



# Treatment and Prognosis of Hepatic Epithelioid Hemangioendothelioma: A SEER Database Analysis

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## Abstract

**Background** Hepatic epithelioid hemangioendothelioma (HEH) is a rare tumor that can affect multiple organs. Little is known about the pathophysiology, clinical course and management of this disease. The aim of this study is to determine survival rates and elucidate the role of various prognostic factors and therapeutic modalities as compared to surgery on patients with HEH.

**Methods** A retrospective analysis on patients diagnosed with HEH between 2004 and 2016 was performed utilizing the SEER database. Kaplan–Meier curves were constructed to determine overall and cancer-specific survival, and the log-rank test was used to compare between groups. To explore prognostic factors and treatment outcomes, univariable and multivariable Cox proportional hazard models were developed.

**Results** A total of 353 patients with HEH (median age: 50.4 years) were identified. The most common surgery performed was liver resection (90.8%). One-year OS in the surgical group and non-surgical group was 86.6% and 61.0%, respectively, while 5-year OS was 75.2% and 37.4%, respectively. On multivariable analysis, surgery emerged as a favorable prognostic factor [HR (95%CI): 0.404 (0.215–0.758)  $p$  value=0.005]. Age > 65 years [HR (95%CI): 2.548 (1.442–4.506)  $p$  value=0.001] and tumor size > 10 cm [HR (95%CI): 2.401 (1.319–4.37)  $p$  value=0.004] were shown to be poor survival prognostic factors.

**Conclusion** HEH is a rare disease that is poorly understood. Surgical intervention is associated with improved survival rates. Multicenter prospective collaborations are needed to improve our limited knowledge about this neoplasm and determine the optimal treatment strategy.

## Introduction

Epithelioid hemangioendothelioma is a rare tumor that can affect multiple organs [1]. It was first described by Weiss and Enzinger in 1982 as a rare vascular tumor that was often mistaken for metastatic carcinoma [2]. These neoplasms most commonly arise in the liver, lungs and bones [3]. Of these, the liver is the most commonly involved organ and the incidence rate of hepatic epithelial hemangioendothelioma (HEH) is as low as 1 per 1 000 000 [1, 4].

HEH is a low-grade neoplasm with pathology ranging between benign hemangioma and aggressive angiosarcoma [5]. While some patients are asymptomatic, others report

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right upper quadrant pain, weight loss, jaundice as well as general gastrointestinal symptoms such as nausea and anorexia. These neoplasms have been associated with multiple diseases including: Kasabach–Merritt syndrome and Budd–Chiari syndrome, although their association still remains rare [6]. Little is known about the pathophysiology, clinical course and management of this disease because of its low incidence rate. Although different treatment modalities have been utilized, a consensus for the single best has not been established yet [7]. Treatment options include medical therapy with propranolol and prednisone, chemo/immunotherapy with different suggested regimens, radiotherapy and radiofrequency ablation, as well as different surgical interventions including liver resection and liver transplantation [8–10].

Due to relatively low number of cases, studies investigating therapeutic outcomes are conflicting and limited. Chemotherapy has been associated with remission induction in some studies, while it has also been associated with disease progression in others [10–12]. Similarly, surgical resection has been associated with promising results often leading to partial or even complete response [13]. The ELTR study, the largest case series on the surgical management of HEH, has also shown a significant value for liver transplantation [14]. However, other studies have shown no significant difference in survival between patients undergoing surgery and those treated medically [13, 15].

Accordingly, the literature on the management of HEH is mostly comprised of case reports and small case series. The principle goal of this study is to determine survival rates and elucidate the role of various prognostic factors and therapeutic modalities as compared to surgical approach on patients with HEH leveraging the large US population-based Surveillance, Epidemiology, and End Results (SEER) Program database.

## Materials and methods

### Data retrieval

The SEER registry is a well-established and reliable database for cancer research. The registry includes data from 17 regions in the USA, involving around 28% of the entire US population. The information collected and added to the SEER registry contains patient demographics, primary cancer site, grade/stage of disease, utilization of surgical procedures or radiation therapy and follow-up on vital status [16]. Data also include whether death was due to the cancer or due to another cause, allowing to calculate cancer-specific survival (CSS) and overall survival (OS), respectively. All data concerning HEH were retrieved from

the SEER registry between 2004 and 2016. Patients from earlier years (1973–2003) were excluded due to missing variables and in order to reflect more contemporary trends in the survival of HEH patients.

