Review Article

Giant cavernous liver hemangiomas: is it the time to change the size categories?

Isidoro Di Carlo, Renol Koshy, Saif Al Mudares, Annalisa Ardiri,

Gaetano Bertino and Adriana Toro

Catania, Italy

BACKGROUND: Four different sizes (4, 5, 8 and 10 cm in diameter) can be found in the literature to categorize a liver hemangioma as giant. The present review aims to clarify the appropriateness of the size category "giant" for liver hemangioma.

DATA SOURCES: We reviewed the reports on the categorization of hemangioma published between 1970 and 2014. The number of hemangiomas, size criteria, mean and range of hemangioma sizes, and number of asymptomatic and symptomatic patients were investigated in patients aged over 18 years. Liver hemangiomas were divided into four groups: <5.0 cm, 5.0-9.9 cm, 10.0-14.9 cm and ≥15.0 cm in diameter. Inclusion criteria were noted in 34 articles involving 1972 (43.0%) hemangiomas (>4.0 cm).

RESULTS: The patients were divided into the following groups: 154 patients (30.0%) with hemangiomas less than 5.0 cm in diameter (small), 182 (35.5%) between 5.0 cm and 9.9 cm (large), 75 (14.6%) between 10.0 and 14.9 cm (giant), and 102 (19.9%) more than 15.0 cm (enormous). There were 786 (39.9%) asymptomatic patients and 791 (40.1%) symptomatic patients. Indications for surgery related to symptoms were reported in only 75 (3.8%) patients. Operations including 137 non-anatomical resection (12.9%) and 469 enucleation (44.1%) were unclearly related to size and symptoms.

CONCLUSIONS: The term "giant" seems to be justified for liver hemangiomas with a diameter of 10 cm. Hemangiomas categorized as "giant" are not indicated for surgery. Surgery should be performed only when other symptoms are apparent.

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KEY WORDS: giant hemangioma; cavernous hemangioma; liver hemangioma

Introduction

Cavernous liver hemangiomas are described as congenital vascular malformations usually affecting the liver.[1] They are the most common benign tumors in the liver, with an incidence of 3%-20% in autopsy series.[2] Being small in size and unique, they are usually asymptomatic and discovered incidentally.[3] Up to one-third of these tumors can be multiple and a fifth large enough to cause symptoms.[4] The right lobe is the most common site. Cavernous liver hemangiomas are approximately five times more common in women,[5] most likely due to their hormonal milieu.[1] The tumors can be found at any age, although 60%-80% are found in 30- to 50-year-old patients.[4]

Liver hemangiomas are conventionally categorized as giant when the diameter is >4 cm.[6] This measurement was first reported in 1970 as a limit to categorize this type of tumor as giant.[7] However, other sizes were subsequently specified to categorize a liver hemangioma as giant. In 1978, 5 cm was specified for the first time;[8] in 1995, a limit of 8 cm was suggested;[9] and in 2009, 10 cm was proposed to categorize a liver hemangioma as giant.[10] Between these measurements, a limit of 4 cm was the size that was most used to categorize a liver hemangioma as giant.

Proper indications for surgery have been established within the last 50 years with much effort to specify the effective necessity of surgical removal for this tumor.[11]

Author Affiliations: Departments of General Surgery, Hamad General Hospital, Doha, Qatar (Di Carlo I, Koshy R and Al Mudares S); Department of Surgical Sciences and Advanced Technologies "G.F. Ingrassia", University of Catania, Catania, Italy (Di Carlo I); Hepatology Unit, Department of Medical and Pediatric Science, University of Catania, Catania, Italy (Ardiri A and Bertino G); Department of Surgery, Patti Hospital, Messina, Italy (Toro A)

Corresponding Author: Isidoro Di Carlo, MD, PhD, FACS, Professor of Surgery, Department of Surgical Sciences and Advanced Technologies "G.F. Ingrassia", University of Catania, Cannizzaro Hospital, via Messina 826, 95126 Catania, Italy (Tel: +390957264863; Fax: +390957263020; Email: idicarlo@unict.it)

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The giant definition itself and the variations in size categorization have caused serious confusion, especially when justifying a surgical indication for this tumor solely in relation to size. Consequently, the primary aim of this study is to clarify the appropriateness of the size category "giant" for liver hemangioma. As a secondary endpoint, we wish to establish if and when "giant" represents a valid indication for surgery to treat liver hemangioma.

