ORIGINAL ARTICLE

Indications and Long-term Outcome of Treatment for Benign Hepatic Tumors

A Critical Appraisal

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Hypothesis: The natural history and clinical behavior of benign hepatic tumors during long-term follow-up may not justify primary surgical treatment.

Design: Retrospective study.

Setting: Tertiary referral center.

Patients: Two hundred eight patients diagnosed as having a benign liver tumor between January 1, 1979, and December 31, 1999.

Intervention: Seventy-four patients underwent hepatic surgery and 134 were managed conservatively by radiological follow-up.

Main Outcome Measures: Symptoms and complications were assessed during management and follow-up.

Results: In the surgically treated population, the liver lesion was symptomatic in 47 patients (64%) and an incidental finding in 27 (36%). The operative morbidity and mortality were 27% (20 of 74 patients) and 3% (2 of 74 patients), respectively. Overall, 28 (80%) of 35 patients with complaints were asymptomatic after surgery. During observation of the tumor in the conservatively managed group, 39 (87%) of 45 patients who presented with complaints were asymptomatic during a mean follow-up of 45 months; 6 patients had mild abdominal pain considered to be unrelated to the tumor.

Conclusions: Conservative management of solid benign liver lesions such as focal nodular hyperplasia and hemangioma can be performed safely, irrespective of their size. We only advise surgery for liver lesions when there is an inability to exclude malignancy or in the case of severe complaints related to the tumor. Resection is always advocated in the case of a large hepatocellular adenoma (>5 cm) to reduce the risk of rupture and malignant degeneration.

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In contrast with hemangioma, focal nodular hyperplasia (FNH) and hepatocellular adenoma are uncommon benign liver tumors that are detected more frequently because of improvements in radiological modalities and the widespread use of ultrasonography (US).[1,2] They are often recognized as incidental hepatic masses during imaging for nonspecific abdominal symptoms. It is important to establish the diagnosis of an indeterminate hepatic mass to apply either surgical or conservative treatment. During management, it is essential to decide whether the mass is the cause of the patient's symptoms, since simple observation might afford the best clinical approach in the case of a benign liver lesion. In addition, the benefit of resection should be carefully balanced against the risk inherent to liver surgery.

Several reports[1,3-8] have documented the cause, differential diagnosis, and treatment of FNH, hepatocellular adenoma, and hemangioma of the liver. Although findings in these studies provide a framework for the management of benign hepatic tumors, the most appropriate treatment remains controversial.[9-11] Especially in the case of a hepatocellular adenoma, many[5,6,9] prefer surgery to conservative treatment because of the risk of rupture and potential malignancy.

We summarize a single-center experience with the diagnosis and management of benign hepatic tumors. This study reviews the indications for surgery and the outcome of long-term follow-up in the treatment of these tumors.

RESULTS

SURGICAL TREATMENT

In the case of an incidentally detected tumor (32%, or 24 of 74 patients), the in-

PATIENTS AND METHODS

A total of 208 patients with a benign liver tumor were analyzed between January 1, 1979, and December 31, 1999. A total of 74 patients underwent surgery and 134 were observed in our clinic (**Table 1**). The medical records of these 208 patients were reviewed to document clinical presentation, imaging studies, surgical or conservative treatment, complications, and follow-up.

The male-female ratio for FNH was 1:7.5; for hepatocellular adenoma, 1:7.3; and for hemangioma, 1:2.8 (Table 1). Seventy-five percent (45/60) of the women with FNH used oral contraceptives for a mean±SD of 137±44 months, and 93% (27/29) of those with a hepatocellular adenoma used oral contraceptives for a mean±SD of 144±84 months.

Mainly since 1990, laboratory analyses included hepatitis B and C serologic tests (hepatitis B surface antigen, anti–hepatitis B core [antigen], and anti–hepatitis C virus) and levels of α-fetoprotein as surrogate markers for malignancy.