The International Classification of Disease (ICD) and 3rd edition histology codes (9130 for hemangioendothelioma and 9133 for epithelioid hemangioendothelioma) were combined with the code C22.0 (for liver) to retrieve the data from patients with HEH. Patient baseline characteristics included age, gender and race. Tumors were divided by size into  $\leq 10$  or  $>10$  cm. Tumor stage was defined as localized (confined to the liver), regional (either direct extension or regional lymph nodes) or distant (metastatic to distant lymph nodes or distant organs). Treatment modalities included chemotherapy, radiotherapy and surgery. The SEER database does not provide details on the chemotherapy administered. Surgical treatment included wedge/segment resection (codes 20–29), lobectomy (codes 30–59), liver transplantation (codes 60–89) or surgery not otherwise specified (code 90).

### Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) (version 24.0, IBM Corp., Armonk N.Y., USA). Continuous data were reported as means and standard deviations (SD) with comparisons made using the independent t test. Categorical data were reported as counts and proportions, with comparisons made using the Chi-square test, or the Fisher's exact test, as appropriate. Kaplan–Meier curves were constructed to determine OS and CSS, and the log-rank test was used to compare between groups. To explore prognostic factors, univariable and multivariable Cox proportional hazard models were developed. Variables significant on univariable analysis were included in the multivariable model. Risk-adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (95% CI) were calculated. A two-sided  $p$  value  $<0.05$  was used to indicate statistical significance.

## Results

### Study population

A total of 353 patients with HEH were identified (Table 1). The mean age of all patients was  $50.4 \pm 18.8$  years with 42.4% aged between 40 and 60 years. The mean age of patients undergoing surgery was significantly lower ( $48.3$  vs  $52.7$ ,  $p$  value =  $0.03$ ) with around half of patients in the 40- to 60-year age category. Most patients were female ( $n=196$ , 55.5%) and white ( $n=280$ , 79.0%), and there was no

**Table 1** Baseline characteristics of all patients with hemangioendothelioma stratified by surgery status

Variable		Number (%)			<i>p</i> -value
		Overall	No Surgery	Surgery	
Patients		353	168	185	
Age	Mean (SD)	50.4 (18.8)	52.7 (20.5)	48.3 (17)	<b>0.030</b>
	<40	101 (28.6)	45 (26.8)	56 (30.3)	<b>0.008</b>
	40–60	149 (42.2)	61 (36.3)	88 (47.6)	
	>60	103 (29.2)	62 (36.9)	41 (22.2)	
Gender	Female	196 (55.5)	90 (53.6)	106 (57.3)	0.482
	Male	157 (44.5)	78 (46.4)	79 (42.7)	
Race	White	280 (79.3)	132 (78.6)	148 (80)	0.718
	Black	34 (9.6)	15 (8.9)	19 (10.3)	
	Others	36 (10.2)	20 (11.9)	16 (8.6)	
	Unknown	3 (0.8)	1 (0.6)	2 (1.1)	
Stage	Localized	114 (32.3)	25 (14.9)	89 (48.1)	<b>&lt;0.001</b>
	Regional	77 (21.8)	22 (13.1)	55 (29.7)	
	Distant	111 (31.4)	81 (48.2)	30 (16.2)	
	Unknown/ Unstaged	51 (14.4)	40 (23.8)	11 (5.9)	
Size	0–10 cm	164 (46.5)	52 (31.0)	112 (60.5)	<b>&lt;0.001</b>
	>10 cm	55 (15.6)	26 (15.5)	29 (15.7)	
	Unknown	134 (38)	90 (53.6)	44 (23.8)	
Chemotherapy	No/Unknown	252 (71.4)	95 (56.5)	157 (84.9)	<b>&lt;0.001</b>
	Yes	101 (28.6)	73 (43.5)	28 (15.1)	
Radiotherapy	No/Unknown	305 (86.4)	167 (99.4)	138 (74.6)	<b>&lt;0.001</b>
	Yes	48 (13.6)	1 (0.6)	47 (25.4)	

Values in bold are statistically significant

difference in gender or ethnic distribution between the two groups. Patients in the surgery group mostly comprised of localized ( $n=89$ , 48.1%) and regional ( $n=55$ , 29.7%) malignancy, while those not receiving surgery most often had distant ( $n=81$ , 48.2%) or unstaged ( $n=40$ , 23.8%) malignancy. Similarly, most patients ( $n=112$ , 60.5%) had tumor size  $\leq 10$  cm in the surgery group, while 69.0% ( $n=115$ ) of patients were had tumor size  $>10$  cm in the non-surgical group. The overall median follow-up time for all patients was 29 months (IQR: 6–80).