Methods

Study selection

Relevant articles in English, Italian and French were extensively searched from the databases of MEDLINE (PubMed), the Cochrane Library, Scopus and Google Scholar. The period of the articles published was between 1970 and 2014. The date of the last search was July 30, 2014. The key words used for the search were "giant hemangioma", "cavernous hemangioma", and "liver hemangioma". These words were used individually or with the Boolean operator "AND". We collected the articles citing the number of patients over 18 years old, the number of hemangiomas, the size criteria for classification, the mean and range of hemangioma sizes, the number of asymptomatic and symptomatic patients, and the types of symptoms.

Data extraction

By analyzing the category of giant hemangioma and the mean diameter of liver hemangiomas in the articles, we divided the liver hemangiomas into four groups: <5.0 cm, between 5.0 and 9.9 cm, between 10.0 and 14.9 cm, and ≥15.0 cm.

Treatments like hepatic resection (HR), transarterial chemoembolization (TACE), and radiofrequency ablation (RFA) were also analyzed. Indications for HR included spontaneous rupture, traumatic or iatrogenic rupture, intratumoral bleeding, Kasabach-Merritt syndrome with abnormal laboratory results (anemia, thrombocytopenia, fibrinolysis, and hypofibrinogenemia), organ, vessel or biliary duct compression, and others. The reported indications were screened to assure a proper correlation between symptoms and the presence of hemangioma.

In accordance with Brisbane's definition, the extent of resection was divided into right trisectionectomy, left trisectionectomy, right hepatectomy, left hepatectomy, bisectionectomy (including left sectionectomy), segmentectomy, non-anatomical resection and enucleation.[12] The extent of resection is related to the size of the resected hemangioma.

Early complications occurred within 30 days after surgery and were analyzed using the Dindo-Clavien classification.[13] When possible, the results of follow-up for the patients who were subjected to resection were reported. Recurrence in the patients who underwent surgery and the increase in size and/or complications in those who were only observed were reported.

Results

Literature search

A total of 12 920 articles were searched. After assessment of the abstracts of the articles, 12 886 articles were excluded: 7207 were excluded because other organs were analyzed, 1109 were excluded because hemangiomas <4 cm were analyzed, and 1155 were excluded because animals were analyzed. Of the remaining 3449 articles, 2202 were excluded as case reports, 912 articles had no data, 168 were published in other languages, and 133 articles were relevant to children (Fig. 1).

Ultimately, 34 articles published between 1970 and 2014 described inclusion criteria, and these articles were consequently included in the present study.[2, 4-7, 10, 14-41] The articles covered a total of 4587 patients, and 1972 (43.0%) hemangiomas with a diameter greater than 4 cm (Table 1). Moreover, 2615 (57.0%) patients with hemangiomas with a diameter less than 4 cm were excluded in addition to those who had other liver diseases (adenoma, focal nodular hyperplasia, or other types of tumors).[33] All articles categorized the hemangioma as giant when it was more than 4, 5 or 10 cm in diameter; the mean diameter of hemangiomas was 13.5 cm with a range of 4-45 cm (Table 1).

Size category

The new classification was used to classify the hem-

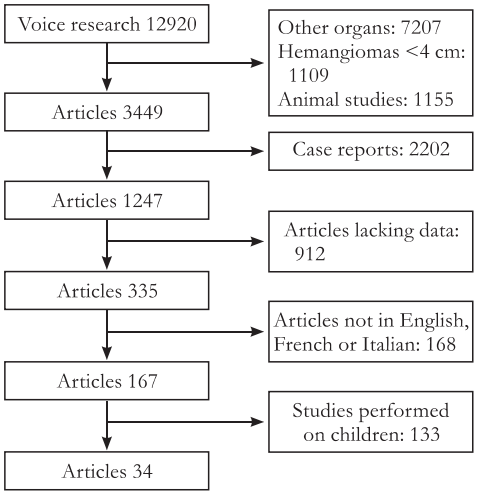

Fig. 1. Flowchart for literature search.