The radiological investigation consisted of US, computed tomography (CT), magnetic resonance imaging (MRI), angiography, technetium Tc 99m sulfur colloid liver scintigraphy, and cholescintigraphy with the diisopropyl iminodiacetic acid hepatobiliary agent. The tumor was classified using predefined criteria as FNH, hepatocellular adenoma, hemangioma, or undetermined (**Table 2**).[12-14] Angiography has an additive value for diagnosis when a central feeding artery is visible. At scintigraphy, a normal or increased uptake within a lesion is typical for FNH because of the presence of Kupffer cells and allows differentiation from a hepatocellular adenoma, which is associated with a focal defect.

The findings of diagnostic imaging were compared with the outcome of the histological examination of the resected specimen; the latter was taken as the gold standard for confirmation of the diagnosis.

Hepatic surgery consisted of hemihepatectomy or a segmental or local resection. In the case of multiple tumors, resection was performed for the largest tumor, unless all tumors were located in the same segment or lobe. When surgical morbidity was calculated, all complications requiring treatment were included in the analysis.

ability to differentiate between FNH, hepatocellular adenoma, or carcinoma was an indication for surgery (**Table 3**). Small tumors that allowed simple surgery during laparotomy for other reasons were also resected. Abdominal symptoms were the reason for resection in 47 (64%) of the 74 patients, even when there was a clear diagnosis of FNH or hemangioma. The tumor diameter was significantly greater in patients with abdominal pain than in those with an incidental finding (median [range], 8.0 [4.0-21.0] vs 5.5 [2.5-19.0] cm; $P=.01$ vs $<.02$). Rupture of the tumor was observed in 8 (42%) of the 19 patients with hepatocellular adenoma.

Routine laboratory analyses did not contribute to the diagnosis. α-Fetoprotein levels were determined in 129 (62%) of all 208 patients and were found to be normal. Hepatitis B and C serologic tests (hepatitis B surface antigen, anti–hepatitis B core [antigen], and anti–hepatitis C virus) were performed in 135 (65%) of the 208 patients, and the results were negative in all samples.

The diagnostic workup usually included US and contrast-enhanced CT (**Table 4**). Computed tomographic scanning led to the imaging diagnosis in 37% of the patients with FNH, in 56% of those with hepatocellular adenoma, and in 70% of those with hemangioma. The most important diagnostic difficulty was in differentiating FNH from hepatocellular adenoma and in some cases from carcinoma. It is remarkable that the sensitivity rate of US and CT scanning for FNH has increased significantly between the first 10-year period (1979-1989) (14% and 33%, respectively) and the last 10 years (46% and 39%, respectively) ($P=.04$). In addition, MRI was used in 11 patients; in all 4 patients with a hemangioma, the diagnosis was established unequivocally.

The results of a preoperative needle biopsy, performed in 38 patients, were confirmatory, with the histopathological diagnosis of the resected tumor in 8 (50%) of the 16 patients with FNH, in 8 (67%) of the 12 with a hepatocellular adenoma, and in 10 (100%) of the 10 with a hemangioma.

In the surgically treated population, 5 patients with FNH and 9 with hemangioma had 2 or more tumors in the liver. Hepatocellular adenoma was solitary in all patients. Major hepatic resections were performed in 17 patients (23%), including right (extended) and left hemihepatectomies. Nonanatomic resection (enucleation or wedge resection) was performed in 25 patients, and a (bi)segmental resection was performed in 32 (**Table 5**).

Table 1. Characteristics of the 208 Patients With Benign Liver Tumors

Type of Tumor	Sex, M/F	Age, y*	Patients Who Underwent Surgery	Patients Who Underwent Observation	Total No.
Focal nodular hyperplasia	8/60	36 (24-61)	26	42	**68**
Hepatocellular adenoma	4/29	34 (15-49)	19	14	**33**
Hemangioma	27/76	48 (30-77)	25	78	**103**
Cystadenoma	1/0	. . .	1	0	**1**
Angiomyolipoma	0/2	. . .	2	0	**2**
Rhabdomyoma	1/0	. . .	1	0	**1**
Total	**41/167**	. . .	**74**	**134**	**208**

*Data are given as the mean (range). Ellipses indicate data not available.