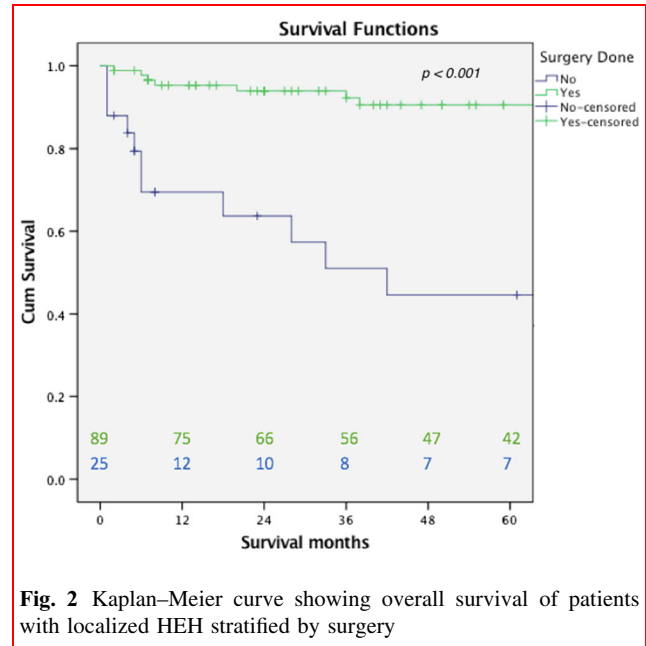
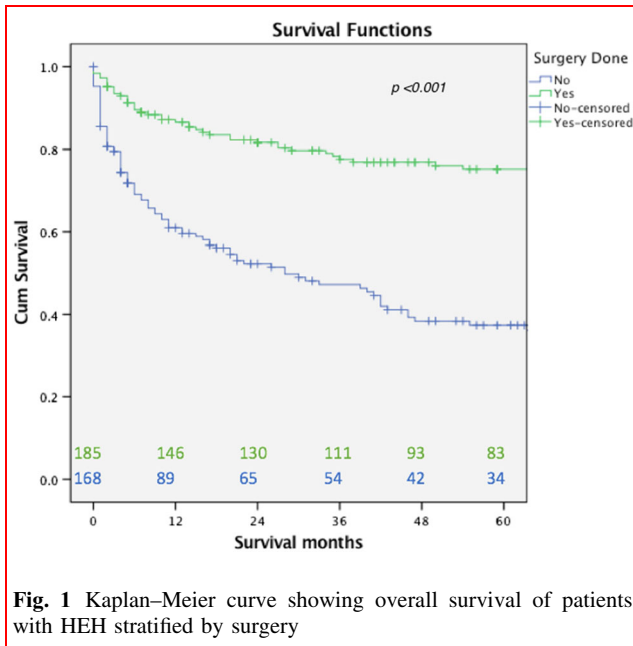
### Treatment modalities

Chemotherapy was administered to 84.9% ( $n=157$ ) of patients undergoing surgery, compared to 56.5% ( $n=95$ ) of those who were not. Radiotherapy was used in treating 25.7% ( $n=47$ ) of the patients in the surgical group, while it was only used in treating one patient (0.6%) in the non-

surgical group. The most common surgery performed was wedge/segment resection ( $n=86$ , 47.0%), followed by major liver resection ( $n=82$ , 44.8%) and transplant ( $n=15$ , 8.2%). Table 2 presents the different combinations in treatment modalities in patients undergoing surgery. Radiotherapy was administered to 22 patients (25.6%) undergoing wedge/segment resection, 23 patients (12.6%)

**Table 2** Distribution of patients over different treatment modalities

Type of Surgery	Chemotherapy	
	No	Yes
Wedge/Segment Resection	73 (39.9)	13 (7.1)
Lobectomy	74 (40.4)	8 (4.4)
Transplantation	10 (5.5)	5 (2.7)
Surgery Not Otherwise Specified	1 (0.5)	1 (0.5)



undergoing major liver resection and 2 patients (13.3%) undergoing transplant.

