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DIAGNOSIS AND MODERN TREATMENT METHODS FOR HEPATIC HEMANGIOMA (LITERATURE REVIEW)

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The authors declare that they
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Abstract

Background. Hepatic hemangioma is the most common form among benign liver tumors. The vast majority is asymptomatic, usually detected accidentally during screening. A thorough study is required to distinguish it from other local liver pathologies, therefore, in the review paper below we have analyzed important issues during the diagnosis and treatment of liver hemangioma in international experience.

The aim of this study differentiation of modern methods of diagnosis and treatment of liver hemangioma in clinical practice.

Material and methods. In the review work, a literature review of randomized, meta-analyses, clinical trials and international clinical recommendations in English and Russian, published only from January 2010 to August 2023 in bibliographic and other electronic medical databases such as PubMed, Scopus, Web of Science, GoogleScholarship, Springer, rare clinical cases were carried out. Criteria for inclusion in the study: 1) full-text research published in the database; 2) research in English or Russian; 3) research carried out or published in the last 2010-2023 years.

Conclusions. As the most common benign liver tumor, the incidence of hepatic hemangioma during autopsy is from 0.4 to 20%. Most hepatic hemangiomas are asymptomatic, small-sized forms do not require intervention. Liver hemangioma can be easily diagnosed using ultrasound, or cop phase spiral contrast computer tomography. An indication for surgical resection is a feeling of progressive pain in the abdomen and a size of more than 5 cm. Some patients also have giant hemangiomas with minimal symptomatic. Giant hemangiomas (>10cm) are most often manifested by symptoms and require mandatory surgical intervention. The most commonly used method for the treatment of hemangiomas today is transaortic embolization, surgical resection. But to date, there is no consensus on the best treatment for patients with symptomatic and/or large hemangiomas.

Keywords:
hepatic hemangioma, embolization
of hepatic arteries, benign tumor,
radiofrequency ablation,
liver resection and hepatotomy

Бауыр гемангиомасының диагностикасы мен заманауи емдеу әдістері (әдебиеттік шолу)

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Түйіндеме

Өзектілігі. Бауыр гемангиомасы - бауырдың қатерсіз ісіктерінің ішінде ең жиі кездесетін формасы. Басым көпшілігі асимптоматикалық түрде өтеді, әдетте скрининг барысында

кездейсоқ анықталады. Бауырдың басқа да жергілікті патологияларынан ажырату үшін мұқият зерттеуді талап етеді, сондықтан төмендегі шолу жұмысында халықаралық тәжірибедегі бауыр гемангиомасының диагностикасы мен емдеу барысындағы маңызды мәселелерге талдау жасадық.

Клиникалық тәжірибеде бауыр гемангиомасының диагностикасы мен емінің заманауи әдістерін саралау.

Зерттеу материалдары мен әдістері. Шолу жұмысында әдебиеттерді іздеу жұмыстары PubMed, Scopus, Web of Science, GoogleScholarship, Springer секілді библиографиялық және өзге де электронды медициналық мәліметтер базасындағы тек 2010 жылдың қаңтары мен 2023 жылдың тамыз аралығында жарияланған ағылшын және орыс тілдеріндегі рандомизацияланған, мета-анализдерге, клиникалық зерттеулер мен халықаралық клиникалық ұсыныстарға, сирек клиникалық жағдайларға әдебиеттік шолу жүргізілді. Зерттеуге қосу критерийі: 1) мәліметтер базасында жарияланған толық мәтінді зерттеулер; 2) ағылшын немесе орыс тілдеріндегі зерттеулер; 3) соңғы 2010-2023 жылдары орындалған немесе жарияланған зерттеулер.

Қорытынды. Бауырдың ең көп таралған қатерсіз ісігі болғандықтан, аутопсия кезінде бауыр гемангиомасының пайда болу жиілігі 0,4-тен 20% - ға дейін кездесіп отырады. Бауыр гемангиомаларының көпшілігі асимптомды түрде, көлемі кіші формалары араласуды қажет етпейді. Бауыр гемангиомасын ультрадыбыснемесе коп фазалық спиральды контрастты компьютер томограф көмегімен жеңіл диагноз қоюға болады. Хирургиялық резекцияға көрсеткіш ретінде іштегі прогрессивті ауыру сезімі және көлемі 5 см ден жоғары болуы болып табылады. Кей науқастарда минимальды симптоматикамен гиганттық гемангиомалар да кездеседі. Гиганттық гемангиомалар (>10см) көбінесе симтомдармен көрінеді және міндетті хирургиялық араласуды қажет етеді. Гемангиомаларды емдеуге қазіргі таңда жиі қолданылатын әдіс трансартериялық эмболизация, хирургиялық резекция. Бірақ бүгінгі күнге дейін симптоматикалық және/немесе үлкен гемангиомасы бар науқастарды емдеудің ең жақсы әдісі туралы консенсус жоқ.

