.4	9.9
WT ≤ 120 days	0.9	0.4	0.01	2.5	1.2	5.3
Pathological invasion hilar LN	0.8	0.4	0.03	2.2	1.1	4.5

–2Log Likelihood: 317.534.

Variables initially analyzed in the multivariable model: pathological MaVi (Y/N), period of LT (1984-1999), WT ≤ 120 days (Y/N), pathological micro-invasion of the hilar LN (Y/N).pathological MaVi (Y/N), recipient gender (M/F), neoadjuvant therapy (Y/N), EHD at radiology (Y/N).

B, beta coefficient; SE, standard error; CI, confidence intervals.

3-5; n = 74) and markedly lower in case of a "high-score" (score, 6-10; n = 17) (38.5%; *P* <0.001) (Table 6, Figure 2).

Based on these results, a therapeutic algorithm for the treatment of HEHE has been proposed (Figure 3).

Sub-Analysis 1: Comparison Between First (1984-1999) and Second LT Period (2000-2014)

Results of LT between 1984-1999 (n = 52 patients) and 2000-2014 (n = 97 patients) were compared. Incidences of EHD (34.6% vs 23.7%; *P* = 0.11) and neoadjuvant treatment (23.1% vs 30.9%; *P* = 0.21) were similar. During the first period, a "fast-track" approach (WT ≤120 days: 65.4% vs 47.4%; *P* = 0.03) and complementary surgery at LT (50.0% vs 35.1%; *P* = 0.06) were more common. Patients transplanted during the first period also had a higher incidence of MaVi (23.1% vs 8.2%; *P* = 0.01) and hilar LN metastases (34.6% vs 22.7%; *P* = 0.09).

Sub-Analysis 2: PSM for EHD

EHD was not a risk factor for post-LT recurrence in neither survival nor inferential analyses. With the intention of validating the (important) statement that EHD is not a formal contraindication for LT further, a propensity score analysis was done after a 1:1 PSM comparing2 cohorts of 23 EHD and no-EHD patients transplanted between 2000 and 2014. To obtain more homogeneous results patients transplanted between 1984 and 1999 were not considered in this analysis. No statistical differences were observed in relation to female gender (73.9% vs 60.9%; *P* = 0.27), WT ≤120 days (30.4% vs 52.2%; *P* = 0.12), neoadjuvant therapy (43.5% vs 30.4%; *P* = 0.27), additive surgery during LT (34.8% vs 43.5%; *P* = 0.38), MaVi (17.4% vs 4.3%; *P* = 0.17), MiVi (43.5% vs 56.5%; *P* = 0.28), LN invasion (26.1% vs 30.4%; *P* = 0.50), and overall recurrence (21.7% vs 17.4%; *P* = 0.50). DFSs were similar between EHD and no-EHD patients (5 years: 73.5 vs 81.6%; *P* = 0.54). The HEHE scores were similar in both groups (median score points, 2 vs 3; *P* = 0.67) as well as the percentages of patients having a high score (13.0% vs 4.3%; *P* = 0.27).

DISCUSSION

Adult HEHE is a rare vascular liver tumor with a very variable clinical presentation and behavior. In an extensive literature review on 434 HEHE patients, 87% and 37% had a multifocal tumor and EHD.[13] Lung, peritoneum, LNs, bones, spleen, brain, breast, and adrenal glands are the most common sites of EHD.[13,14]

Despite previous "favorable" LT registry reports both from Europe and United States, a standardized treatment algorithm for HEHE is still lacking.[13] The (previous) detailed "HEHE-ELTR" report, including 59 liver recipients, showed excellent 5-year post-LT overall survival and DFS rates (83% and 82%, respectively); the recurrence rate was 25%. In the, much less detailed, US survey, including 110 adults, 5-year patient survival and recurrence rates were 67% and 11%. Finally, the small Canadian multicenter analysis, including only 11 cases, showed 5-year patient survival and DFS rates of 82% and 69%; the recurrence rate was 36%.[4,11,12]

Despite these encouraging results, the attitude of the medical as well as of the transplant professionals toward this disease remains hesitant. This can be explained by the high incidence of EHD localization (present in up to one third of patients), the absence of good clinical and histological markers predicting tumor evolution as well as recurrence after transplantation and the reported long-term (up to 28 years!) survival rates in the absence of any treatment.

