Review

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Surgical indications for solid hepatic benign tumors: An updated literature review

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SUMMARY Hepatic hemangioma, focal nodular hyperplasia, and hepatic adenoma are the most common benign solid liver tumors. However, their surgical indications have been the subject of debate. Minimally invasive liver resection reduces the cost of surgery and may lead to overtreatment of benign liver tumors. Recently, there has been a growing understanding of the etiology, pathogenesis, and natural history of these tumors. Great progress has also been made in imaging. The use of MRI and contrast agents has improved the accuracy of non-invasive diagnosis of these tumors, and especially in the identification of specific molecular subtypes of liver adenoma. These factors have resulted in alterations of surgical indications for these tumors. This article examines recent literature and it discusses the surgical indications for hepatic hemangioma, focal nodular hyperplasia, and hepatic adenoma while summarizing modifications in clinical management.

Keywords benign liver tumors, surgery, management

1. Introduction

There are many types of benign liver tumors with different histomorphology, clinical biological behavior, and imaging findings. Based on the molecular phenotype of tumors, their histological and imaging features, as well as their histopathological classification, the World Health Organization classifies these tumors into three major categories. The first category includes hepatocellular adenoma (HCA), focal nodular hyperplasia (FNH), intrahepatic bile duct adenoma, bile duct hamartoma, intrahepatic bile duct cystadenoma, and biliary papillomatosis; the second category includes hepatic hemangioma (HH), angiomyolipoma, lymphangioma and lymphangiomatosis; and the third category includes teratomas and solitary fibrous tumors (*1*). The precise prevalence of these lesions in the population is unknown, but autopsy series have reported an incidence of up to 50% for these tumors (*2*).

With the widespread availability of imaging techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), the likelihood of detecting a liver mass in asymptomatic patients has increased (*3*). At the same time, the accuracy of non-invasive diagnosis of benign liver tumors is increasing, reducing the need for a histological examination to distinguish between benign and malignant tumors. In recent years, MRI with specific contrast agents has been proven to be the most accurate and specific radiological tool for diagnosing benign liver tumors. More importantly, imaging features can indicate molecular subtypes of HCA (*4-6*). Imaging follow-up for benign liver tumors appears to be increasingly feasible and reasonable (*2,7*).

Surgical indications for benign liver tumors have been controversial, but generally observation is preferred (*8*). However, the development of minimally invasive liver resection techniques has the potential to reduce surgical costs and increase postoperative benefits for treatment of benign liver tumors compared to open hepatectomy. This may lead to overtreatment of some benign liver tumors (*9*). The technical training required of the surgeon may also potentially influence surgical indications. In addition, as the etiology, pathogenesis, and natural history of HH, FNH, and HCA continue to be researched, they are classified in more detailed and disease progression can be predicted more accurately (*10*). New clinical, biological, and molecular tools have gradually been incorporated into diagnostic and therapeutic algorithms for the classification of benign liver tumors and improvement of patient management, resulting in changes to surgical indications.

This article reviews the latest relevant literature and discusses surgical indications for HH, FNH, and HCA.

2. Hepatic Hemangioma (HH)

HH is the most common solid benign liver tumor, with an incidence of 1-20% and a rate of detection of 7% in autopsy studies. It is more common in females (female: male ratio = 5:1), and the average age at diagnosis is around 50 years (*11*). This lesion originates from the proliferation of vascular endothelial cells and is usually a hypervascular lesion with well-defined boundaries. Most hemangiomas are cavernous, liver function tests are normal, and there is no possibility of malignant transformation (*12*). The risk factors contributing to the development of HH are currently unknown, as is the pathophysiology of these hypervascular lesions. The incidence of HH is higher in female patients, raising suspicions about the association between estrogen and HH. Moreover, angiogenesis has been clearly linked to estrogen. However, subsequent studies have confirmed that HHes do not express estrogen or progesterone receptors and there is no significant difference in the growth pattern of hemangiomas between males and females, thus ruling out a relationship between estrogen and HH (*13*). Therefore, oral estrogen contraception can be used safely and pregnancy does not pose a risk (*10*).

2.1. Imaging

HH is usually diagnosed by chance. Most cases are detected and diagnosed by ultrasound, while other suspected cases can also be diagnosed by CT and MRI (*10,14*). A study of 151 HH patients found that only four patients had a radiographically inconclusive diagnosis related to hemangioma over the ten-year study period, and no patient had a preoperative diagnosis of hemangioma that was ultimately inconsistent with postoperative pathology (*2*). Hepatectomy to rule out malignancy is very rare in the treatment of HH. Generally, HH can be easily diagnosed through imaging.

2.2. Natural history

Most hemangiomas increase in size at a slow rate of about 2 mm per year, with an increase in volume of approximately 17.4% per year (*15*). A study indicated that the growth peak for hemangiomas (<30 years old) was 0.46±0.41 cm per year, and the growth rate decreased significantly after age 50 to 0.21±0.40 cm per year. When the size of the hemangioma reaches 8-10 cm, there is another peak in its growth rate of 0.80±0.62 cm per year. However, when the size exceeds this range, the growth rate rapidly decreases to 0.47±0.91 cm per year (*13*). HHes typically exhibit a slow growth pattern, with minimal risk of complications during the progression phase, thus resulting in a non-surgical intervention as the prevailing approach for most patients.

2.3. Surgical indications

In the case of incidentally detected asymptomatic HHes, neither treatment nor imaging follow-up is warranted until clinical symptoms suggestive of hemangioma manifest (*8*). Hepatectomy is necessary for patients with significant hemangioma-related clinical symptoms, but the potential surgical risk and extent of postoperative alleviation of symptoms need to be carefully considered.

Large hemangiomas (giant: ≥ 5 cm, super large: ≥ 10 cm) are believed to be associated with clinical symptoms mainly due to compression, such as abdominal pain, obstructive jaundice, and decreased appetite (*16*). A tumor size greater than 5 cm is considered to be a predictor of clinical symptoms associated with HH (*17*). Therefore, hemangioma equal to or larger than 5 cm has long been regarded as a surgical indication. However, a point worth noting is that caution should be exercised when associating clinical symptoms with HH. Other causes such as gallstones and gastroduodenal diseases should be ruled out. Studies have indicated that about 25% of patients experience persistent symptoms after liver resection (*11,18*). Another study also suggested that surgery for 5-10 cm asymptomatic hemangiomas should be limited (*19*). Comprehensive considerations must be made before making surgical decisions. Table 1 shows the main surgical indications cited in recent studies.