Диагностика и современные методы лечения гемангиомы печени (обзор литературы)

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Аннотация

Актуальность. Гемангиома печени является наиболее распространенной формой среди доброкачественных опухолей печени. Подавляющее большинство протекает бессимптомно, обычно обнаруживается случайно во время скрининга. Требуется тщательное исследование, чтобы отличить его от других местных патологий печени, поэтому в приведенной ниже обзорной работе мы проанализировали важные вопросы в ходе диагностики и лечения гемангиомы печени в международном опыте.

Целью исследования является дифференцировать современные методы диагностики и лечения гемангиомы печени в клинической практике.

Материалы и методы. В обзорной работе проведен литературный обзор рандомизированных, мета-анализов, клинических исследований и международных клинических рекомендаций, редких клинических случаев на английском и русском языках, опубликованных в библиографических и иных электронных медицинских базах данных, таких как PubMed, Scopus, Web of Science, GoogleScholarship, Springer только в период с января 2010 года по август 2023 года. Критерий включения в исследование: 1) полнотекстовые исследования, опубликованные в базе данных; 2) исследования на английском или русском языках; 3) исследования, выполненные или опубликованные за последние 2010-2023 годы.

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абляция, резекция печени и
гепатотэктомия

Заключение. Поскольку это наиболее распространенная доброкачественная опухоль печени, частота появления гемангиомы печени при вскрытии колеблется от 0,4 до 20%. Большинство гемангиом печени протекают бессимптомно, а малые формы не требуют вмешательства. Гемангиомы печени можно легко диагностировать с помощью ультразвука, или спирально-контрастной компьютерной томографии. Показанием к хирургической резекции является прогрессирующая боль в животе и размер более 5 см. У некоторых пациентов также встречаются гигантские гемангиомы с минимальной симптоматикой. Гигантские гемангиомы (>10 см) часто проявляются симптомами и требуют обязательного хирургического вмешательства. В настоящее время наиболее часто используемым методом лечения гемангиом является трансартериальная эмболизация, хирургическая резекция. Но на сегодняшний день нет единого мнения о том, как лучше всего лечить пациентов с симптоматическими и/или большими гемангиомами.

Introduction

Hepatic hemangioma (HH) is a benign mesodermal tumor consisting of flat endothelial cells of the vessels.^{1,2,3} According to the results of various studies, the incidence of liver hemangioma ranges from 0.4-7.3% to 4-20%,^{2,3,4,5} in adults aged 30-50 years³ and in children it is common mainly in the first 6 months of life and accounts for 12% of all lesions.^{6,7}

We present a review of the latest literature on HH and new developments in diagnostic imaging techniques and surgical treatments for HH. This topic is relevant because diagnostic methods are improving, which makes it possible to visualize small hemangiomas that were not previously diagnosed. In addition, liver surgery techniques have improved and allow treatments previously considered surgically inaccessible.

Small and medium-sized types of HH in size range from 1.0 mm to 20.0 cm,^{1,8} continue to meet even in giant forms (40.0-50.0 cm and above).^{2,7} Location in the liver in most cases only in the singular, located in the right part of the liver, most often in the IV segment.^{8,9}

HH is classified according to microscopic data into three main types: cavernous, capillary and anastomose forms, of which the cavernous form is the most common type.^{10,11,12}

And according to the latest edition of Weerakkody Y., et al. on February 28, 2023, HH classified several types:

- I. Type hemangioma of the liver;
- II. atypical liver hemangioma:
 - a) giant hemangioma of the liver
 - b) Unscheduled filled HH: up to 16% of all hepatic hemangiomas
 - c) calcified liver hemangioma
 - d) Hyalinized / sclerosed liver hemangioma
 - e) other special types:
 - with capsular retraction
 - surrounded by regionary nodule hyperplasia with fatty infiltration
 - hepatic sclerosed hemangioma is a rare form disease.
 - fused with the extremities
 - cystic liver hemangioma (occur rare)
 - is fluid-based on the amount of fluid in the liver hemangioma.¹²