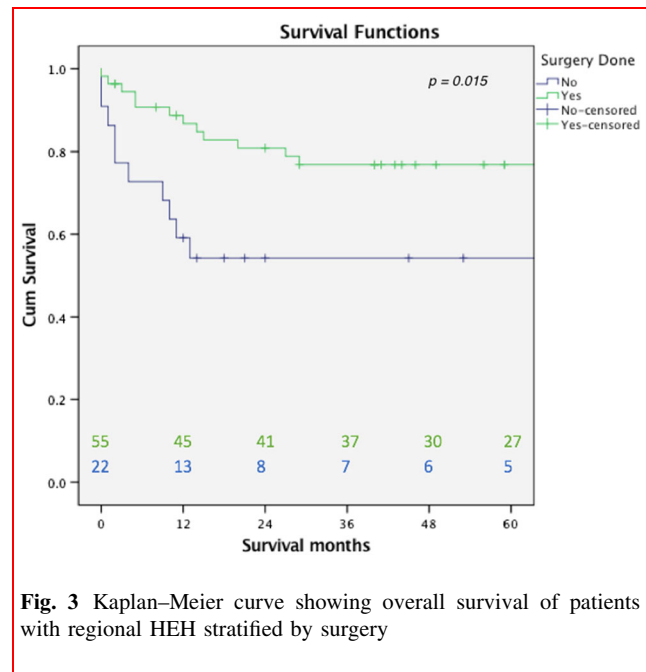
**Survival**

In the overall study population, the OS rates at 1 and 5 years were 74.6% and 57.6%, respectively, while CSS rates were 80.1% and 66.8%, respectively. OS and CSS between the surgical and non-surgical groups were statistically different (*p* value<0.001). One-year OS in the surgical group and non-surgical group was 86.6% and 61%, respectively, while 5-year OS was 75.2% and 37.4%, respectively (Fig. 1). One-year CSS in the surgical group and non-surgical group was 90.8% and 67.6%, respectively, while 5-year CSS was 83.7% and 46.2%, respectively.

On subgroup analysis, patients with localized and regional disease had significantly higher overall survival when undergoing surgery (Figs. 2, 3). Overall survival was not different between the surgical and non-surgical groups in patients with distant metastasis (Fig. 4). Table 3 displays the 1- and 5-year OS for each disease stage.

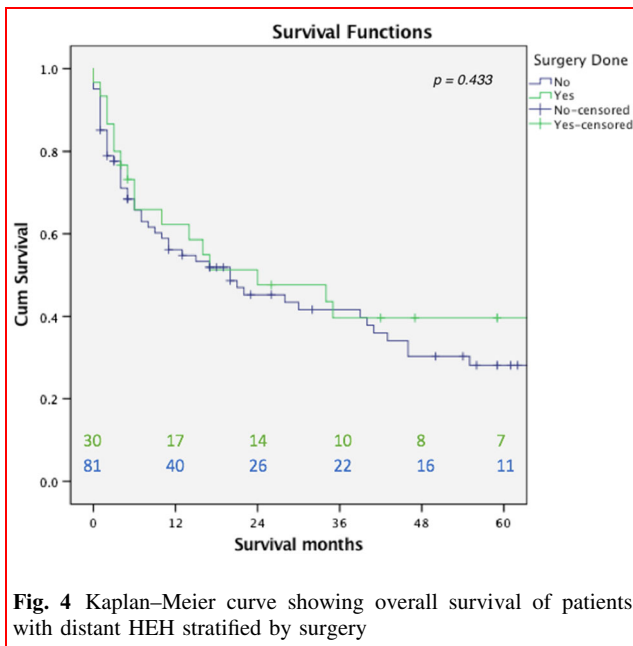
**Prognostics factors**

Using univariable analysis, surgery was associated more favorable outcomes [HR (95%CI): 0.339 (0.241–0.478), *p*-value<0.001]. Distant malignancy as compared to localized [HR (95%CI): 3.46 (2.248–5.324), *p* value< 0.001], tumor size>10 cm [HR (95%CI): 2.664 (1.531–4.636), *p* value=0.001] and chemotherapy [HR (95%CI):



2.083 (1.489–2.916), *p* value<0.001] were shown to be poor survival prognostic factors (Table 4).