Rupture of a growing hemangioma is also a concern that can cause anxiety. Although hemangioma rupture is a mandatory indication for surgery, a study has indicated that the risk of spontaneous rupture and bleeding is extremely low even for large hemangiomas, and especially for those deep in the liver (*20*). Kasabach-Merritt syndrome is a rare disorder caused by large hemangiomas (≥ 10 cm) that results in thrombocytopenia and consumptive coagulopathy (*21*). It is also one of the mandatory surgical indications, and orthotopic liver transplantation has been reported in severe cases (*22*). These rare conditions should not affect the routine management of HH patients. A multicenter retrospective study also noted that serious complications associated with the observation period were very rare, and surgical treatment of hemangiomas should be carefully considered (*23*). Surgery is inevitable in cases involving HH and hepatocellular carcinoma (HCC) that pose challenges in imaging-based differentiation or that exhibit significantly elevated oncologic indicators (*19*).

2.4. Surgery

Both anatomical hepatectomy and enucleation are effective surgical approaches that should be decided based on the specific location of the lesion. Enucleation is appropriate for a superficial hemangioma with a clear border with the liver, which allows for more preservation of liver parenchyma. Enucleation does not lead to bile leakage and reduces the risk of bleeding because there is no Glisson system crossing the HH and parenchymal

Table 1. Surgical indications for hepatic hemangioma cited in recent studies

Literature	Type of literature	Country or region	Surgical indications
Miura et al. (2014) (*23*)	Multicenter retrospective study	United States	Abdominal symptoms; anxiety (patient's willingness to undergo surgery); tumor enlargement; life-threatening complications (such as traumatic rupture)
Practice Parameters Committee of the American College of Gastroenterology (2014) (*33*)	Clinical guideline	United States	Tumor size >10 cm; symptoms of compression; recurrent abdominal pain
Brazilian Society of Hepatology (2015) (*21*)	Clinical recommendations	Brazil	Large tumors with compression symptoms; rare complications (such as tumor rupture); Kasabach-Merritt syndrome
European Association for the Study of the Liver (EASL) (2016) (*8*)	Clinical guideline	Europe	Tumor enlargement; symptoms of compression; Kasabach-Merritt syndrome
Yuan *et al*. (2022) (*13*)	Observational study	China	Only severe complications (such as Kasabach-Merritt syndrome, spontaneous rupture, obstructive jaundice, gastric outlet obstruction, Budd-Chiari syndrome)
Aziz *et al.* (2022) (*18*)	Review	United States	Uncertain diagnosis; tumor enlargement; certain occupation or hobbies are associated with the risk of abdominal trauma; compression of organs or blood vessels (gastric outlet obstruction, Budd-Chiari syndrome); Kasabach-Merritt syndrome

boundary of the liver. If this condition is not met, anatomical hepatectomy should be selected.

Transarterial embolization (TAE) has also been used in the treatment of HH, initially mainly for high-risk patients who are not candidates for hepatectomy or to temporarily stop bleeding in patients with ruptured HH. More recently, superselective transarterial chemoembolization (TACE) with bleomycin has been used for the safe and effective treatment of giant HHes. Clinical remission was achieved in all patients, with a mid-term (≥ 3 years) and long-term (≥ 5 years) tumor reduction of 85.2% and 86.5%, respectively (*24*). However, considering the benign characteristics of HH and especially its amenability to conservative treatment, a more careful discussion is needed to determine whether the use of chemotherapy drugs for benign diseases is reasonable. In addition, limitations of this technique include other complications associated with embolization, such as migration of the embolic agent to other organs, pain, nausea, fever, liver abscesses, and sepsis. Despite complete ablation of the lesion, radiofrequency ablation (RFA) has been reported to have a high complication rate for the treatment of HH (*25,26*). Insufficient data on the rationale and efficacy of TACE and RFA in treating HH do not support recommending them as first-line treatment.

HH in children is a special condition. Infantile HH grows rapidly in the first year, followed by spontaneous recurrence in most cases, which can lead to elevated AFP levels, abdominal pain, congestive heart failure, Kasabach-Merritt syndrome, or hypothyroidism (*27,28*). For symptomatic children, glucocorticoids and/or propranolol can be used as first-line medical therapy while TACE and hepatectomy are second-line options (*29-31*).

3. Focal Nodular Hyperplasia (FNH)

FNH is the second most common solid benign liver tumor, with a reported rate of detection of 3% in autopsy series (*6*) and an estimated prevalence in the global population of approximately 1%. FNH is highly prevalent among women (female: male ratio = 8:1), and it typically occurs between the ages of 30 and 50 years (*32*). FNH is thought to be caused by portal vein injury, which leads to the formation and enlargement of arterial-to-venous shunts. This causes hyperperfusion and oxidative stress in local arteries, triggering a hepatic stellate cell response that produces a central scar (*33*). The development of hyperplasia is restricted to the vascular region. In most cases, FNH is isolated and smaller than 5 cm; only about 20% are multifocal (*8*). In the vast majority of cases, FNH has a consistent size and little chance of becoming malignant (*14*). Estrogen is highly unlikely to be associated with FNH, so pregnancy, oral contraceptives, or anabolic steroids are not contraindicated (*32*).

3.1. Imaging

FNH is usually asymptomatic and is incidentally diagnosed by imaging. The tumor is well-circumscribed and non-encapsulated, characterized by a central fibrous scar with a fibrous septum radiating from the center in a "spoke-wheel" pattern, surrounded by normal hepatocytes (*6*). The imaging features of FNH are very similar to its histological manifestations, and central scarring is present in about 50% of cases regardless of whether imaging is by ultrasound, CT, or MRI (*14,33*). The use of hepatobiliary contrast agents, such as Eovist and Gd-EOB-DTPA, enables MRI to distinguish between FNH and hepatic adenomas due to the presence of bile ducts within the FNH that absorb contrast medium in the delayed phase, while hepatic adenomas do not (*34*). Studies have reported that hepatobiliary contrast-enhanced MRI has a sensitivity

of 90 to 96.9% and a specificity of 91 to 100% for differentiating FNH from hepatic adenoma (*6,14*). The combination of typical imaging features with contrast-enhanced ultrasound (CEUS), CT, or MRI has close to 100% specificity in diagnosing FNH, and CEUS performs better than MRI in detecting small (< 3 cm) FNH without central scars (*8*).