According to the study of Christison-Lagay ER, et al and others, the authors classified 3 main categories of hepatic hemangioma in children: focal, multifocal and diffuse. However, there is currently no clear classification criterion for hepatic hemangioma.^{13,14}

Another type of hemangioma is epithelioid hemangioendothelioma is malignant vascular tumor. Pathogenesis mechanisms on the development have not been clarified, however, there is evidence that an increase in vascular endothelial growth factor (VEGF) may be an important proangiogenic factor in the development of hemangioma. This is confirmed by a decrease in hemangioma size after anti-VEGF treatment.^{14,15} Also, the increase in hemangiomas can be influenced by hormone replacement therapy with estrogen, especially after taking oral contraceptives or after pregnancy.^{16,17,18}

Clinical manifestations of hemangioma usually pass asymptotically, but symptoms may appear when the size is greater than > 5 cm.¹⁹ Pain under the right ribs, mainly associated with stretching of Glisson's capsule, accompanied by symptoms of loss of appetite, nausea, vomiting, jaundice, as well as due to compression of other organs with manifestations of bloating and shortness of breath.^{18,19}

Giant HH can be induces Kasabach-Merrit syndrome, manifested by consumption coagulopathy as a thrombocytopenia, anemia, hypofibrinogenem, reduced prothrombin time. Treatment for Giant hemangioma with Kasabach-Merrit syndrome definitely is removal of the vascular tumor by transarterial embolization (TAE), transarterial lipiodolization (TAL), radiofrequency ablation (RFA), surgical resection (SR) and liver transplantation (LT) but the alternative use of systemic glucocorticoids in combination with beta-blockers has shown a positive effect.^{20,21,22,23}

Diagnosis of hemangioma

Physical examination does not occur with significant changes in other research studies, including biochemical blood tests.^{1-4,13,18} Hypofibrinogenemia is caused by intra-tumor fibrinolysis, and thrombocytopenia is associated

with large lesions that are a consequence of sequestration and destruction of the spleen.

Shigeo M. et al. (2022) in a study of 283 patients (Table 1), normal serum values were

recorded in 255(90.7%) patients. Only in 26 patients there was a slight increase in the level of alanine aminotransaminase, alkaline phosphatase.²⁴

| Parameters | Value |
|---------------------------------|-------------|
| Age (years) | 54 ± 15 |
| Male/female (n) | 98/183 |
| Biochemistry | |
| Total bilirubin (mg/dL) | 0.6 ± 0.2 |
| Albumin (g/dL) | 4.2 ± 0.2 |
| ALT (U/L) | 20 ± 13 |
| GGT (U/L) | 39 ± 42 |
| ALP (U/L) | 236 ± 76 |
| BUN (mg/dL) | 14.1 ± 3.7 |
| Cr (mg/dL) | 0.70 ± 0.17 |
| LDL-chol (mg/dL) | 100 ± 25 |
| HDL-chol (mg/dL) | 68 ± 18 |
| Glucose (mg/dL) | 102 ± 28 |
| HbA1c (%) | 5.5 ± 0.6 |
| Hematology | |
| Hemoglobin (g/dL) | 13.5 ± 1.3 |
| WBC (/μL) | 5700 ± 1600 |
| Platelet (×10 ⁴ /μL) | 22.4 ± 5.2 |
| Coagulation | |
| PT (%) | 94.2 ± 12.7 |
| Fibrinogen (mg/dL) | 282 ± 74 |
| TAT (ng/mL) | 1.39 ± 0.97 |
| D-dimer (μg/mL) | 0.70 ± 0.69 |
| FDP (μg/mL) | 1.68 ± 1.04 |
| Serology | |
| M2BPGi (COI) | 0.55 ± 0.32 |
| AFP (ng/mL) | 3.6 ± 1.5 |
| PIVKA-II (mAU/mL) | 20.1 ± 5.8 |

Table 1. Laboratory values of 281 patients presented by Shigeo M. et al.²⁴

Tumor markers: alpha-fetoprotein (AFP), CA 19-9 (carcinogenic antigen 19-9) and carcinogenic embryonic antigen (CEA) show a benign nature of the lesion within normal limits.⁹

Wang HY. et al. in a 47-year-old man with cavernous hemangioma, a clinically determined serum AFP level of 371.51 μg/l (normal 0-20