Table 1. Total number of patients affected by liver hemangiomas more than 4 cm in diameter and their characteristics

No.	Authors	Year	Pts	GH	A Pts (*n*, %)	S Pts (*n*, %)	AP	AD	AM	O	SC (cm)	MS (cm)	R (cm)	<5.0 cm	5.0-9.9 cm	10.0-14.9 cm	≥15.0 cm
1	Adam et al[7]	1970	106	22	11 (50)	11 (50)	7	4	6	5	4	17.7	6-45	0	4	4	9
2	Starzl et al[14]	1980	15	15	-	15 (100)	4	1	8	2	4	13.4	4-22.5	3	1	2	9
3	Trastek et al[15]	1983	49	49	29 (59)	20 (41)	na	na	na	na	4	9.5	4-22	na	na	na	na
4	Schwartz et al[4]	1987	28	28	19 (68)	9 (32)	9	na	4	4	na	8	3-32	1	10	4	2
5	Iwatsuki1 et al[16]	1988	411	100	38 (38)	62 (62)	45	17	na	na	na	12	4-41	na	na	na	na
6	Seo et al[17]	1991	7	7	3 (43)	4 (57)	4	na	3	na	4	9	4-15	1	3	1	2
7	Vishnevsky et al[18]	1991	16	16	-	16 (100)	16	na	na	na	na	19.9	5-31	0	2	0	16
8	Lise et al[6]	1992	51	51	29 (57)	22 (43)	na	na	na	na	4	8.5	5-20	na	17	5	3
9	Baer et al[19]	1992	10	10	-	10 (100)	10	na	na	na	4	13.9	5-25	na	5	2	4
10	Demiryürek et al[20]	1997	23	26	4 (17)	19 (83)	16	3	na	4	5	na	5-25	na	na	na	na
11	Brouwers et al[21]	1997	28	28	6 (21)	22 (79)	22	na	na	6	4	11	5-20	na	na	na	na
12	Ozden et al[22]	2000	42	42	9 (21)	33 (79)	33	na	na	na	na	10	7-45	na	na	na	na
13	Terkivatan et al[23]	2002	49	49	27 (55)	22 (45)	22	na	na	na	na	8	4-25	1	7	2	1
14	Lerner et al[5]	2004	52	52	na	na	na	na	na	na	4	10.9	3-23	na	na	na	na
15	Hamaloglu et al[24]	2005	22	28	5 (23)	17 (77)	17	na	na	5	4	9	4-27	na	na	na	na
16	Herman et al[25]	2005	249	68	38 (56)	30 (44)	30	na	na	na	4	20#	10-30	na	na	1	7
17	Demircan et al[26]	2005	15	15	4 (27)	11 (73)	11	na	na	na	na	12.5	6-30	na	na	na	na
18	Di Carlo et al[27]	2005	17	17	10 (59)	7 (41)	4	3	na	na	5	9.5	4-20	4	8	5	2
19	Fan et al[28]	2006	27	11	16 (59)	11 (41)	na	na	na	na	4	7	5.5-10	na	na	na	na
20	Gourgiotis et al[29]	2006	15	15	-	15 (100)	6	na	4	5	4	na	5.6-26	na	na	na	na
21	Erdogan et al[30]	2007	34	19	na	na	na	na	na	na	5	5.0#	5-25	15	na	na	na
22	Singh et al[31]	2007	21	21	3 (14)	18 (86)	18	na	na	3	4	9.5	4-25	na	na	na	na
23	Ng et al[32]	2007	64	63	40 (63)	23 (37)	23	na	na	na	4	5.5	4-20	na	na	na	na
24	Fu et al[10]	2009	172	172	89 (52)	83 (48)	83	na	25	na	10	10.5#	4-32	na	na	na	na
25	Schnelldorfer et al[33]	2010	492	289	223 (77)	66 (23)	na	na	na	na	4	7	4-30	128	95	36	30
26	Xia et al[34]	2010	115	115	na	na	na	na	na	na	na	12	5-22	na	na	na	na
27	Xu et al[35]	2010	11	11	-	11 (100)	na	na	na	na	na	9.7	4.5-20	1	4	5	1
28	Jiang et al[36]	2011	14	14	-	14 (100)	6	3	na	5	5	22.9	20.1-28.4	na	na	na	14
29	Jhaveri et al[37]	2011	55	42	22 (52)	20 (48)	20	na	na	na	4	12.5	8-25	na	na	na	na
30	Etemadi et al[38]	2012	198	36	19 (53)	17 (47)	17	na	na	na	5	na	5-25	na	na	na	na
31	Ho et al[39]	2012	61	61	25 (41)	36 (59)	26	13	na	21	4	10#	na	na	2	4	2
32	Yedibela et al[2]	2013	307	224	107 (48)	117 (52)	92	na	na	na	4	8.4	4-23	na	na	na	na
33	van Tilborg et al[40]	2013	4	4	-	4 (100)	na	na	na	na	4	15.2	10.6-14.5	na	na	4	na
34	Gao et al[41]	2013	1807	252*	10 (28)	26 (72)	26	na	na	na	5	10#	5-21.5	na	24	na	na
Total			4587	1972 (43.0)	786 (39.9)	791 (40.1)	567 (72.7)	44 (5.6)	50 (6.4)	60 (7.7)		13.5	4-45	154 (30.0)	182 (35.5)	75 (14.6)	102 (19.9)