3.2. Natural history

The natural history of FNH is unremarkable, acute complications are rare, changes in tumor size over time are not significant, and there is no evidence that FNH undergoes malignant transformation (*11*). Only a very small number of patients with FNH present with clinical symptoms, and assessing the relationship between clinical symptoms and FNH is difficult. A higher proportion of liver tumors in children is malignant, making a definitive diagnosis even more important. Although FNH in children is more likely to cause symptoms, management protocols are generally consistent with those in adults (*35*).

3.3. Surgical indications

Surgical resection can significantly improve the quality of life in patients with definite symptoms (*36*). Symptoms are specific to the tumor's aspects, such as stomach compression caused by a large FNH in the left lobe of the liver or abdominal pain from acute torsion of a pedicled tumor. Asymptomatic FNHs do not require treatment or follow-up regardless of size or number (*33*). Malignant transformation of FNH or acute complications such as tumor bleeding and rupture are also extremely rare (*11*), so prophylactic treatment is unnecessary (*37*). When imaging studies cannot distinguish between FNH and HCC, surgical resection and pathological examination are preferred. Liver biopsy may be required if surgical resection is difficult, but it is not routinely recommended due to its high false negative rate of 30% (*14,33*). Table 2 shows the main surgical indications cited in recent studies.

3.4. Surgery

Hepatectomy is preferred over enucleation due to the frequent presence of large blood vessels around the lesion. Methods that preserve more liver parenchyma are chosen during hepatectomy unless malignancy is suspected (*14*). Two small case series have reported that TACE can reduce the size of FNH in adults and children and relieve symptoms (*38,39*). Currently, there is no consensus on the choice of embolization material for TACE (*40*). RFA has also been reported to be an effective treatment for symptomatic FNH (*41,42*). Despite the increasing use of TACE and RFA, however, there is currently insufficient evidence to support their use as first-line treatment options.

4. Hepatocellular Adenoma (HCA)

HCA is the third most common solid benign liver tumor, with a prevalence of less than 0.05% in the general population and a higher incidence in women (female: male = 9:1) (*6*). The presence of more than 10 adenomas is referred to as hepatic adenomatosis. Unlike HH and FNH, hormones are closely related to the development and progression of HCA. Recently, the major risk factors for HCA have shifted from oral contraceptives to obesity and metabolic syndrome (*43*). Elevated androgen levels, steroid abuse, and obesity are also associated with HCA (*44*). In addition, several rare genetic syndromes, such as glycogen storage disorders type I and type III, maturity-onset diabetes of the young type 3 (MODY3), and McCune-Albright syndrome, have been significantly associated with the development of HCA (*45*).

4.1. Pathological molecular subtypes

At present, at least eight different HCA subtypes have been identified based on molecular pathology, each with distinct histopathological features, clinical characteristics, complications and risks of malignant transformation, as well as unique management recommendations. The most common subtypes are inflammatory HCA

Table 2. Surgical indications for focal nodular hyperplasia cited in recent studies

Literature	Type of literature	Country or region	Surgical indications
Practice Parameters Committee of the American College of Gastroenterology (2014) (*33*)	Clinical guideline	United States	Definite tumor-related symptoms
Margonis *et al*. (2015) (*14*)	Review	United States	Definite tumor-related symptoms (such as pain, rupture, and bleeding); suspected malignant tumor or hepatic adenoma
European Association for the Study of the Liver (EASL) (2016) (*8*)	Clinical guideline	Europe	Definite tumor-related symptoms; pedunculated, enlarged, or exogenous
Perrakis *et al*. (2017) (*37*)	Review	Germany	An uncertain diagnosis and a history of malignancy; clinical symptoms; tumor enlarged during follow-up
Fodor *et al*. (2018) (*11*)	Review	Austria	Definite tumor-related symptoms; imaging and biopsy could not rule out malignancy
Nault *et al*. (2022) (*10*)	Review	France	Abdominal pain, compression of surrounding organs

(IHCA), *HNF1α* inactivated HCA (HHCA), β-*catenin* exon 3-mutated HCA (β^{ex3}-HCA), β-*catenin* exon 7 or 8-mutated HCA ($\beta^{ex7,8}$-HCA), sonic hedgehog HCA (shHCA), and unclassified HCA (*10, 44, 46*). The characteristics, risks of complications, and management strategies of specific subtypes of HCA are shown in Table 3.

4.2. Imaging

Approximately 35% of HCAs are incidentally diagnosed by imaging (*44*) , and MRI is the best choice for diagnosis and classification. HCA is sometimes difficult to distinguish from other hypervascular tumors due to the pseudocapsule surrounding it, and the imaging findings of HCA vary greatly between subtypes. The use of a contrast agent in MRI can better distinguish the subtypes of HCA based on the two pathological features of fat and telangiectasia. For example, the atoll sign and hyperintensity are used to distinguish IHCA; scarring and hyperintensity are used to distinguish β-HCA; and steatosis and hypointensity are used to distinguish HHCA (*47*). Contrast-enhanced MRI is reported to have a sensitivity of 87-91% in diagnosing HHCA and a specificity of 89-100%. Contrast-enhanced MRI has a sensitivity of 85-88% in diagnosing IHCA and a specificity of 88-100% (*48*). The diagnostic accuracy of contrast-enhanced MRI is increasing. A recent study found that gadoxetate disodium-enhanced MRI had an accuracy rate of 98% for diagnosing HHCA, 83% for IHCA, and 95% for β-HCA or β-IHCA (*49*).

β-HCA and unclassified HCA can sometimes appear atypical on imaging, making them difficult to distinguish from HCC. A recent study indicated that the uptake of hepatobiliary contrast in gadobenate dimeglumine-enhanced MRI is closely related to the activation of the β-*catenin* signaling pathway, which enables better identification of β-HCA (*50*). A case report also suggested that the degree of β-*catenin* activation in ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced MRI may be correlated with tumor signal intensity in the hepatobiliary phase (*51*). Overall, the advantages of MRI will continue to be exploited, and its non-invasive diagnosis of HCA subtypes will remain the focus of future attention. Although CEUS also has some value in identifying HCA subtypes, its sensitivity and specificity are not as good as those of MRI.