For this reason, it was decided to revisit to the ELTR-ELITA HEHE registry to corroborate the value of LT in the

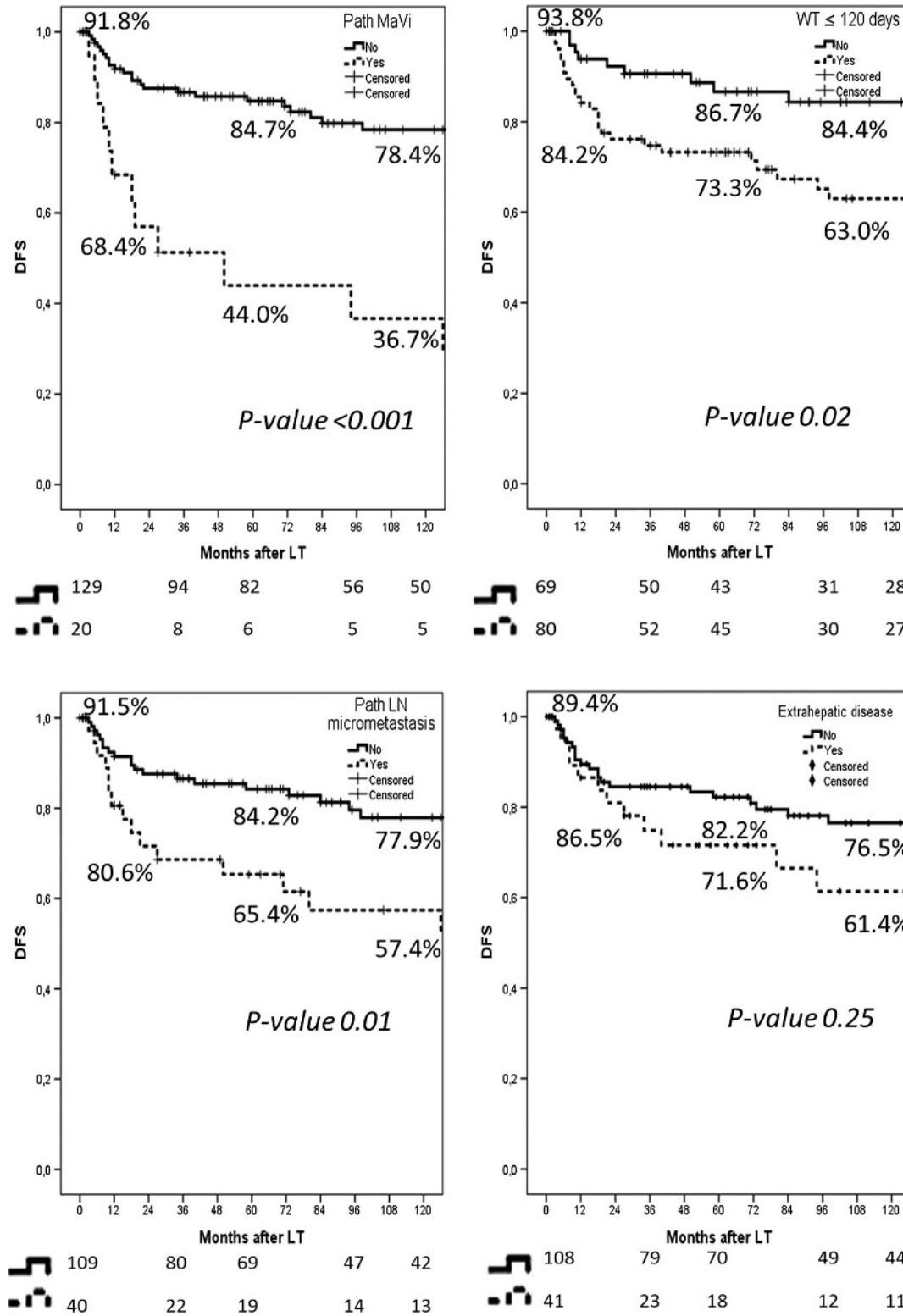

FIGURE 1. Post-liver transplant 1-, 5-, and 10-year DFS rates according to the presence of specific risk factors for HEHE recurrence. Path MaVi, pathological MaVi; Path LN: pathological LN metastasis.

therapeutic algorithm of HEHE further. It was postulated that the much larger patient cohort (almost triple) and the much longer posttransplant follow-up (almost two thirds. and almost half of the studied recipients had a follow-up of 5 and 10 years, respectively) would make this possible. Indeed, this updated and detailed ELITA-ELTR HEHE survey not only confirmed the previously reported findings, but more importantly, achieved more robust statistical results and the development of a user-friendly prognostic score (based on a multivariate analysis) as well as a propensity score aimed to improve the definition of the role of EHD in as a risk factor for post-LT recurrence.