Table 2. Lesion Characteristics for Each Imaging Modality*

Type of Lesion	US	CT Scanning	MRI
Hemangioma	90% hyperechoic, a well-defined spherical or lobulated lesion; in 68% homogeneous signal	Low density on unenhanced CT; after delivery of contrast media, peripheral nodular enhancement; fill-in of the lesion over time (5-10 min)	Round or lobulated mass, low SI on T1 and high SI on T2; typical peripheral nodular enhancement after the administration of Gd
FNH	Hypoechoic and a well-defined lesion with a smooth border	Unenhanced well-defined hypodense or isodense lesion; after delivery of contrast media, homogeneous increase in density; 50% of the lesions may show a central scar	Slightly lower SI on T1 and slightly higher SI on T2, homogeneous enhancement after the administration of Gd; may show a central scar
Hepatocellular adenoma	Hypoechoic, mostly localized at the periphery of the liver parenchyma; a well-defined lesion with a smooth border	Well-defined hypodense lesion, rapid transient enhancement on dynamic CT; may show hemorrhage	Isointense SI on T1 and T2 and transient enhancement after the administration of Gd

*US indicates ultrasonography; CT, computed tomographic; MRI, magnetic resonance imaging; SI, signal intensity; T1, T1-weighted image; T2, T2-weighted image; Gd, gadolinium; and FNH, focal nodular hyperplasia.

The mean±SD greatest diameter of the resected tumor was 8.3±4.1 cm (median, 7.5 cm; range, 3.0-19.0 cm) for FNH, 10.3±3.4 cm (median, 9.0 cm; range, 7.0-20.0 cm) for hepatocellular adenoma, and 9.0±5.3 cm (median, 7.0 cm; range, 2.5-21.0 cm) for hemangioma.

During the postoperative hospital stay (median, 11 days; range, 2-33 days), overall morbidity, including all minor complications, was 27% (20 of 74 patients) (**Table 6**). Two patients (3%) died of continued bleeding and a severe consumptive coagulopathy after liver surgery for a large and symptomatic tumor (14 and 15 cm). One of these tumors, located centrally in the liver, compressed the duodenum from the outside and caused gastric outlet obstruction, which necessitated surgical treatment. Six patients required additional surgical intervention during the same period of hospitalization, 5 with secondary bleeding for control of hemorrhage and 1 with thrombosis of the inferior vena caval for thrombectomy. All complications were randomly distributed during the period of study and were not related to surgical experience.

The mean follow-up was 39 months (median, 11 months; range, 1-182 months). Of 27 patients who were asymptomatic at presentation, 6 (22%) had complaints related to surgery and 21 (78%) remained asymptomatic. The long-term morbidity related to surgery was as follows:

Complaint	No. of Patients (n=72)*
Abdominal pain	5
Incisional pain	3
Incisional hernia	2
Fatigue	3
Total	13

*Two patients who died are excluded. The total percentage of patients with complaints was 18.

Of the patients who presented with complaints (n=35), symptoms resolved in 28 after surgery. However, in 7 patients (3 with FNH and 4 with hemangioma), symptoms persisted. All women with previous hepatocellular adenoma stopped using oral contraceptives. Tumor recurrence was not detected during radiological follow-up of all patients.

Table 3. Clinical Presentation in 74 Patients With a Benign Liver Tumor, Treated Surgically*

Clinical Presentation	Focal Nodular Hyperplasia (n = 26)	Hepatocellular Adenoma (n = 19)	Hemangioma (n = 25)
Incidental	12 (46)	4 (21)	3 (12)
Suspected metastases	1 (4)	0	4 (16)
Abdominal pain	10 (38)	6 (32)	15 (60)
Nonspecific complaints	2 (8)	1 (5)	1 (4)
Palpable mass	1 (4)	0	2 (8)
Bleeding	0	8 (42)	0

*Data are given as the number (percentage) of patients. Four patients with cystadenoma, angiomyolipoma, and rhabdomyoma had abdominal complaints.