Pts: patients; GH: giant hemangiomas; A Pts: asymtomatic patients; S Pts: symptomatic patients; AP: abdominal pain; AD: abdominal discomfort; AM: abdominal mass; O: other; SC: size criteria (cm) for the definition of "giant"; MS: mean size; R: range; na: not available; *: only 36 patients treated with radiofrequency ablation were analyzed; #: patients data were partly available.

angiomas by size: small, hemangiomas with a diameter of less than 5.0 cm in 154 patients (30.0%); large, those with a diameter ranging between 5.0 cm and 9.9 cm in 182 patients (35.5%); giant, those with a diameter ranging between 10.0 cm and 14.9 cm in 75 patients (14.6%); and enormous, those with a diameter being greater than 15.0 cm in 102 patients (19.9%) (Table 1 and Fig. 2).

In this series, 786 (39.9%) patients were asymptomatic and 791 (40.1%) symptomatic. Abdominal pain was noted in 567 patients (72.7%), abdominal discomfort in 44 (5.6%), abdominal mass in 50 (6.4%), and other symptom in 60 (7.7%) (Table 1). In 1062 (54.0%) patients who were treated, hemangiomas had a mean diameter of 11.6 cm, and in 564 (28.6%) patients who were followed up hemangiomas had a mean diameter of 9.0 cm (Table 2).

Indications of surgery

Clear indications for surgery were described in 75 patients (3.8%). Kasabach-Merritt syndrome was present in 44 patients (2.2%), intratumoral bleeding in 15 (0.8%), traumatic or iatrogenic rupture in 15 (0.8%), organ or

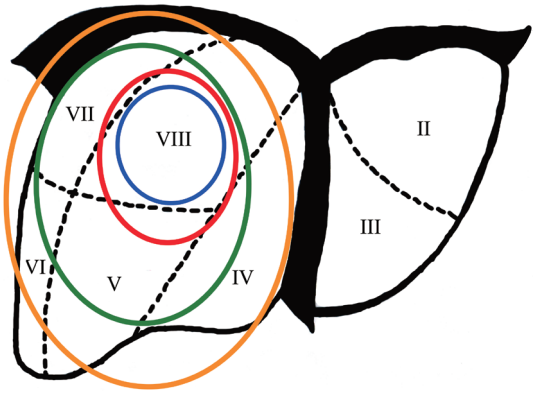

Fig. 2. Proposal for a new classification for hepatic hemangiomas in relation to their size. Small: blue line, less than 5.0 cm; Large: red line, between 5.0 cm and 9.9 cm; Giant: green line, between 10.0 cm and 14.9 cm; Enormous: orange line, greater than 15.0 cm.

vessel compression in 7 (0.4%), and spontaneous rupture in 4 (0.2%) (Table 2). None of the remaining 1897 (96.2%) patients had clear symptoms, and in all the articles analyzed, the indications for surgery were abdominal pain or discomfort.

The number of hemangiomas treated surgically was 1062 (54.0%), including 113 (10.6%) by right trisectionectomy, 11 (1.0%) by left trisectionectomy, 49 (4.6%) by right hepatectomy, 25 (2.3%) by left hepatectomy, 106 (10.0%) by bisectionectomy including left lateral bisectionectomy, 59 (5.5%) by sectionectomy, 137 (12.9%) by non-anatomical resection, 469 (44.0%) by enucleation, and 38 (3.6%) by unspecified HR. Non-surgical procedures were performed in 58 patients (5.4%) (Table 3).