μg/l), in the second week after surgical treatment the level AFP decreased to 24.45 μg/L.²⁵

Jang S. et al. published the results of a 10-year study on AFP levels in 195 patients with HH, that showed higher AFP levels (p<0.001) and monitoring for them during 13 months not determined cancer or other liver disease.²⁶ And

rare cases have been reported that sclerosing hepatic hemangioma mimics malignant tumors of the gallbladder and liver.^{27,28}

In the diagnosis of HH, ultrasound, magnetic

resonance imaging, contrast CT are used to distinguish it from other liver tumors, metastases, cysts and other angiogenic formations.

Table 1.
Analysis of diagnostic methods

| Diagnostic methods | Description | Advantages | Disadvantages |
|----------------------------------|---|--|---|
| Ultrasound ^{9,29,30} | Appears as a hyperechogenic homogeneous node | Convenient, popular as the first diagnostic method due to its availability Minimum radiation risk | Ultrasound can cause similar acoustic patterns from some liver tumors (hepatocellular carcinoma and liver metastases) and other imaging methods must be used to confirm the diagnosis |
| CEUS ^{29,30} | Shows three different vascular phases using the hepatic artery and portal vein after contrast agent | Proven to be a reliable method for describing focal liver damage Monitors multiple types of damage at the same time. An accurate diagnosis is made, which is currently reaching about 95% of cases. Does not require additional verification. | Allergies, caused by the effects of the use of contrast agents, can lead to liver and kidney failure. |
| CT ^{1,31,32} | CT shows an increase in contrast in nodular or spherical shape at the edges of the tumor at the initial stage and the contrast increases evenly throughout the tumor. | The importance indicates the type of upper, hypodense, well-defined lesion. In addition, if there is intra-tumor bleeding, the hemangioma looks like a mass with a very dense inner part. Allows you to determine the localization of the lesion area. | Hemangiomas that show diffuse homogeneous enlargement in the arterial phase may resemble hypervascular cancers such as tumor. It is difficult to detect small lesions with a size of <5 mm. Exposure to radiation and the use of iodine contrast agents can cause nephropathy |
| MRI ³¹⁻³³ | Can be recognized as informative, shows smooth, uniform lesions, hypointensive imaging. | Differential diagnosis can be made with cancer. Gadolinia contrast agent can be continued to be used in patients who are allergic to iodine, with renal failure. | Not available Magnetic wave effect |
| Tc-99m scintigraphy ⁹ | When the patient's erythrocyte cells are saturated with Tc-99m radiopharm, they go to places of increased blood supply. 1cm indicates minor lesions. | Scintigraphy is always performed in parallel with CT or ultrasound to determine the location, shape and number of lesions. | The limited availability, high cost and duration of the procedure, the nature of its radiation, and the variety of potentially competing imaging technologies have led it to be used less as a diagnostic method of HH. |

Ultrasound examination (hereinafter referred to as ultrasound), convenient, popular as the first diagnostic method due to its availability. HH appears on ultrasound as a hyperechogenic homogeneous node with well-defined edges and back acoustically amplified.^{1,27} Hepatic hemangioma can cause similar acoustic patterns from some liver tumors (hepatocellular carcinoma and liver metastases) on ultrasound, and other imaging methods must be used to confirm the diagnosis.^{1,30}

Contrast-enhanced ultrasound (CEUS) has been shown to be a reliable method for describing focal liver damage,^{29,30,34} which is a sensitive and specific method for diagnosing hemangiomas.³⁴ CEUS significantly improved the exact diagnosis of hepatic hemangiomas, which is currently reaching about 95% of cases.³⁴ Even this can ensure the diagnosis of hemangioma in most cases without the need for additional examination.³⁵

The CEUS liver examination shows three different vascular phases using the hepatic artery and portal vein after the injected contrast agent:³³

a) arterial phase: provides information on the extent and nature of the blood supply to the arterial vessels in the case of local liver damage;

B) portal vein phase: provides information through the portal system, leading to a diffuse and maximum enlargement of the normal parenchyma of the liver;

c) late phase: lasts until the contrast agent is removed from the circulation and provides

information about the absorption of the contrast agent by phagocytic cells (e.g. Kupfer cells).^{32,33}