Table 4. Imaging Modality and Sensitivity Rates for FNH, Hepatocellular Adenoma, and Hemangioma*

Imaging Modality	FNH	Hepatocellular Adenoma	Hemangioma
US	6/18 (33)	6/18 (33)	12/24 (50)
CT scanning	7/19 (37)	9/16 (56)	16/23 (70)
MRI	1/4 (25)	1/3 (33)	4/4 (100)
Angiography	2/8 (25)	2/3 (67)	4/6 (67)
Liver scintigraphy	2/7 (29)	0/2	1/4 (25)
Cholescintigraphy	1/6 (17)	1/1 (100)	0/2

*Data are given as the number of patients in whom the specific imaging modality led to the diagnosis/the total number of patients in that group (percentage). FNH indicates focal nodular hyperplasia; US, ultrasonography; CT, computed tomographic; and MRI, magnetic resonance imaging.

CONSERVATIVE TREATMENT

A total of 134 patients (42 with FNH, 14 with hepatocellular adenoma, and 78 with hemangioma) were managed by observation. In 43% of the patients with FNH, in 43% with a hepatocellular adenoma, and in 78% with a hemangioma, the tumor was found incidentally during abdominal imaging or laparotomy for other indica-

Table 5. Surgical Procedure in 74 Patients*

Procedure	Focal Nodular Hyperplasia (n = 26)	Hepatocellular Adenoma (n = 19)	Hemangioma (n = 25)	Other (n = 4)
Right hemihepatectomy	2	5	5	1
Right extended hemihepatectomy	0	0	1	0
Left hemihepatectomy	1	0	2	0
Segmental resection	13	11	7	1
Nonanatomic resection	10	3	10	2

*Data are given as the number of patients.

Table 6. Surgical Morbidity*

Complication	Focal Nodular Hyperplasia (n = 26)	Hepatocellular Adenoma (n = 19)	Hemangioma (n = 25)	Other (n = 4)
Pneumonia	2	0	0	0
Pleural effusion	0	0	2	0
Pulmonary embolism	0	0	1	0
Urinary tract infection	0	0	1	0
Wound infection	2	1	0	0
Venous thrombosis	0	2	0	0
Secondary bleeding	3	1	1	0
Perihepatic abscess	0	0	1	1
Ascites	2	0	0	0
Total, No. (%)	**9** (35)	**4** (21)	**6** (24)	**1** (25)

*Data are given as the number of patients.

Table 7. Clinical Presentation in 134 Patients With a Benign Liver Tumor, Treated Conservatively*

Clinical Presentation	Focal Nodular Hyperplasia (n = 42)	Hepatocellular Adenoma (n = 14)	Hemangioma (n = 78)
Incidental	18 (43)	6 (43)	61 (78)
Abdominal pain	14 (33)	2 (14)	9 (12)
Nonspecific complaints	10 (24)	2 (14)	8 (10)
Bleeding	0	4 (29)	0

*Data are given as the number (percentage) of patients.

tions (**Table 7**). Abdominal pain was noted in 33%, 14%, and 12% of those with FNH, a hepatocellular adenoma, and a hemangioma, respectively. Four patients presented with a ruptured hepatocellular adenoma and were managed conservatively by hemodynamic stabilization and control of coagulation disorders. When the tumor was an incidental finding during laparotomy, the diagnosis was confirmed by incisional biopsy peroperatively. In all other patients, imaging methods led to the diagnosis. In case of doubt, a needle biopsy was performed (in 25 patients with FNH, in 16 with a hepatocellular adenoma, and in 15 with a hemangioma).