TABLE 6.

DFS according to the proposed HEHE-LT SCORE

Variables	No. cases	N recurrences (%)	DFS 1 y	DFS 3 y	DFS 5 y	DFS 10 y
Score 0-2	58	5 (8.6)	98.2	96.3	93.9	91.1
Score 3-5	74	21 (28.4)	85.7	78.5	76.9	68.4
Score 6-10	17	11 (64.7)	68.8	48.1	38.5	28.9

Log-rank analysis.
Score, 0-2 vs 3-5: $P = 0.006$.
Score, 0-2 vs 6-10: $P < 0.001$.
Score, 3-5 vs 6-10: $P = 0.001$.

The argument of "transplant opponents" that HEHE does not need to be aggressively treated because many patients survive for long periods (up to 10 years) in the absence of any treatment is counteracted by the excellent long-term DFS obtained in the analyzed ELTR-ELITA cohort and by the rapid and fatal disease evolution observed in some HEHE patients.[15] The "wait-and-see" approach should be discouraged in our opinion, particularly when dealing with mostly young (female) patients.[16,17] These considerations are also in line with a large HEHE literature review confirming that LT is the best strategy for HEHE.[13] Indeed, partial liver resection, CHTH or therapeutic abstention showed 5-year survival rates of 50%, 30%, and less than 10%. These numbers are very different from those obtained in the present study with 5- and 10-year patient survival rates from the time of diagnosis of 80.8% and 77.1% and from LT of 79.5 and 74.4%. Five-year DFS rates from the time of diagnosis are 80% and the recurrence rate is 24.8%. The latter number is in line with previously reported 11% to 36% recurrence rates.[11,12]

The previous HEHE-ELTR report of 2007 identified MaVi combined with MiVi as a predictor of recurrence.[4] In the present study, MaVi alone is the main risk factor for recurrence. This finding is very important as MaVi can nowadays be diagnosed at pre-LT work-up. The analysis in the Cox regression model was restricted to the pathological MaVi in the total hepatectomy specimen only, due to the major discrepancy observed in these series between radiological and pathological data. At imaging, 60 (40.3%) patients were said to present portal and/or hepatic vein (tumor) thrombosis. However, MaVi could only be confirmed at examination of the hepatectomy specimen in 19 (12.8%) of them; in only 8 (42.1%) of them MaVi was effectively diagnosed before LT, thereby indicating a tremendous number of false positives (52/60; 86.7%). These data reflect the poor ability of radiological imaging to diagnose MaVi preoperatively (42.1% sensitivity and 58.1% specificity). Possible explanations for these results are the varying quality of imaging over a 30-year study period, as well as the fact that differential diagnosis between vascular compression/occlusion and true vessel invasion is difficult, especially in the presence of a large tumor.[18-21] The continuous refinement of imaging techniques will improve the ability to correctly identify MaVi before LT, important information to inform the therapeutic algorithm.[22-24]

A new finding was that a short WT (≤120 days from waiting-list registration) was identified as the second risk factor for post-LT recurrence. This has not been explored in previous studies focused on HEHE. As observed in other liver tumors, WT is not only a tool to observe tumor behavior and aggressiveness, but is also a means to permit the delivery of neoadjuvant therapy. The "fast track" approach eliminates the possibility of "selecting" patients based on tumor aggressiveness.[25] In the context of the difficult differential diagnosis between HEHE and HHS, WT is of supplementary value to avoid futile LT. Indeed, as reported before, all HHS recipients recurred within 6 months after LT and none survived more than 2 years.[26] A mandatory WT from waitlist registration is moreover justified as survival rates of HEHE recipients estimated from the time of diagnosis and from the date of transplant (the difference being around 3 years) were similar. When updating the ELTR-ELITA HEHE registry, it was unfortunately impossible to obtain information about waitlist drop-outs, despite multiple contacts with all participating centers. Such intention-to-treat approach should however be looked at in the future to definitively rule out the doubts of the medical and transplant communities in relation to the indication for LT in the treatment of, even asymptomatic, HEHE.