4.3. Natural history

Since only 15 to 20% of HCAs are at risk of complications and malignant transformation, most HCAs tend to stabilize in their natural course. A study of 118 patients indicated that 78% of HCAs remained stable or resolved with long-term MRI follow-up (*52*).

The natural history of different molecular subtypes of HCA varies. Studies have long recommended discontinuing hormone use in female patients. However, tumor regression and the risk of malignant transformation may persist even after discontinuation of hormone therapy (*53*). Estrogen is mainly associated with IHCA, HHCA, and shHCA. Therefore, recommending that patients with these conditions discontinue estrogen use and undergo imaging follow-up is reasonable. Special considerations must be made for the possibility of hormone-induced adenoma growth and HCA rupture during pregnancy. There are no clear recommendations for treating HCA tumors that consistently grow to more

Table 3. The characteristics, risk of complications, and management strategies for major subtypes of HCA

Subtypes	Proportion	Pathology	Clinical features	Risk of complications	Management
Inflammatory HCA (IHCA) 40-50% were mixed β^{ex3}-IHCA and mixed $\beta^{ex7,8}$-IHCA	34-50%	Inflammatory infiltrate; sinusoidal dilatation; dystrophic arteries	Estrogen; obesity; alcohol intake; glycogen storage disease	HCC: low; Bleeding: low; Inflammatory paraneoplastic syndrome: high	Follow-up
HNF1α inactivated HCA (HHCA)	30-40%	Pronounced steatosis	Estrogen; *HNF1α*-associated hepatic adenomatosis MODY3	HCC: low; Bleeding: low	Follow-up
β-*catenin* exon 3 mutated HCA (β^{ex3}-HCA) 15% were mixed β^{ex3}-IHCA	7-15%	Cytological atypia; pseudoglandular formation; cholestasis; Expression of GS (IHC)	Male; androgen	HCC: high; Bleeding: low	Surgery
β-*catenin* exon 7 or 8-mutated HCA ($\beta^{ex7,8}$-HCA) 10% were mixed $\beta^{ex7,8}$-IHCA	4-10%	No or faint expression of GS (IHC)	No specific	HCC: low; Bleeding: low	Follow-up
Sonic hedgehog HCA (shHCA)	4%	Histological hemorrhage	Obesity; estrogen	HCC: low; Symptomatic bleeding: high	Surgery
Unclassified HCA	7-10%	No specific pathology	No specific features	No specific risk	Follow-up

β^{ex3}-IHCA, HCA with β-*catenin* mutations in exon 3 and an inflammatory phenotype; $\beta^{ex7,8}$-IHCA, HCA with β-*catenin* mutations in exon 7 or 8 and an inflammatory phenotype; HCC, hepatocellular carcinoma; MODY3, maturity-onset diabetes of the young type 3; IHC, immunohistochemistry; GS, glutamine synthetase.

than 5 cm during pregnancy.

The overall risk of malignant transformation in HCA is approximately 5-10%, but this risk can vary greatly among different molecular subtypes, ranging from almost 0% to nearly 50% (up to 50% for β^{ex3}-HCA). Male patients have a higher risk of malignant transformation regardless of tumor size, with a risk that is six to 10 times greater than that for female patients. This increased risk is clearly associated with the previously described molecular subtypes. Considering β^{ex3}-HCA as a true precancerous lesion is reasonable. In addition, up to 42% of HCAs present with spontaneous intratumoral hemorrhage, peritoneal hemorrhage, and shock. Risk factors for bleeding include tumor > 5 cm, IHCA, a visibly diseased artery, a left hepatic tumor, and exophytic growth (*54*). Hepatic adenomatosis is associated with a higher risk of hemorrhage, necrosis, and malignant transformation (*52*). Although the proportion of male and female patients with *HNF1α*-related hepatic adenomatosis is equal, males have a higher incidence of bleeding (*55*).

4.4. Surgical indications

Previous studies have recommended surgery and lifelong observation for all patients with HCA (*56*), but the broad surgical indications need to be reconsidered as our understanding of the biological behavior of different molecular subtypes of HCA continues to improve. Overall, only about 15-20% of patients require surgery (*10*). A multidisciplinary team (MDT) discussion of a benign tumor is recommended for all patients requiring surgery. Previous studies have also emphasized the importance of MDT in the treatment of both benign and malignant diseases (*57-59*). Follow-up is necessary for all patients, typically with imaging every 6 months. After 12 months, the frequency of follow-up can be reduced if the tumor remains stable. Patients suspected of having HCC require more frequent MRI scans or surgical resection and biopsy.

Regardless of the subtype, HCAs larger than 5 cm carry a higher risk of bleeding and malignant transformation. Studies have recommended surgical removal for those larger than 5 cm (*60*). However, a study has pointed out that tumor size should not be an independent indication for surgery because surgical or non-surgical weight loss can shrink the tumor to less than 5 cm in some patients (*61*). Whether the surgical decision is based on the risk of bleeding or malignant transformation, combining individualized treatment decisions with molecular subpopulations is more reasonable.

Female patients who require continued oral contraceptives may need more frequent imaging, as well as surgery when the tumor is larger than 5 cm (*44*). All β^{ex3}-HCAs require surgical resection due to the significantly increased risk of malignant transformation. shHCA requires an MDT evaluation, but surgical resection is preferred. Surgical resection is required for all male patients with HCA. Table 4 shows the main surgical indications cited in recent studies.

Liver transplantation is recommended for hepatic adenomatosis in patients with large symptomatic tumors, tumors occupying almost the entire liver, significantly elevated alpha-fetoprotein levels, confirmed malignancy, and tumor progression after hepatectomy, due to the difficulty of achieving complete resection of all tumors (*62*). However, a study has pointed out that the risk of complications is not related to the number of tumors. Liver transplantation is unnecessary for patients with hepatic adenomatosis, and two-stage resection can be performed for large bilateral liver tumors (*63*). The risks of liver transplantation itself need to be weighed against those of the disease (*64*). In addition, studies have indicated that 71% of tumors in patients with multiple HCAs belong to the same subtype. In the remaining cases, β^{ex3}-HCA is often the largest tumor associated with the risk of malignant transformation. Therefore, biopsy of the largest nodule in hepatic adenomatosis to determine whether surgical resection is necessary may be

Table 4. Surgical indications for hepatic adenomas cited in recent studies

Literature	Type of literature	Country or region	Surgical indications
Belghiti *et al*. (2014) (*6*)	Review	France	Tumor > 5 cm (unless HHCA); male patients
Practice Parameters Committee of the American College of Gastroenterology (2014) (*33*)	Clinical guideline	United States	Tumor > 5 cm; β-HCA
Brazilian Society of Hepatology (2015) (*21*)	Clinical recommendations	Brazil	Tumor > 5 cm in women of reproductive age; male patients
European Association for the Study of the Liver (EASL) (2016) (*8*)	Clinical guideline	Europe	Male patients; β-HCA; tumor > 5 cm in female patients; residual tumor after embolization
Haring *et al*. (2023) (*60*)	Original article	Netherlands	Suspected malignancy; male patients; tumor > 5 cm; previous bleeding; symptoms leading to impaired quality of life
Tse *et al*. (2023) (*46*)	Review	United States	Male patients; β^{ex3}-HCA; female patients whose tumors progressed or remained > 5 cm after weight loss and discontinuation of oral contraceptives

a valuable option (*44*).