On multivariate analysis, surgery retained its significance as a favorable prognostic factor [HR (95%CI): 0.404 (0.215–0.758), *p* value=0.005], while age>65 years [HR (95%CI): 2.548 (1.442–4.506), *p* value=0.001] and tumor size>10 cm [HR (95%CI): 2.401 (1.319–4.37), *p* value= 0.004] retained their significance as poor prognostic factors (Table 5). On subgroup analysis, chemotherapy [HR (95% CI): 3.51 (1.023–12.042), *p* value=0.046] was also shown



**Fig. 4** Kaplan–Meier curve showing overall survival of patients with distant HEH stratified by surgery

**Table 3** Overall survival of patients based on stage

	OS	Localized	Regional	Distant
Surgery performed	1-year	94.2	86.8	62.2
	5-year	86.1	76.8	39.6
No Surgery performed	1-year	56.2	59.1	56.1
	5-year	36.1	54.2	28.1

to be a poor survival prognostic factor in patients with localized disease in the multivariable regression model (Table 6).

### Discussion

Hepatic endothelial hemangioendothelioma remains one of the less understood neoplasms of the liver with limited consensus regarding its management. In this study, the national scale SEER database was employed to elucidate the prognosis of patients with this malignancy as well as the factors associated with survival outcomes. Specifically, we investigated the role of surgery in the treatment of this neoplasm.

Various case reports and series have suggested different clinical outcomes in HEH, from spontaneous complete regression (reported once in the literature) to aggressive rapid progression and poor survival [17–19]. Reported survival rates vary between studies due to dissimilarities in patient characteristics and differences in treatment

**Table 4** Univariable Cox proportional hazard regression model on all patients

Variable	Overall survival	
	HR (95% CI)	p value
Age	0–65 years	Reference
	>65 years	3.043 (2.182–4.243) <b>&lt;0.001</b>
Gender	Female	Reference
	Male	1.296 (0.937–1.794) 0.117
Surgery	No	Reference
	Yes	0.339 (0.241–0.478) <b>&lt;0.001</b>
Stage	Localized	Reference
	Regional	1.167 (0.678–2.01) 0.577
	Distant	3.46 (2.248–5.324) <b>&lt;0.001</b>
Size	0–10 cm	Reference
	>10 cm	2.664 (1.531–4.636) <b>0.001</b>
Chemotherapy	No/Unknown	Reference
	Yes	2.083 (1.489–2.916) <b>&lt;0.001</b>
Radiotherapy	No/Unknown	Reference
	Yes	0.851 (0.525–1.379) 0.513

Values in bold are statistically significant

**Table 5** Multivariable Cox proportional hazard regression model on all patients

Variable	Overall Survival	
	HR (95% CI)	p-value
Age	0–65 years	Reference
	>65 years	2.548 (1.442–4.506) <b>0.001</b>
Surgery	No	Reference
	Yes	0.404 (0.215–0.758) <b>0.005</b>
Stage	Localized	Reference
	Regional	1.356 (0.707–2.601) 0.359
	Distant	1.589 (0.75–3.367) 0.227
Size	0–10 cm	Reference
	>10 cm	2.401 (1.319–4.37) <b>0.004</b>
Chemotherapy	No/Unknown	Reference
	Yes	1.412 (0.741–2.692) 0.295

Values in bold are statistically significant

strategies. As a low-grade neoplasm, prognosis of HEH is better than that of benign liver hemangioma but worse than the prognosis of malignant liver hemangiosarcoma

**Table 6** Multivariable Cox proportional hazard regression model on patients with localized disease

Variable	Overall Survival	
	HR (95% CI)	<i>p</i> -value
Age	1.03 (1.004–1.057)	<b>0.026</b>
Surgery	No	Reference
	Yes	0.226 (0.081–0.627)
Size	0–10 cm	Reference
	>10 cm	5.28 (1.661–16.78)
Chemotherapy	No/Unknown	Reference
	Yes	3.51 (1.023–12.042)

Values in bold are statistically significant

[20, 21]. Table 7 summarizes survival outcomes based on the interventions performed in different reports [8, 13–15, 21–28].