Hilar LN involvement at the time of LT was the third significant risk factor for tumor recurrence. It is important to underline that routine extensive lymphadenectomy should be a full part of the LT procedure and that correct pathologic LN staging needs to include both routine H&E and IH staining. The FVIIIRA marker is commonly used together with other vascular markers to confirm the nature of the tumor.[27-29] In the present series, LN involvement was based on the combination of positive H&E and/or FVIIIRA IH staining.[5] Although the observed long-term DFS results are less good (84.2% vs 65.4% in case of LN-positivity), LN invasion should not be considered per se as an absolute contraindication to LT.

The combination of the 3 risk factors reported here have allowed the development of a HEHE-LT score to stratify the patients into "low" (score, 0-2) and "high" risk for recurrence (score, 6-10); such information may be of value in posttransplant follow-up. High-risk patients should have their immunosuppression minimized and/or switched to immunosuppressants displaying antineoplastic effects as well as being exposed to newer adjuvant-directed approaches.[30-34] Patients with a low risk can be taken considered for a "safer"

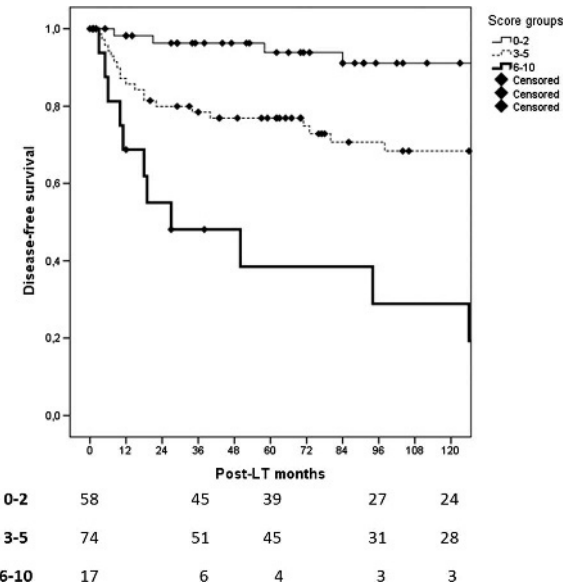

FIGURE 2. Post-liver transplant 1-, 5-, and 10-year DFS rates according to the HEHE-LT SCORE.

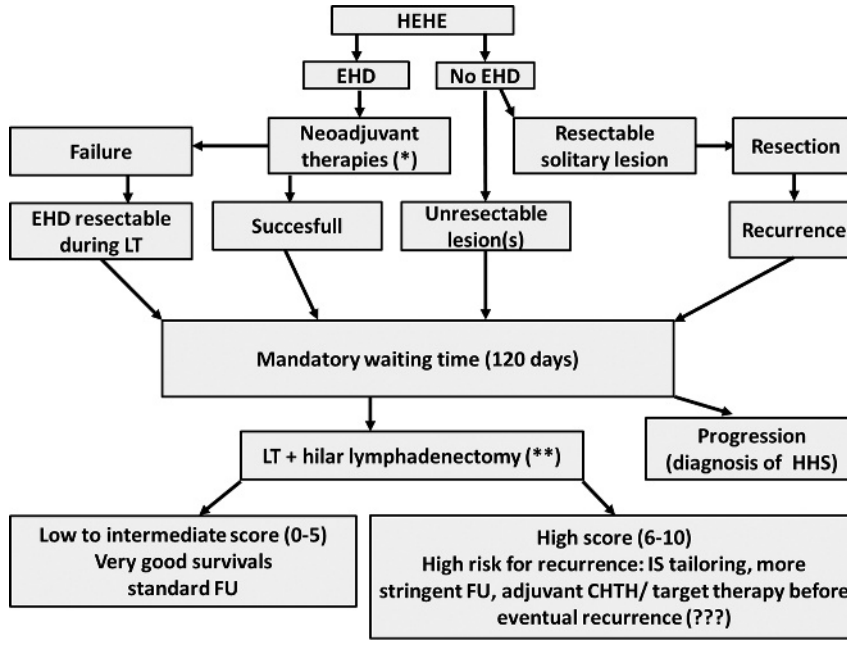

FIGURE 3. HEHE therapeutic algorithm (*) no standardized neoadjuvant approach; (**) histological examination combining immunohistochemistry and H&E staining. FU, follow-up.

living donation process, possibly implementing more accurate preoperative staging approaches (laparoscopic sampling of suspected hilar LN, use of radiological methods able to detect MaVi more accurately).