Table 2. Hemangiomas submitted to observation and to treatment through correct and clear indications

No.	Authors	THO	MSHO (cm)	THT	MSHT (cm)	SR	TIR	IB	KMS	OVC
1	Adam et al[7]	12	20.4	10	15.2	1	1	na	na	na
2	Starzl et al[14]	na	na	15	13.4	1	2	na	na	na
3	Trastek et al[15]	36	8.4	13	13	na	1	na	na	na
4	Schwartz et al[4]	12	4.7	16	10	na	na	na	na	na
5	Iwatsuki et al[16]	-	-	100	na	2	8	15	25	na
6	Seo et al[17]	-	-	7	9	na	na	na	1	na
7	Vishnevsky et al[18]	-	-	16	19.9	na	na	na	7	na
8	Lise et al[6]	26	na	25	8.5	na	na	na	na	na
9	Baer et al[19]	na	na	10	13.9	na	na	na	na	na
10	Demiryürek et al[20]	-	-	23	na	na	na	na	na	2 (biliary tract)
11	Brouwers et al[21]	-	-	28	na	na	na	na	5	na
12	Ozden et al[22]	-	-	42	na	na	na	na	na	na
13	Terkivatan et al[23]	38	6.5	11	9.5	na	na	na	na	na
14	Lerner et al[5]	-	-	52	na	na	na	na	na	na
15	Hamaloglu et al[24]	-	-	22	9	na	na	na	na	na
16	Herman et al[25]	8	na	8	20	na	na	na	na	na
17	Demircan et al[26]	-	-	15	12.5	na	na	na	na	na
18	Di Carlo et al[27]	9	7.6	8	12.3	na	1	na	na	4 (2 stomach, 2 colon)
19	Fan et al[28]	-	-	11 (RFA)	na	na	na	na	na	na
20	Gourgiotis et al[29]	-	-	15	na	na	na	na	6	na
21	Erdogan et al[30]	8	na	11	12.6	na	na	na	na	na
22	Singh et al[31]	-	-	21	9.5	na	na	na	na	na
23	Ng et al[32]	61	na	2	na	na	na	na	na	na
24	Fu et al[10]	0	-	172	na	na	na	na	na	na
25	Schnelldorfer et al[33]	233	7.6	56	11.5	na	2	na	na	1 (biliary tract)
26	Xia et al[34]	-	-	115	12	na	na	na	na	na
27	Xu et al[35]	-	-	11	9.7	na	na	na	na	na
28	Jiang et al[36]	-	-	14	22.9	na	na	na	na	na
29	Jhaveri et al[37]	na	na	na	na	na	na	na	na	na
30	Etemadi et al[38]	na	na	9	na	na	na	na	na	na
31	Ho et al[39]	-	-	61	10	na	na	na	na	na
32	Yedibela et al[2]	121	7.6	103	9.1	na	na	na	na	na
33	van Tilborg et al[40]	na	na	4 (RFA)	15.2	na	na	na	na	na
34	Gao et al[41]	na	na	36 (RFA)*	10	na	na	na	na	na

THO: total number of hemangiomas observed; MSHO: mean size (cm) of the hemangiomas observed; THT: total number of hemangiomas submitted to treatment; MSHT: mean size (cm) of the hemangiomas treated; SR: spontaneous rupture; TIR: traumatic or iatrogenic rupture; IB: intratumoral bleeding; KMS: Kasabach-Merritt syndrome; OVC: organ or vessel compression; na: not available; *: Only 36 patients treated with radiofrequency ablation were analyzed.