4.5. Surgery

In most cases, anatomical hepatectomy or segmental resection is preferable due to the risk of malignant transformation and the need to ensure resection margins. The prevalence of HCA is higher in obese patients, indicating a possible role of obesity in the development and progression of HCA. One case series reported complete resolution of HCA in two patients within 1-2 years after bariatric surgery, as well as a >50% reduction in the diameter of the largest HCA and complete resolution of smaller HCAs in another patient within 2.5 years after surgery (*61*). Clearly, the IHCA and shHCA subtypes are associated with obesity. Therefore, patients with these subtypes need to lose weight if they are overweight (*65*). However, using bariatric surgery alone to treat these subtypes of HCA presents a challenge.

TAE is used more frequently in HCA because patients with bleeding tumors may require arterial embolization as initial treatment. TACE has been found to result in partial or complete regression of HCA, allowing 45% of patients to avoid surgery. In addition, TACE can reduce the size of large, bilateral, or multiple liver tumors before surgical resection (*66*). However, whether TACE reduces symptoms and averts the risk of malignant transformation remains unknown.

RFA was initially recommended for residual or progressive tumors after resection, or as the initial treatment of tumors < 3 cm (*67*). Recently, RFA has been increasingly used in patients with HCA and appears to be a potential alternative to lifelong imaging follow-up or elective surgery. This approach seems to offer the best quality-adjusted life expectancy, lifetime costs, and net health benefits compared to hepatectomy, TACE, or no treatment (*68*). However, RFA does not produce specimens for pathological analysis, and ablation is difficult to accept in cases of diagnostic uncertainty (*53*). Its overall use remains limited, and there is no consensus on the indications for RFA, particularly regarding the number, size, and localization of treatable lesions. Therefore, the precise role of this technique remains to be determined.

5. Management

The management algorithms for HH, FNH, and HCA are shown in Figure 1.

6. Role of minimally invasive hepatectomy

The widespread use of laparoscopic surgical equipment and improvements in surgeons' laparoscopic liver resection techniques have led to a continuous reduction in surgical costs (*69-71*). Two studies indicated that quality of life scores were significantly better after laparoscopic surgery for benign liver tumors than after open surgery (*36,72*). A third study indicated that postoperative scarring of benign liver tumors is a common cause of residual symptoms, and laparoscopic surgery has an advantage in this regard (*73*). Laparoscopy is constantly developing towards robot-assisted laparoscopy, which offers more technical advantages (*74*). These benefits of minimally invasive hepatectomy will continue to impact the clinical management of benign liver tumors. However, whether surgical treatment is necessary for benign liver tumors remains a problem that requires continued attention in the field of liver surgery. After all, no matter how minimally invasive the surgery may be, it cannot be as inexpensive as reasonable observation.

7. Conclusion

In conclusion, surgical indications for HH and FNH focus solely on clinical symptoms clearly associated with the tumor and rare complications, while tumor size is not critical. The surgical indications for HCA are closely related to the molecular subtype. Male patients and those with β^{ex3}-HCA require surgical resection. shHCA requires an MDT discussion, but surgery is preferable. Attention should be paid to obesity in IHCA and shHCA, as surgical or non-surgical weight loss may control or even reduce the tumor. Female patients with tumor progression or those whose tumors are larger than 5 cm

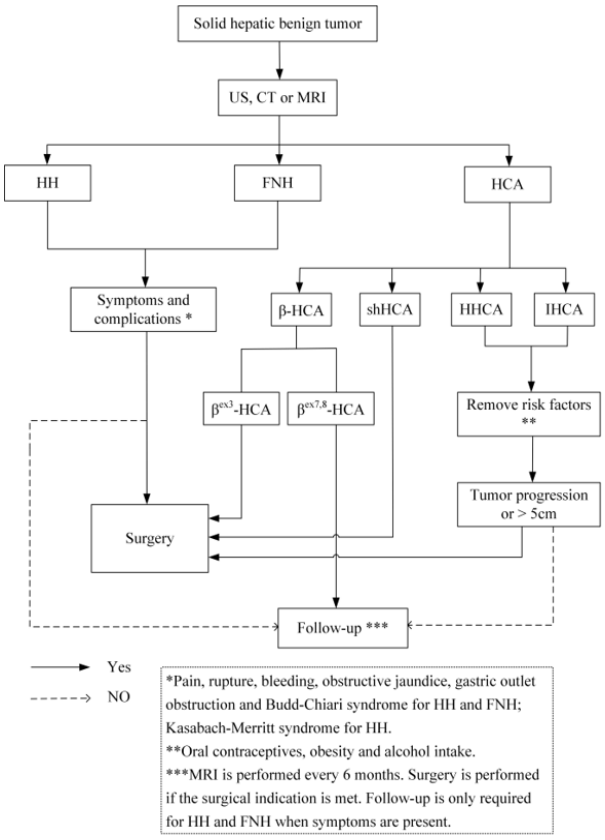

Figure 1. Management algorithms for hepatic hemangioma, focal nodular hyperplasia, and hepatic adenoma.

after cessation of oral contraceptives and weight loss are eligible for surgery. Accurate identification of molecular subtypes of HCA through contrast-enhanced MRI will be crucial to personalized clinical management in the future.