Two SEER studies about HEH were previously published. In the first study with limited number of patients ( $n=56$ ), 1-year OS rate of HEH was 57% in patients undergoing surgical resection, 67% in patients not undergoing surgery and 80% for patients undergoing liver transplant [21]. In the more recent study, yet limited ( $n=79$ ), analysis of the SEER database, 1- and 5-year CSS was reported to be 74.1% and 57.8%, respectively, regardless of disease stage and treatment modality [29]. In this study, which includes only patients diagnosed after 2004, CSS rates were higher reaching 80.1% and 66.8% at 1 and 5 years, respectively. This reflects an improvement in the understanding and management of the disease and might be explained by both diagnosis at earlier stages and by the different treatment modalities adopted over time. In this cohort, 31.4% of patients had distant metastasis compared to 39.2% in the former cohort. Similarly, only 26.9% of patients had no treatment and 52.4% underwent surgery as

**Table 7** Reported outcomes of patients with HEH in different reports

Study	Study Design	Year	Treatment Modality	No of Patients	Outcomes
Mehrabi et al	Systematic Review	2006	Liver transplantation	128	1- and 5-year survival rates of 96% and 54.5%
			Liver resection	27	1- and 5-year survival rates of 100% and 75%
			Chemo/Radiotherapy	60	1- and 5-year survival rates of 73.3% and 30%
			No treatment	71	1- and 5-year survival rates of 39.3% and 4.5%
Lerut et al	Retrospective	2007	Liver transplantation	59	1-, 5- and 10-year disease free survival rates of 90%, 82% and 64%
Rodriguez et al	Retrospective	2007	Liver transplantation	110	1-, 3- and 5-year overall patient survival rates of 80%, 68% and 64%
Nudo et al	Retrospective	2008	Liver transplantation	11	5-year survival rate of 82%
Mosoia et al	Retrospective	2008	Liver transplantation	6	78% alive after median follow-up of 117 months
			Liver resection	3	
Cardinal et al	Case Series	2009	Liver transplantation	17	mean survival of 172 (95% CI, 124–220) months
			TACE	4	mean survival of 83 (95% CI, 54–112) months
Grotz et al	Case Series	2010	Liver transplantation	11	1-, 3- and 5-year Overall survival rates of 91%, 73% and 73%
			Liver resection	11	1-, 3- and 5-year Overall survival rates of 100%, 86% and 86%
Wang et al	Retrospective	2012	Liver resection	17	3-year survival rate of 74.1%
			TACE	12	3-year survival rate of 81.6%
Thomas et al	Case Series	2014	Liver resection	7	5-year survival rate of 83%
			Chemotherapy or Embolization	18	5-year survival rate of 71%
			No treatment	25	5-year survival rate of 72%
Groeschl et al	Retrospective	2014	Liver transplantation	5	1-year overall survival rate of 80%
			Liver resection	8	1-year overall survival rate of 57%
Lai et al	Retrospective	2017	Liver transplantation	149	1- and 5-year overall survival rates of 94% and 80.8%
Krasnodebski et al	Retrospective	2020	Liver transplantation	18	1-, 5- and 15-year overall survival rates of 94%, 82.6% and 41.3%

\*TACE: Transcatheter arterial chemoembolization

compared to 39.2% with no treatment and 25.7% undergoing surgery in the previous study [29].

Data on prognostic factors predicting outcomes of HEH are conflicting. Previous studies have suggested multi-organ involvement, male gender, ascites and age above 55 years to be associated with worse prognoses, while suggesting chemotherapy and surgery to be associated with improved outcomes [22, 27, 30]. In this analysis, while considering the different patient characteristics and after risk adjustment, age > 65 years and tumor size > 10 cm were associated with worse prognosis, while surgical intervention was associated with better prognosis. Gender and tumor stage were not associated with difference in survival. In patients with localized tumor, chemotherapy was associated with poor survival outcomes, shedding light on the importance of patient selection before chemotherapy administration.