The importance of CT in the diagnosis of hepatic hemangioma is manifested in the form of upper, hypodense, well-defined lesions.^{1,31} CT shows an increase in contrast in nodular or spherical shape at the edges of the tumor at the initial stage and the contrast increases evenly throughout the tumor.³¹ In addition, if there is intra-tumor bleeding, the hemangioma looks like a mass with a very dense inner part.^{1,31}

Hemangiomas that show diffuse homogeneous enlargement during the arterial phase may resemble hypervascular cancers such as hepatocellular carcinomas or hypervascular metastases.³¹

The magnetic resonance imaging method can also be recognized as informative in the diagnosis of hepatic hemangioma, showing smooth, uniform lesions, hypointensive imaging.^{31,36}

Tc-99m scintigraphy is a non-invasive method that provides the most accurate diagnosis of liver hemangioma.⁹ Scintigraphy is always performed in parallel with CT or ultrasound to determine the location, shape and number of lesions. The limited availability, high cost and duration of the procedure, the nature of its radiation, and the variety of potentially competing imaging technologies have led to it being used less as a diagnostic method of HH.⁹

Due to the high risk of bleeding and low diagnostic effectiveness, puncture biopsy is not recommended in the diagnosis of HH.^{36,37}

| Diagnostic methods | Sensitivity | Specifications |
|--------------------|-------------|----------------|
| Ultra sound | 96,9% | 60,3% |
| CEUS | 98% | 100% |
| CT | 98,3% | 55% |
| MRI | 100% | 85,7% |
| Tc-99 m | 75% | 100% |

Table 3.
Accuracy of diagnostic
methods^{1,9,33}

Selective angiography of hepatic arteries has the highest specificity of detection of HH, this method is used in combination with the embolization method in the treatment of hemangioma.⁹

In histological examination, under microscopy stained with hematoxylin-eosin, HH is expressed as dilated vascular channels lined with a single layer of endothelial cells. Complications of HH include necrosis, thrombin formation, multiple sclerosis or calcification.⁹

Treatment of hemangioma

There is no known pharmacological

therapy capable of reducing the size in the treatment of HH.^{1-4,33} Antiangiogenic therapy with bevacizumab (a monoclonal antibody capable of inhibiting the activity of endothelial growth factor) has been considered, but this has not been proven.⁹

The main treatment is surgical methods as SR of the liver and tumor enucleation,³⁸⁻⁴⁷ LT,^{40,48,49} liver hepatectomy (LH),^{33,50-52} RFA and TAE.^{53,54}

Procedures common worldwide as the "gold standard" method of treating HH are liver resection, hepatectomy, and enucleation (laparotomy, laparoscopy, or robotic

method).^{38-42,51,55-57}

The main indications for surgery are a rapid increase in the size of the hemangioma (>5 cm), the presence of pain despite analgesics, complications of hemangioma: risk of thrombosis, rupture, location, compression of neighboring organs, etc.^{33,56} At the same time, hemangioma $d \geq 10$ cm, abdominal symptoms, signs of coagulopathy will be an absolute indication for surgery.²⁰

Symptomatic hepatic hemangiomas are usually treated surgically (liver resection or

enucleation, open, laparoscopic, or robotic). However, surgery for giant hemangiomas of the liver can cause intraoperative bleeding with a high mortality rate. In addition, it is known that many patients at risk of sudden rupture of hepatic hemangioma cannot tolerate surgery due to hypovolemia. And the TAE method is a method that allows tumor shrinkage and remission of symptoms to be achieved with minor complications, which is especially indicated for patients with high surgical risk.⁵⁵