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References

1. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020; 76:182-188.
2. Mezhir JJ, Fourman LT, Do RK, Denton B, Allen PJ, D'Angelica MI, DeMatteo RP, Fong Y, Jarnagin WR. Changes in the management of benign liver tumours: An analysis of 285 patients. HPB (Oxford). 2013; 15:156-163.
3. Choi SH, Kwon HJ, Lee SY, Park HJ, Kim MS, Sohn JH, Chung EC, Park HW. Focal hepatic solid lesions incidentally detected on initial ultrasonography in 542 asymptomatic patients. Abdom Radiol (NY). 2016; 41:265-272.
4. McInnes MD, Hibbert RM, Inácio JR, Schieda N. Focal nodular hyperplasia and hepatocellular adenoma: Accuracy of gadoxetic acid-enhanced MR imaging--A systematic review. Radiology. 2015; 277:413-423.
5. Kim TH, Woo S, Ebrahimzadeh S, McInnes MDF, Gerst SR, Do RK. Hepatic adenoma subtypes on hepatobiliary phase of gadoxetic acid-enhanced MRI: Systematic review and meta-analysis. AJR Am J Roentgenol. 2023; 220:28-38.
6. Belghiti J, Cauchy F, Paradis V, Vilgrain V. Diagnosis and management of solid benign liver lesions. Nat Rev Gastroenterol Hepatol. 2014; 11:737-749.
7. Campos Amico E, de Souza IK, Grigório Trigueiro JR, Cunha Miranda F, Lacerda Sousa R, de Araújo Lima Liguori A. Should focal nodular hyperplasia still be operated upon? Analysis of a case series. Dig Dis. 2019; 37:309-314.
8. EASL Clinical Practice Guidelines on the management of benign liver tumours. J Hepatol. 2016; 65:386-398.
9. Ardito F, Aldrighetti L, Guglielmi A, *et al*. Surgical management of hepatic benign disease: Have the number of liver resections increased in the era of minimally invasive approach? Analysis from the I Go MILS (Italian Group of Minimally Invasive Liver Surgery) Registry. J Gastrointest Surg. 2020; 24:2233-2243.
10. Nault JC, Paradis V, Ronot M, Zucman-Rossi J. Benign liver tumours: Understanding molecular physiology to adapt clinical management. Nat Rev Gastroenterol Hepatol. 2022; 19:703-716.
11. Fodor M, Primavesi F, Braunwarth E, Cardini B, Resch T, Bale R, Putzer D, Henninger B, Oberhuber R, Maglione M, Margreiter C, Schneeberger S, Öfner D, Stättner S. Indications for liver surgery in benign tumours. Eur Surg. 2018; 50:125-131.
12. Toro A, Mahfouz AE, Ardiri A, Malaguarnera M, Malaguarnera G, Loria F, Bertino G, Di Carlo I. What is changing in indications and treatment of hepatic hemangiomas. A review. Ann Hepatol. 2014; 13:327-339.
13. Jing L, Liang H, Caifeng L, Jianjun Y, Feng X, Mengchao W, Yiqun Y. New recognition of the natural history and growth pattern of hepatic hemangioma in adults. Hepatol Res. 2016; 46:727-733.
14. Margonis GA, Ejaz A, Spolverato G, Rastegar N, Anders R, Kamel IR, Pawlik TM. Benign solid tumors of the liver: Management in the modern era. J Gastrointest Surg. 2015; 19:1157-1168.
15. Hasan HY, Hinshaw JL, Borman EJ, Gegios A, Leverson G, Winslow ER. Assessing normal growth of hepatic hemangiomas during long-term follow-up. JAMA Surg. 2014; 149:1266-1271.
16. Hoekstra LT, Bieze M, Erdogan D, Roelofs JJ, Beuers UH, van Gulik TM. Management of giant liver hemangiomas: An update. Expert Rev Gastroenterol Hepatol. 2013; 7:263-268.
17. Maruyama S, Matono T, Koda M. Prevalence and characteristics of hepatic hemangioma associated with coagulopathy and its predictive risk factors. J Clin Med. 2022; 11.
18. Aziz H, Brown ZJ, Baghdadi A, Kamel IR, Pawlik TM. A comprehensive review of hepatic hemangioma management. J Gastrointest Surg. 2022; 26:1998-2007.
19. Sakamoto Y, Kokudo N, Watadani T, Shibahara J, Yamamoto M, Yamaue H. Proposal of size-based surgical indication criteria for liver hemangioma based on a nationwide survey in Japan. J Hepatobiliary Pancreat Sci. 2017; 24:417-425.
20. Mocchegiani F, Vincenzi P, Coletta M, Agostini A, Marzioni M, Baroni GS, Giovagnoni A, Guerrieri M, Marmorale C, Risaliti A, Vivarelli M. Prevalence and clinical outcome of hepatic haemangioma with specific reference to the risk of rupture: A large retrospective cross-sectional study. Dig Liver Dis. 2016; 48:309-314.
21. Strauss E, Ferreira Ade S, França AV, Lyra AC, Barros FM, Silva I, Garcia JH, Parise ER. Diagnosis and treatment of benign liver nodules: Brazilian Society of Hepatology (SBH) recommendations. Arq Gastroenterol. 2015; 52 Suppl 1:47-54.
22. Prodromidou A, Machairas N, Garoufalia Z, Kostakis ID, Tsaparas P, Paspala A, Stamopoulos P, Sotiropoulos GC. Liver transplantation for giant hepatic hemangioma: A systematic review. Transplant Proc. 2019; 51:440-442.
23. Miura JT, Amini A, Schmocker R, *et al*. Surgical management of hepatic hemangiomas: A multi-institutional experience. HPB (Oxford). 2014; 16:924-928.
24. Yuan B, Zhang JL, Duan F, Wang MQ. Medium and long-term cutcome of superselective transcatheter arterial embolization with lipiodol-bleomycin emulsion for giant hepatic hemangiomas: Results in 241 patients. J Clin Med. 2022; 11.
25. Wen SQ, Wan M, Len KM, Hu QH, Xie XY, Wu Q, Liao GQ. Safety and Efficacy of laparoscopic radiofrequency ablation for hepatic hemangiomas: A multicenter retrospective study. Ann Hepatol. 2018; 17:268-273.
26. Wu S, Gao R, Yin T, Zhu R, Guo S, Xin Z, Li A, Kong X, Gao J, Sun W. Complications of radiofrequency ablation for hepatic hemangioma: A multicenter retrospective analysis on 291 cases. Front Oncol. 2021; 11:706619.
27. Zavras N, Dimopoulou A, Machairas N, Paspala A, Vaos G. Infantile hepatic hemangioma: Current state of the art, controversies, and perspectives. Eur J Pediatr. 2020; 179:1-8.