Table 3. Surgical procedures

No.	Authors	Treatment	RT	LT	RH	LH	BS (+LL)	S	NAR	E	HRNWD	Ot (+LT)
1	Adam et al[7]	10	3	0	0	0	1 (1)	0	6	0	0	0
2	Starzl et al[14]	15	7	0	0	0	3 (3)	0	5	0	0	0
3	Trastek et al[15]	13	4	0	0	0	2 (2)	0	7	0	0	0
4	Schwartz et al[4]	16	3	3	0	0	5 (5)	2	3	0	0	0
5	Iwatsuki et al[16]	100	38	1	0	0	11 (11)	0	50	0	0	0
6	Seo et al[17]	7	1	0	0	0	2 (2)	0	4	0	0	0
7	Vishnevsky et al[18]	16	4	0	0	0	12 (7)	0	0	0	0	0
8	Lise et al[6]	25	0	0	3	3	4	0	12	3	0	0
9	Baer et al[19]	10	1	0	0	0	0	0	0	9	0	0
10	Demiryürek et al[20]	23	0	0	0	0	0	0	0	23	0	0
11	Brouwers et al[21]	28	2	2	10	3	3 (3)	1	3	0	0	4 (4)
12	Ozden et al[22]	42	2	0	0	0	4 (4)	0	0	33	0	3
13	Terkivatan et al[23]	11	1	0	2	2	0	3	0	3	0	0
14	Lerner et al[5]	52	0	0	0	0	0	0	0	27	25	0
15	Hamaloglu et al[24]	22	5	0	0	0	1 (1)	0	6	10	0	0
16	Herman et al[25]	8	0	0	3	3	2	0	0	0	0	0
17	Demircan et al[26]	15	0	0	0	0	0	0	0	11	4	0
18	Di Carlo et al[27]	8	0	0	0	0	1	1	1	5	0	0
19	Fan et al[28]	11 (RFA)	0	0	0	0	0	0	0	0	0	11
20	Gourgiotis et al[29]	15	10	0	0	1	2 (2)	2	0	0	0	0
21	Erdogan et al[30]	14	0	0	3	0	6	3	2	0	0	0
22	Singh et al[31]	21	0	0	3	0	5 (3)	0	4	9	0	0
23	Ng et al[32]	2	0	0	0	0	2 (2)	0	0	0	0	0
24	Fu et al[10]	172	0	0	0	0	0	0	0	172	0	0
25	Schnelldorfer et al[33]	56	0	0	0	0	0	0	34	22	0	0
26	Xia et al[34]	115	0	0	0	0	0	0	0	115	0	0
27	Xu et al[35]	11	0	0	0	0	0	11	0		0	0
28	Jiang et al[36]	14	3	1	4	4	0	0	0	2	0	0
29	Jhaveri et al[37]	n.t.	na	na	na	na	na	na	na	na	na	na
30	Etemadi et al[38]	9	0	0	0	0	0	0	0	0	9	0
31	Ho et al[39]	61	17	0	0	0	19 (19)	0	0	25	0	0
32	Yedibela et al[2]	103	12	4	21	9	21	36	0	0	0	0
33	van Tilborg et al[40]	4 (RFA)	0	0	0	0	0	0	0	0	0	4
34	Gao et al[41]	36 (RFA)	0	0	0	0	0	0	0	0	0	36
Total		1065 (54.0%)	113 (10.6%)	11 (1.0%)	49 (4.6%)	25 (2.3%)	106 (69) (10.0% [6.5%])	59 (5.5%)	137 (12.9%)	469 (44.0%)	38 (3.6%)	58 (5.4%)

RT: right trisectionectomy; LT: left trisectionectomy; RH: right hepatectomy; LH: left hepatectomy; BS (+LL): bisectionectomy (more left lateral bisectionectomy,); S: sectionectomy; NAR: non-anatomical resection; E: enucleation; HRNWD: hepatic resection not well defined; Ot (+LT): other procedures including liver transplantation; na: not available; RFA: radiofrequency ablation; n.t.: no treatment.

Postoperative complications

According to the Dindo-Clavien classification,[13] the most important post-operative complications were bleeding (24 patients, 1.2%) (grade IIIb), abdominal abscesses (19, 1.0%) (grade II), pleural effusion (12, 0.6%) (grade I), biliary fistula or leakage (16, 0.8%) (grade I) and other complications (53, 2.7%) (grade I). Ultimately, 8 patients (0.4%) died.

Five hundred and sixty-four hemangiomas (28.6%) were not treated. During the follow-up (1-300 months), no spontaneous or traumatic rupture or malignant transformation occurred in any patients. The remaining complications included progressive symptoms (pain)(14 patients, 0.7%), tumor enlargement (5, 0.3%), and a decrease of tumor size (17, 0.9%).