Table 1.
Analysis of diagnostic methods

| Type of surgical treatment | Authors | Number of people who participated in the study | Age | Description of the diagnosis of HH | Results |
|----------------------------|--|--|----------------------------------|--|---|
| TAE | <i>Kalogiru M. et al.</i> ⁵⁵ (2018) | n=2 | 1-43 years old (y/o) 2-79 y/o | The presence of exophytic hemangioma in segments n1-VI and VII $d > 7.5$ cm, signs of fracture and bleeding, as well as accumulation of fluid under the liver were found (Figure 4). n2-the size of 7.7 to 15 cm diagnosed with giant hemangioma (Figure 5) | After the n1-TAE procedure, he developed mild post-TAE syndrome, which resolves on its own. A follow-up CT scan one month after TAE showed a decrease in the size of the hemangioma from 7.5 cm to 6.9 cm from TAE. Within 10 months after TAE, the patient had no symptoms. Complications associated with n2 - TAE were not observed in the patient. After the procedure, the laboratory values returned to normal and the symptoms gradually disappeared. After 9 months, all the observed symptoms disappeared, and CT showed a slight decrease in the size of the tumor. |
| | <i>Furumaya A., et al.</i> ⁵⁴ (2019). | n=1284 | 18±76 y/o | Tumor size from 9.79 ± 0.79 CM | 4.00±1.36 cm showed a significant decrease ($P < 0.001$) Decreased tumor size in 1100/1223 (89.9%) of patients 1080/1096 (98.5%) of patients resulted in improvement or loss of symptoms Grade 3 complications occurred in 37(2.9%) out of 1,284 patients Surgical treatment required 35 (2.7%) of 1,284 patients |
| | <i>Torkian P, et al.</i> ⁵⁸ (2020) Lipiodol-based treatment compared to PVS. | n=1450 | 46.3±3.6 y/o | Diameter average $d=9.69 \pm 10.4 \pm 2.95$ | Overall reduction in diameter (CM) 4.37-4.70 |

| | | | | | |
|-------------|---|------|------------------------------|---|--|
| RFA | Sun JH. et al. ⁵⁹ (2012) | n=36 | 49.5±6.5 y/o | 20 patients with 24 hemangiomas d≥5 cm 16 patients with 17 hemangiomas d<10 cm | 41 hemangioma has subcapsular damage. 22 patients showed 62 signs of complications. According to the Dindo-Clavien Classification, 2 patients had: fistula in the lower esophagus, acute respiratory distress syndrome (degree 2,4). Successfully passed the rest of the patients, the average decreased to d=6±3. 15±6 months no relapse was observed. Alternative method for the treatment of hemangiomas only d≤5 cm. d≥5 cm with 24 hemangiomas in 20 patients 16 patients with 17 hemangiomas d<10 cm successful completion In 2 patients: esophageal fistula, acute respiratory distress syndrome developed. |
| Enucleation | Li H., et al. ⁴⁵ (2023) | n=58 | Different age features | HH: 1.NLG - normal location group 2.SLG - special location group (I, IVa, VII и VIII- segments) | Complications encountered sizeNLG: Bile leakage: 11% Vascular thrombosis: 6.5% Ascites: 9.7% SLG: Bile leakage: 12.9% Vascular thrombosis: 7.4% Ascites: 11.1% Duration of hospital stay NLG 7.3±2.6 day SLG 11.5±3.4 day As a result, the enucleation of hepatic hemangioma, located in a special segment, leads to serious complications. |

Kalogiru M. et al. described in their studies 2 cases of bleeding giant hepatic hemangiomas that were successfully treated with TAE. In the first case, a 43-year-old man with a giant liver hemangioma presented with acute pain in the right costal arch of the abdomen; in the second case, a 79-year-old woman with a giant liver hemangioma with complaints for severe fatigue and anorexia. In both cases, the giant hemangioma continued to grow to 7.5 and 15 cm, respectively. In the first case, CT showed signs of rupture and bleeding, as well as fluid accumulation under the liver, and the patient underwent superselective embolization with 6 ml of lipiodol with the embolic agent used in the form of microspheres ranging in size from 100 to 500 microns. A control CT scan a month after TAE showed a decrease in the size of the hemangioma to 6.9 cm. In the second case, the patient was prescribed selective TAE in a

volume of 8 ml of Lipiodol, with microspheres as an embolic agent from 100 to 700 microns. CT scan showed a slight decrease in tumor size after TAE.⁵⁵

The successful use of TAE before surgery for a ruptured hemangioma was first reported in 1991 by Yamamoto T., et al. According to Srinivas D., et al TAE is a successful hemostatic method in 80% of cases. Lipiodol is a microvascular embolizing agent that has anticancer properties and can block the blood flow of the tumor.^{5,56,60}

Furumaya A., et al. (2019) conducted a meta-analysis of 18 cohort studies, to evaluate the effectiveness and safety of treatments for TAE/TAL liver hemangiomas in 1284 patients. According to their data, TAE/TAL reduced tumor size from 9.79 ± 0.79 cm to 4.00 ± 1.36 cm ($P < 0.001$) in 89.9% patients, improved or resolved hemangioma symptoms in 98.5% patients. Complications occurred in 37(2.9%)

patients. Than TAE/TAL is a productive and safe treatment for reducing the size of cancerous liver hemangioma and can be considered as an alternative to resection.⁵⁴