Surgical intervention is considered as one of the therapeutic options for HEH. Hepatic artery ligation, hepatic resection and liver transplantation have all been utilized [31]. Resection is mainly reserved for localized single lesions while transplantation for multiple bilobar disease [32]. In a retrospective review of 30 HEH patients treated at the Mayo Clinic, a similar pattern of surgical intervention selection was observed; patients with lower number of nodules and liver segments involvement underwent resection as compared to those with higher numbers who underwent transplantation [26]. Most patients undergoing surgery (82%) had no extrahepatic involvement at the time of surgery. However, Grotz et al. found that OS was not different between patients with and without extrahepatic involvement and argued that metastases may not be a contraindication for surgery [26]. This observation was also made in the ELTR study [14].

Survival analysis in this study is partially in agreement with the previous argument. OS rates were higher in patients undergoing surgery compared to no surgery both if the malignancy was localized or if it was regional. When metastasis was distant, OS was not different between the surgical and the non-surgical group. However, it is important to note that of the 30 patients with distant metastatic disease undergoing surgery, most patients underwent liver resection, while only three underwent liver transplantation.

The ELTR study, and in-depth study of 210 patients and the world's largest transplantation series for patients with HEH, showed that distant extrahepatic disease was not a risk factor for worse survival outcomes. In this series, which included 40 patients with extrahepatic disease, liver transplantation resulted in a 5-year survival of 71.6% in this patient category, remarkably higher than the 39.6% survival in this study's patient cohort undergoing surgery [14]. Our study further supports the algorithm proposed by

the ELTR study, suggesting liver transplantation as the treatment modality in patients with unresectable tumor or contained extrahepatic disease.

However, the question that remains to be answered is whether to perform tumor resection or liver transplantation when regional but no extrahepatic disease is present. One- and 5-year survival rates of this patient category from the ELTR study were 91.5% and 84.2% after transplantation, higher than those reported from this study (86.8% and 76.8%, respectively). While this could be due to difference in patient characteristics, such difference cannot be established due to the limitations on variables in the SEER database. A prospective study comparing surgical strategies taking relevant patient characteristics is needed. Due to the low incidence of HEH, collaborations between different medical institutions and multicenter randomized controlled trials conducted over the different continents might be the only way to provide a confident answer to this question and establish an evidence-based treatment algorithm.

Novel treatment modalities are always emerging for rare diseases such as HEH. One novel technique in the management of this disease was presented by Lau et al. where they utilized a combination of capecitabine and bevacizumab in treating a patient with metastatic HEH. Their results showed significant regression in the tumor sizes and present a new approach for patients who are awaiting liver transplantation or are non-surgical candidates [7]. Along the same line, ongoing clinical trials are utilizing different chemo and immune therapy agents against HEH. A phase II trial is currently exploring the potential of Trametinib (MEK inhibitor) in patients with locally advanced, metastatic or unresectable tumor [33]. Another phase II trial is studying Eribulin (microtubule growth inhibitor) as a possible treatment for metastatic or locally advanced HEH [34].

To the best of our knowledge, this is the largest study and one of the most contemporary reports comparing the treatment outcomes of patients with HEH. It further supports the recommendations for surgical intervention for patients with HEH when possible. As a SEER-based study with patients representing a large national scale, the results of this study have relatively high external validity and can be generalized. However, it is a retrospective study with several limitations. First, the SEER database entails a limited number of patients' variables and characteristics. No data exist on disease free survival, number of nodules, localization of tumor and liver lobes involved, lymph nodes involved, vascular invasion, sites of distant metastasis, chemotherapy regimen details and completeness of resection (R0-R1-R2). Data on the specific type of liver resection are also limited. Second, treatment of patients might have been based on physicians' assessment of patient's

performance status and specific comorbidities not captured by the database, which may lead to a selection bias in the patients referred to surgery. Finally, limited by the small number of patients undergoing transplantation in our cohort, a comparison between tumor resection and transplantation was not performed. While the value of liver transplantation has been clearly shown in different reports, liver resection still occupies its role in the treatment of HEH depending on number of lesions and localization. Further investigations are merited to decide on the better treatment strategy for the different presentations of HEH.

## Conclusion

Hepatic hemangioendothelioma is a rare disease that is poorly understood. Surgical intervention, whether liver resection or liver transplantation, might be warranted regardless of disease stage. Multicenter collaborations are needed to improve our limited knowledge about this neoplasm and determine the best treatment strategy.

## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

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