Discussion

Giant cavernous liver hemangioma (GCLH) is currently defined as a benign solid tumor located in the liver with a diameter of greater than 4 cm,[3] which was proposed by Adam et al in 1970.[7] They analyzed 106 patients who were divided into two groups: one group had small solitary or multiple hemangiomas less than 4 cm in diameter,

and the other group had massive or giant hemangiomas greater than 4 cm in diameter. The diameter of 4 cm was chosen because none of the hemangiomas smaller than 4 cm were symptomatic. However, they found that 84 hemangiomas with at diameter of less than 4 cm were discovered incidentally at laparotomy. Only 22 patients were considered to have giant hemangiomas. Of these 22 patients, 18 were symptomatic and 4 were asymptomatic. Surprisingly, hemangiomas of the 4 patients had an average diameter of 11.6 cm (range 6-20).

Moreover, in the period in which the classification was used, liver surgery was not particularly common. Few centers worldwide routinely performed liver surgery, and the rarity of liver surgery in that era likely determined the criterion of a diameter of greater than 4 cm for classifying a giant hemangioma. Indeed, 359 articles regarding liver hemangiomas were published between 1928 and 1969 and listed in PubMed, whereas 4287 were published between 1970 and 2014.

The majority of GCLHs run an uncomplicated course; however, a minority of them show progressive growth although not all patients affected by hemangiomas with increased size become symptomatic. An increase in size is observed in up to 20% of patients due to ectasia.[3, 4] Hemangiomas with estrogen receptors grow during puberty and pregnancy and after ovarian stimulation therapy with clomiphene citrate and human chorionic gonadotropin, oral contraceptive use, and androgen and/or steroid administration.[42] The female/male ratio of this tumor is as high as 5:1, indicating the importance of excessive female sex hormones.[43] Glinkova and coworkers[44] compared 94 female patients who had hormonal treatment with a group of untreated patients. The increase in size was 22.7% in the treated patients, compared with 9.7% in the untreated patients. The growth rate was reported by Schnelldorfer et al[33] as 1 cm+ at a mean of 5.1±4.4 years since diagnosis, with a doubling time of 17-178 months,[7] as observed by Yeh et al.[45]

There is no consensus on the definition and decision-making pathway for GCLH. In fact, most studies[2, 7, 12, 13, 38] found that symptoms occur when hemangioma is greater than 4 cm in diameter, which justifies surgery. The present study revealed that the size of hemangiomas resected and pre-operative symptoms are not related. In fact, many studies did not provide a clear definition for symptoms. Consequently, abdominal pain justifies most of HR for so-called GCLH, and this contrast exists especially when the size of the tumor is small (4 cm). Of course, tumors of this size (4 cm) can thrombosize or show intratumoral bleeding, but it is still surprising that most reports on surgical procedures did not describe specific symptoms except for vague abdominal pain. However, if these small tumors are located in the liver parenchyma close to the hepatic pedicle or the hepatic vein, they might lead to obstruction of the vessels or/and biliary tract, which is indicated for HR.

Rationally, a hemangioma larger than 10 cm in diameter located in the left lobe can cause symptoms by the compression of other organs (e.g., the stomach), as opposed to a hemangioma smaller than a Couinaud liver segment.[46] Therefore, a minimum diameter of 10 cm as an indication for surgery is of the utmost importance because of the possibility of organ compression, especially if patient's symptoms are vague or indefinite. Organ compression by hemangiomas must be considered because anxious patients or those with discomfort are not feasible for surgery.[47]

The total liver volume (TLV) is estimated at 1070± 227.52 cm^3, for which the right lobe constitutes two-thirds and the left lobe one-third of the TLV,[47] and the proportion of the volume of the lobe occupied by the tumor appears to be another important variable. For a 5-cm tumor, the volume is 125 cm^3, which would be one-sixth and one-third of the right and left lobe volume, respectively. This size represents less than a segment, and except for the central hepatic localization described previously, it is unlikely that there are symptoms directly related to the small size of the tumor. On the contrary, the tumor diameter of 10 cm or more can overwhelm the liver lobes, especially the left lobe.