In addition, the study by *Torkian P., et al* (2020) included 21 studies involving 1450 patients with a total hemangioma. The average follow-up time after embolization was 12 months. Lipiodol-based treatment showed a significant effect of a decrease in the size of the hemangioma after TAE ($p < 0.001$). Overall reduction in diameter from (-4.37cm) to (-0.93cm) for general TAE treatment, lipiodol-based and lipiodol-free treatment accordingly. The main complications were post-embolization syndrome and increased transient activity of liver enzymes. No any reports of fatal complications and clinical improvement was observed in 63.3-100% studies.⁵⁸

In conclusion, the use of TAE for the treatment of giant hemangioma of the liver has the advantages of minimal trauma, fewer complications and good efficacy, especially in patients with high surgical risk. TAE therapy for giant hemangioma of the liver is safe and effective and is an alternative to surgery.⁵⁹

In recent years, RFA has been increasingly used for the treatment of cavernous hemangiomas of the liver due to its unique advantages such as minimal invasiveness, efficacy, high safety, rapid recovery and wide application^{38,53} in the early stages, this method has only been used for hepatic hemangiomas up to < 10 cm in size, however, the question of whether RFA should be used to treat hemangiomas is still debated due to the need for longer ablation times.³⁸

Previously, hepatologists-surgeons believed that the only radical method of treating patients with focal liver diseases, which can significantly extend and improve the quality of life, is liver resection.³⁹ And in recent years, several studies have evaluated the effectiveness of enucleation compared to hepatectomy, and most of them have concluded that enucleation is associated with a lower incidence, shorter surgery time, lower blood loss, and fewer complications.^{40,42}

Enucleation is technically easier in a peripherally located HG, and when performed in a centrally located HG, it leads to an increase in operation time and increased blood loss.^{40,42,44}

Li H., et al. published the results of 58 patients who underwent laparoscopic enucleation of hepatic hemangioma in 2023.^{43,45} Depending on the location of the hemangioma, the authors considered patients in two groups: special location group (SLG) and normal location Group (NLG). In

the study, serum transaminases and bilirubin levels increased in the postoperative period, reaching their maximum level on the third or fourth day after surgery, and then gradually decreased to normal levels. There are no reliable differences in biochemical parameters between the two groups ($p > 0.05$). However, the duration of postoperative hospital stay in the SLG of patients was significantly longer than in the NLG, which was 3.8 ± 1.4 and 2.9 ± 0.8 days ($p = 0.03$) and 11.5 ± 3.4 and 7.3 ± 2.6 days ($p < 0.01$), respectively. Postoperative complications, including pleural effusion ($p = 0.362$), ascites ($p = 0.800$), bile leakage ($p = 0.845$) and vascular thrombosis ($p = 0.735$), have not been reported.⁴⁵ The authors concluded that laparoscopic enucleation of hemangiomas in certain segments of the liver is complex and carries a significant risk of massive bleeding during surgery.

Ramanujam A., et al. (2015) published a clinical case of successful enucleation of giant hemangioma, so that they confirmed the advantages of the procedure over resection and other new treatments.⁴⁶

Well, *Muthukumarassamy R., et al.* in their study published in 2021 noted that there is no significant difference between liver resection and enucleation. The study performed a total of 64 patients, including 41 liver resection, 22 tumor enucleation, and 1 LT. The results after the operation were similar in both groups.⁴⁷

Liu Y., et al. in 2017, published in the databases PubMed, Embase, Web of Science and the Cochrane Library, published their research comparing the results of enucleation and anatomical resection of HG. According to the results of nine studies involving a total of 1185 patients: blood loss ($p < 0.00001$), duration of surgery ($p = 0.03$) and duration of hospital stay ($p = 0.03$) were significantly lower in the enucleation group. Thus, the authors hypothesized that enucleation can preserve more liver parenchyma and reduce postoperative complications.⁴⁰

Thus, the advantages of enucleation of hepatic hemangioma differ in lower intraoperative blood loss (enucleation: 400 ml compared to resection: 1330 ml), lower risk of bile leakage (enucleation: 0% compared to resection: 8-17%), maximum preservation of functional liver parenchyma and fewer overall complications.^{40,42,45}