28. Wen R, Zhou ZZ, Chen WJ. Clinical and pathological features of congenital hepatic hemangioma in children: A retrospective analysis. Fetal Pediatr Pathol. 2023; 42:198-206.
29. Krowchuk DP, Frieden IJ, Mancini AJ, *et al*. Clinical Practice Guideline for the Management of Infantile Hemangiomas. Pediatrics. 2019; 143.
30. Odaman Al I, Demirağ B, Erdem M, Genç S, Karapinar TH. A retrospective analysis of clinical characteristics, treatment modalities and outcome of the patients with infantile hepatic hemangiomas: Single-center experience from Turkey. J Pediatr Hematol Oncol. 2023; 45:e259-e265.
31. Macdonald A, Durkin N, Deganello A, Sellars ME, Makin E, Davenport M. Historical and contemporary management of infantile hepatic hemangioma: A 30-year single-center experience. Ann Surg. 2022; 275:e250-e255.
32. Kaltenbach TE, Engler P, Kratzer W, Oeztuerk S, Seufferlein T, Haenle MM, Graeter T. Prevalence of benign focal liver lesions: Ultrasound investigation of 45,319 hospital patients. Abdom Radiol (NY). 2016; 41:25-32.
33. Marrero JA, Ahn J, Rajender Reddy K. ACG clinical guideline: The diagnosis and management of focal liver lesions. Am J Gastroenterol. 2014; 109:1328-1347; quiz 1348.
34. LeGout JD, Bolan CW, Bowman AW, Caserta MP, Chen FK, Cox KL, Sanyal R, Toskich BB, Lewis JT, Alexander LF. Focal nodular hyperplasia and focal nodular hyperplasia-like lesions. Radiographics. 2022; 42:1043-1061.
35. Zarfati A, Chambers G, Pio L, Guerin F, Fouquet V, Franchi-Abella S, Branchereau S. Management of focal nodular hyperplasia of the liver: Experience of 50 pediatric patients in a tertiary center. J Pediatr Surg. 2020; 55:1885-1891.
36. Hau HM, Atanasov G, Tautenhahn HM, Ascherl R, Wiltberger G, Schoenberg MB, Morgül MH, Uhlmann D, Moche M, Fuchs J, Schmelzle M, Bartels M. The value of liver resection for focal nodular hyperplasia: Resection yes or no? Eur J Med Res. 2015; 20:86.
37. Perrakis A, Vassos N, Grützmann R, Croner RS. What is changing in indications and treatment of focal nodular hyperplasia of the liver. Is there any place for surgery? Ann Hepatol. 2017; 16:333-341.
38. Crawford D, Naidu S, Patel I, Knuttinen G, Alzubaidi S, Oklu R. Bland embolization of benign liver tumors: Review of the literature and a single center experience. J Clin Med. 2021; 10.
39. Yan JY, Duan F, Fu JX, Wang Y, Zhang JL, Guan Y, Yuan B, Yuan K, Zhang H, Meng LM, Wang MQ. Outcomes of transarterial embolization for large symptomatic focal nodular hyperplasia in 17 pediatric patients. Dig Liver Dis. 2023.
40. Wang MQ, Duan F, Guan Y, *et al*. Long-term outcomes of transarterial embolization with lipiodol-bleomycin emulsion plus polyvinyl alcohol particles versus the particles alone for large symptomatic focal nodular hyperplasia: A propensity score-matched analysis. Eur Radiol. 2022; 32:6840-6849.
41. Zhang DL, Chen S, Lin YC, Ye W, Li K, Wu SS. Ultrasound-guided thermal ablation versus laparoscopic surgery for focal nodular hyperplasia of the liver: A retrospective controlled study. Front Oncol. 2022; 12:932889.
42. Yu X, Chang J, Zhang D, Lu Q, Wu S, Li K. Ultrasound-guided percutaneous thermal ablation of hepatic focal nodular hyperplasia--A multicenter retrospective study. Front Bioeng Biotechnol. 2021; 9:826926.
43. Zulfiqar M, Sirlin CB, Yoneda N, Ronot M, Hecht EM, Chernyak V, Matsui O, Bastati N, Ba-Ssalamah A, Chatterjee D, Bashir M, Fowler KJ. Hepatocellular adenomas: Understanding the pathomolecular lexicon, MRI features, terminology, and pitfalls to inform a standardized approach. J Magn Reson Imaging. 2020; 51:1630-1640.
44. Nault JC, Couchy G, Balabaud C, *et al*. Molecular classification of hepatocellular adenoma associates with risk factors, bleeding, and malignant transformation. Gastroenterology. 2017; 152:880-894.e886.
45. Haring MPD, Peeks F, Oosterveer MH, Brouwers M, Hollak CEM, Janssen MCH, Langendonk JG, Rennings AJM, Wagenmakers M, Verkade HJ, Derks TGJ, de Meijer VE. High childhood serum triglyceride concentrations associate with hepatocellular adenoma development in patients with glycogen storage disease type Ia. JHEP Rep. 2022; 4:100512.
46. Tse JR, Felker ER, Naini BV, Shen L, Shen J, Lu DSK, Kamaya A, Raman SS. Hepatocellular adenomas: Molecular basis and multimodality imaging update. Radiographics. 2023; 43:e220134.
47. Auer TA, Fehrenbach U, Grieser C, Penzkofer T, Geisel D, Schmelzle M, Müller T, Bläker H, Seehofer D, Denecke T. Hepatocellular adenomas: Is there additional value in using Gd-EOB-enhanced MRI for subtype differentiation? Eur Radiol. 2020; 30:3497-3506.
48. Ronot M, Bahrami S, Calderaro J, Valla DC, Bedossa P, Belghiti J, Vilgrain V, Paradis V. Hepatocellular adenomas: Accuracy of magnetic resonance imaging and liver biopsy in subtype classification. Hepatology. 2011; 53:1182-1191.
49. Tse JR, Felker ER, Cao JJ, Naini BV, Liang T, Lu DSK, Raman SS. Hepatocellular adenoma subtypes based on 2017 classification system: Exploratory study of gadoxetate disodium-enhanced MRI features with proposal of a diagnostic algorithm. AJR Am J Roentgenol. 2023; 220:539-550.
50. Reizine E, Ronot M, Ghosn M, Calderaro J, Frulio N, Bioulac-Sage P, Trillaud H, Vilgrain V, Paradis V, Luciani A. Hepatospecific MR contrast agent uptake on hepatobiliary phase can be used as a biomarker of marked β-catenin activation in hepatocellular adenoma. Eur Radiol. 2021; 31:3417-3426.
51. Minamiguchi K, Marugami N, Uchiyama T, Kusano H, Yasuda S, Sho M, Tanaka T. Imaging features of β-catenin-activated hepatocellular adenoma with weak β-catenin activation: A rare case report. Acta Radiol Open. 2022; 11:20584601221142241.
52. Vernuccio F, Ronot M, Dioguardi Burgio M, Cauchy F, Choudhury KR, Dokmak S, Soubrane O, Valla D, Zucman-Rossi J, Paradis V, Vilgrain V. Long-term evolution of hepatocellular adenomas at MRI follow-up. Radiology. 2020; 295:361-372.
53. Krause K, Tanabe KK. A shifting paradigm in diagnosis and management of hepatic adenoma. Ann Surg Oncol. 2020; 27:3330-3338.
54. McDermott C, Ertreo M, Jha R, Ko J, Fernandez S, Desale S, Fishbein T, Satoskar R, Winslow E, Smith C, Hsu CC. Risk factors for bleeding hepatocellular adenoma in a United States cohort. Liver Int. 2022; 42:224-232.
55. Barbier L, Nault JC, Dujardin F, Scotto B, Besson M, de