The present study confirms previously published findings that pre-LT EHD is not a significant predictor of survival or of recurrence. The present study strengthens this conclusion as it is based on a more sophisticated statistical analysis. Both multivariate Cox regression and a specifically designed propensity score performed in a homogenous population did not show survival differences between EHD and no-EHD cases. Even after deliberate exclusion of patients transplanted before the year 2000, this PSM analysis still concerns the worldwide largest reported series of EHD cases. The good survival rates obtained in EHD patients are important to justify the decision to go towards LT; indeed EHD-HEHE patients represent up to 30% of the HEHE cohort. This approach should furthermore be seen in the context of a multimodal, often aggressive, approach combining neoadjuvant/adjuvant therapies and complementary surgery at moment of LT.[35] The recent discovery of a specific HEHE genetic marker, namely the fusion between genes WWTR1 and CAMTA1, also concurs with the reported results.[36] This translocation not only ends the belief that HEHE is part of a continuum of vascular tumors positioned in-between hemangioma and hemangiosarcoma, but also confirms the monoclonal nature of all the different lesions of a multifocal HEHE in a same patient. Multifocality and possibly EHD location may consequently be interpreted as metastatic implants of the same neoplastic clone rather than a "field-effect" or a synchronous occurrence of multiple different clones, allowing therefore an equally effective neoadjuvant therapy on both hepatic and extrahepatic lesions.[37] Unfortunately, no reports on clonality of simultaneous hepatic and extrahepatic lesions are available yet. Such genetic diagnosis is urgently needed to further improve the care of HEHE patients, especially those having EHD localization at moment of transplantation.

The final aim of the present study was to look at the impact of the previously reported HEHE-ELTR study on today's medical (transplant) practice. The impact of the 2007 HEHE paper was very clear on transplant practice. Not only have the number of transplanted patients doubled in the last years (3 patients/year during the period 1984-1999 vs 6 patients/year during the period 2000-2014), but also the DFS improved by 15%. This may be explained by the fact that more patients were transplanted before the tumor became clinically detrimental: in fact, the number of asymptomatic patients transplanted more than doubled from 13.5% to 28.9% in the 2 periods. Moreover, patients presenting with EHD and LN involvement benefitted from improved and combined neoadjuvant treatments.[38-41] These therapies (surgery, locoregional therapies, CHTH) also seem (as observed in the present analysis) to have reduced the necessity for additional surgery during LT.

The retrospective design of the study unfortunately did not permit investigation of other potential biological markers of tumor aggressiveness such as mitotic index, high cellularity, necrotic/fibrotic areas, cellular pleomorphism and genetic markers.[36,37,42,43] Similarly, the number of patients treated with mammalian Target of Rapamycin inhibitors was too small to look at their role in possible improvement of LT results; it has to be anticipated that newer antiangiogenic and target drugs will play a more and more important role in the future therapeutic algorithm of HEHE.

CONCLUSIONS

This updated long-term, ELTR-ELITA HEHE survey (the largest in the world)strengthens the place of LT in the therapeutic algorithm of HEHE. MaVi, short WT (≤120 days) and LN involvement all are risk factors for post-LT tumor recurrence; EHD in contrast, has been confirmed not to be a formal contra-indication to LT. Based on these findings, a HEHE-LT score has been developed allowing to identify

patients at "low-" and "high-risk" for post-LT recurrence. This information should be taken into consideration to tailor posttransplant follow-up.

Improved tumor staging using refined imaging and tissue sampling (including FVIIIRA IH analysis) together with the development of newer molecular and genetic markers as well as the introduction of anti-angiogenic and target therapies will without doubt further improve the outlook of these, often desperately ill, young patients.

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