LT is not considered a first-line treatment for hepatic hemangioma. A study published in 2015 showed that in the United States, 147(0.17%) patients with benign liver tumors underwent LT, including 25 patients with HH. Indications for LT in patients with HH include the development of severe symptoms, rapid tumor growth, failure of other surgical

methods, and the occurrence of life-threatening complications such as Kasabach-Merritt syndrome.^{40,48,49}

Discussion

Hepatic hemangioma is the most common benign liver tumor. Typical hemangiomas, also known as capillary hemangiomas, range in size from a few mm to 3 cm, do not increase over time and are therefore unlikely to cause symptoms in the future. Giant hemangiomas of the liver can develop symptoms and complications that require immediate surgery or other type of therapy. Since the treatment strategy for hemangioma in the liver depends on the size of the first tumor, it is very important how many cm from the giant hemangioma in the liver area is considered gigantic. There are different criteria for this definition. Most authors use the diameter criterion > 4 cm, while others use a diameter of > 5 cm and some use a diameter of > 10 cm. We believe that the definition of a giant hemangioma should be based on a diameter of ≥ 10 cm, because a 10 cm hemangioma can cause more severe symptoms than a 4 cm tumor. Thus, in this study, we focused on patients with hepatic hemangioma larger than 10 cm.⁶¹

Hemangioma in the liver can be detected in most patients through non-invasive tests, especially MRI. CT angiography is a valuable preoperative study in patients with large tumors.²⁰ In modern diagnostics of BG, the above CEUS examination is proven to be a reliable method for describing focal liver damage, so we agree with the authors' study.^{29,30,34}

Chengming Q., et al., at the initial stage of RFA, only hepatic hemangiomas up to < 10 cm in size were treated with this method, but the question of whether RFA should be used for the treatment of hemangiomas is still being discussed due to the need for a long ablation time.³⁸ One of the most effective methods of treatment is the use of subcutaneous microwave ablation under ultrasound control. This method is currently better than RFA because the time of exposure to thermal energy on tumor tissue is shorter. The main disadvantages are the development of unambiguous hemolysis due to the abundant blood supply to the tumor, the possibility of hemoglobinuria, hemolytic jaundice, anemia and kidney damage, as well as burns of the gastrointestinal tract (stomach, colon and small intestine), when the edge of thermal exposure is located at a distance of less than 1 cm from neighboring organs.

There are also two main types of surgical interventions-resection of a part of the liver affected by hemangioma and enucleation

of hemangioma. The above *Ramanujam A., et al.* according to a study by the authors (2015), successful enucleation of giant hemangioma has been proven. In agreement with the authors, it should be noted the advantages of enucleation over other surgical operations (liver resection).⁴⁶

However, postoperative mortality can be between 0-4%, and the risk of complications can be between 2-7%, depending on the postoperative period. Symptomatic hepatic hemangiomas are usually treated surgically (liver resection or enucleation, open, laparoscopic, or robotic). However, surgery for giant hemangiomas of the liver can cause intraoperative bleeding with a high mortality rate. Therefore, during enucleation and resection in the liver, we think that there is a high risk of developing intraoperative bleeding, which is mainly due not to the large size of the tumor, but to its proximity to large vascular trunks. We decided that this would cause the need to use selective intra-arterial embolization before surgery in patients at high risk of bleeding.

According *Kalogirou M. et al. (2018), Furumaya A., et al. (2019) and Torkian P., et al. (2020)* TAE is considered an effective minimally invasive method of treating complicated liver hemangiomas for patients with a high surgical risk due to the low incidence of complications. In conclusion, TAE can be used as the main treatment for giant hemangiomas, which in individual cases is an effective alternative to surgery.^{54,55,58}

In addition, it is known that many patients with spontaneous rupture of hepatic hemangioma cannot tolerate surgery due to hypovolemia. We support the TAE method of the above authors: this is because TAE allows tumor shrinkage and symptom remission to be achieved with minor complications, which is especially indicated for patients at high risk of surgery.

In recent years, TAE of the liver has been increasingly used to achieve the hemodynamic stability of the patient before surgical treatment and as a method for the preoperative treatment of bleeding giant hemangiomas. Another feature is that when using the TAE method for giant bleeding hemangiomas, subsequent surgery may not be required.

Conclusion

CEUS examination is a reliable method for describing focal liver damage. Treatment of hemangiomas includes transarteric embolization, surgical resection. But to date, there is no consensus on the best treatment for patients with symptomatic and/or large hemangiomas.

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