Muret A, Bourlier P, Zucman-Rossi J, Salamé E, Bacq Y. Natural history of liver adenomatosis: A long-term observational study. J Hepatol. 2019; 71:1184-1192.
56. Cho SW, Marsh JW, Steel J, Holloway SE, Heckman JT, Ochoa ER, Geller DA, Gamblin TC. Surgical management of hepatocellular adenoma: Take it or leave it? Ann Surg Oncol. 2008; 15:2795-2803.
57. Zhang Z, Li Y, Li K, Zhai G, Dang X, Zhong C, Shi Z, Zou R, Wang L, Wei D, Tang B, Ge J. Value of multidisciplinary team (MDT) in minimally invasive treatment of complex intrahepatic bile duct stones. Biosci Trends. 2021; 15:161-170.
58. Zhang Z, Shao G, Li Y, *et al*. Efficacy and safety of laparoscopic common bile duct exploration with primary closure and intraoperative endoscopic nasobiliary drainage for choledocholithiasis combined with cholecystolithiasis. Surg Endosc. 2023; 37:1700-1709.
59. Qiu G, Xie K, Jin Z, Jiang C, Liu H, Wan H, Huang J. The multidisciplinary management of hepatocellular carcinoma with portal vein tumor thrombus. Biosci Trends. 2021; 15:148-154.
60. Haring MPD, Elfrink AKE, Oudmaijer CAJ, *et al*. A nationwide assessment of hepatocellular adenoma resection: Indications and pathological discordance. Hepatol Commun. 2023; 7:e2110.
61. Gevers TJG, Marcel Spanier BW, Veendrick PB, Vrolijk JM. Regression of hepatocellular adenoma after bariatric surgery in severe obese patients. Liver Int. 2018; 38:2134-2136.
62. Bellini MI, Lauro A, D'Andrea V, Marino IR. Benign hepatic tumors and liver transplantation: A literature review. Exp Clin Transplant. 2022; 20:231-236.
63. Dokmak S, Paradis V, Vilgrain V, Sauvanet A, Farges O, Valla D, Bedossa P, Belghiti J. A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas. Gastroenterology. 2009; 137:1698-1705.
64. Mi S, Jin Z, Qiu G, Xie Q, Hou Z, Huang J. Liver transplantation in China: Achievements over the past 30 years and prospects for the future. Biosci Trends. 2022; 16:212-220.
65. Goonawardena J, Ratnayake C, Cheung KT, Fox A. Should bariatric surgery be offered for hepatocellular adenomas in obese patients? Surg Obes Relat Dis. 2020; 16:2117-2124.
66. van Rosmalen BV, Coelen RJS, Bieze M, van Delden OM, Verheij J, Dejong CHC, van Gulik TM. Systematic review of transarterial embolization for hepatocellular adenomas. Br J Surg. 2017; 104:823-835.
67. van Vledder MG, van Aalten SM, Terkivatan T, de Man RA, Leertouwer T, Ijzermans JN. Safety and efficacy of radiofrequency ablation for hepatocellular adenoma. J Vasc Interv Radiol. 2011; 22:787-793.
68. Laimer G, Schullian P, Scharll Y, Putzer D, Eberle G, Oberhuber G, Bale R. Stereotactic radiofrequency ablation as a valid first-line treatment option for hepatocellular adenomas. Int J Hyperthermia. 2022; 39:780-787.
69. van Rosmalen BV, de Graeff JJ, van der Poel MJ, de Man IE, Besselink M, Abu Hilal M, Busch OR, Verheij J, van Gulik TM. Impact of open and minimally invasive resection of symptomatic solid benign liver tumours on symptoms and quality of life: A systematic review. HPB (Oxford). 2019; 21:1119-1130.
70. Hou Z, Xie Q, Liao M, Zeng Y, Huang J. ASO Author Reflections: Laparoscopic anatomical resection of right superior segments *via* anterior transparenchymal approach. Ann Surg Oncol. 2023.
71. Hou Z, Xie Q, Liao M, Zeng Y, Huang J. Laparoscopic anatomical resection of paracaval portion of caudate lobe and segment 8 for HCC in an HCV-related cirrhotic patient. Ann Surg Oncol. 2023.
72. Kneuertz PJ, Marsh JW, de Jong MC, Covert K, Hyder O, Hirose K, Schulick RD, Choti MA, Geller DA, Pawlik TM. Improvements in quality of life after surgery for benign hepatic tumors: Results from a dual center analysis. Surgery. 2012; 152:193-201.
73. van Rosmalen BV, Bieze M, Besselink MG, Tanis P, Verheij J, Phoa SS, Busch O, van Gulik TM. Long-term outcomes of resection in patients with symptomatic benign liver tumours. HPB (Oxford). 2016; 18:908-914.
74. Hou Z, Xie Q, Qiu G, Jin Z, Mi S, Huang J. Trocar layouts in laparoscopic liver surgery. Surg Endosc. 2022; 36:7949-7960.

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