In this review, 39.5% of the patients were symptomatic, with abdominal pain as the most common symptom. In general the pain related to liver hemangioma may be caused by intratumoral thrombosis, tumor inflammation, tumor hemorrhage or even rupture. But rarely, the pain is due to liver capsule distension for a larger tumor. The latter symptom is rare because the tumor grows slowly, allowing the liver to adapt to this new anatomical situation. If hemangioma is not associated with a sign that justifies the attribution of symptoms to the tumor itself, other possible causes of pain must be ruled out. Pain is thought to be due to inflammatory bowel disease, cholelithiasis, peptic ulcer, satiety, or constipation. Because it is not well correlated with tumor dimensions, pain remains the indication for surgery in 48%-60% of patients.[1, 31] The results of this indication is catastrophic; in fact, the pain disappears after surgery in 54% of the patients, but 44% of the patients have persistent pain after surgery.[1] In another series, only 12.6% of the patients were found to have pain purely due to GCLH. The pain in these patients was attributed to infarction, necrosis, capsular extension and pressure affecting adjacent organs. In almost half of the patients, the symptoms were not related to the presence of hemangioma. These patients provided

a good argument for assigning indications for surgery based on symptoms rather than on the dimensions of hemangioma.

Compression of adjacent organs by the tumor is another symptom in patients with hemangioma. In this case, the size and location of the tumor should be thoroughly investigated. Evidence of organ compression should be visualized by CT scan and must be related to the symptoms of the tumor. Other diagnostic tools should be used to exclude other sources of pain or discomfort. Because of its smaller size and proximity to other organs, the left lobe is related to changes in tumor size that produce symptomatic pressure.[1] At present, GCLH located in the right lobe of the liver in patients referred for symptoms of compression should be carefully considered.

Kasabach-Merritt syndrome, also known as hemangioma with thrombocytopenia, is a rare disease that usually occurs in infants. A vascular tumor may lead to decreased platelet counts and sometimes to bleeding that can be life-threatening.[48] Patients uniformly show severe thrombocytopenia, low fibrinogen levels, high fibrin degradation products (due to fibrinolysis), and microangiopathic hemolysis. This represents the main indication for surgery for hemangioma.

The risk of spontaneous rupture is very low. This risk, in association with the risk of degeneration, has frequently been reported as an indication for surgery during the past half century.[49] Indeed, it has been demonstrated that both risks are a proper indication for surgery to treat liver hemangioma. In fact, a search on liver hemangiomas in PubMed yielded 685 articles concerning 8469 patients. Only 44 spontaneous breakage events (0.52%) were reported. The risk of traumatic rupture can be iatrogenic and is connected with the necessity for biopsy. Because of advances in radiological diagnostic tools, biopsy is rarely used for hemangioma at present.

Additionally, there is not risk of malignancy.[50] It has been shown that hemangioma and hemangiosarcoma have different developmental pathways because each is derived from a different cellular clone.[50]

Options for intervention include both surgical and non-surgical techniques, and open or laparoscopic surgical resection or enucleation has been established as the gold standard. The reported resection rates are between 3.2% and 45%,[1] and the morbidity and mortality rates after resection were 10%-27% and 0%-3%, respectively.[41] Laparoscopic approach has substantially increased the resection of liver hemangioma without a proper indication in the recent decades.[51, 52] We found a high incidence of segmentectomy or non-anatomical resection. If symptoms are not solely related to hemangioma, segmentectomy should be avoided. These indicate that surgery is feasible for giant hemangioma. TACE is largely used for intratumoral bleeding or shrinkage before surgery.[39] Successful treatment of hemangioma by RFA has been reported.[40, 41] If this method is effective, it can be useful in the future.

Successful treatment depends on the accurate diagnosis of hemangioma.[53] Indications for surgery must be established without any implications of the size because a giant hemangioma of more than 10 cm in diameter is not a proper indication for surgery. Follow-up should be recommended for asymptomatic patients; no risk of malignancy has been reported during the last 40 years. Additionally, follow-up does not always reveal an increased hemangioma size, suggesting that observations other than tumor size should be used to assess the tumor.

In conclusion, this study suggests the better stratification and management of GCLH. The term "giant" seems justified for liver hemangiomas of 10 cm in diameter but it does not imply an indication for surgery. Surgery should only be performed as other symptoms appear. Otherwise, such patients are subjected to further mornitoring.

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Strive not to be a success, but rather to be of value.

—Albert Einstein