Patients were observed for a mean of 45 months (range, 24-72 months). Of the 42 patients with FNH, 6 (14%) had mild abdominal pain considered to be unrelated to the tumor (mean diameter, 4.7 cm; range, 3.0-5.6 cm) and 6 (14%) had nonspecific complaints of fatigue.

All patients with hepatocellular adenoma were asymptomatic. The mean greatest diameter of the tumor was 3.2 cm (range, 1.5-5.0 cm). Six (43%) of the 14 patients showed regression of the tumor after cessation of oral contraceptive use, and 2 of these tumors were not detectable during the last follow-up. Hepatitis B and C serologic test results were negative in all patients. There was no evidence of malignant transformation or bleeding during follow-up.

One patient with a hemangioma as an incidental finding showed growth of a large tumor (diameter, 20 cm) without any complaints; during a follow-up of 4 years, the tumor diameter increased by 5 cm and, to date, this patient is being managed conservatively. Coagulation disorders and tumor-related mortality were not detected.

COMMENT

The results of our experience indicate that liver surgery for benign liver tumors may relieve complaints in a high percentage of symptomatic patients (80%). However, in many patients, symptoms persist after resection of the tumor and surgery-related complications might occur. Regarding the considerable long- and short-term morbidity and even mortality, careful patient selection is warranted, especially in view of the benign nature of these lesions.

The clinical presentation may be different for FNH and hemangioma on the one hand and for hepatocellular adenoma on the other. Focal nodular hyperplasia and hemangioma are typically incidental findings since 50% to 90% of patients lack symptoms.[5,6,11,15-18] In the case of abdominal pain or discomfort, the clinician must decide whether this is caused by the mass before considering specific treatment of the lesion.[17,19] Patients with a

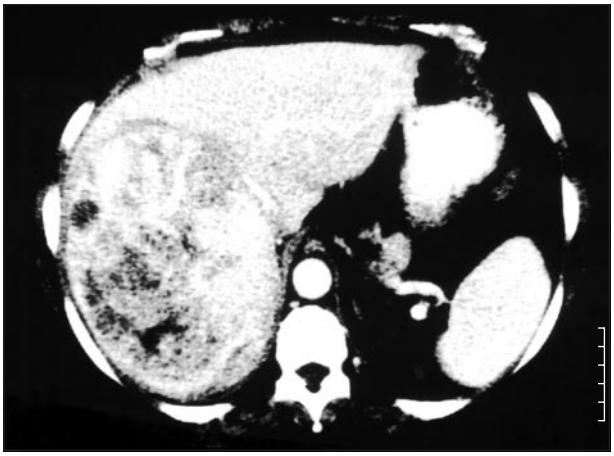

Figure 1. Computed tomographic image of a hepatic tumor with intralesional hemorrhage and necrosis, typical features of a hepatocellular adenoma. This tumor was resected because of its large diameter.

Figure 2. Magnetic resonance image of a conservatively treated patient, showing a typical lobulated hyperdense lesion on T2-weighted sequences, characteristic of a hemangioma.

hepatocellular adenoma, however, have a higher prevalence of symptoms at first presentation, probably caused by the rate of intratumoral or intra-abdominal hemorrhage (50%-65%).[3,7,20]

Problems may arise in obtaining a definite diagnosis in the case of a solid hepatic tumor, and in differentiating between benign and malignant tumors. When clinical evidence of malignant disease is absent, serum α-fetoprotein levels are normal, and hepatitis B and C serologic test results are negative, a benign lesion must be considered in the differential diagnosis. Because additional laboratory tests are not helpful during the diagnostic workup, the combination of US and contrast-enhanced CT can provide a diagnostic yield. Although not specific, findings of an avascular central scar or a feeding artery to the mass are highly supportive of FNH, and the presence of intralesional hemorrhage with necrosis is similarly supportive of hepatocellular adenoma (**Figure 1**). Although the use of more invasive imaging methods, such as liver scintigraphy, cholescintigraphy, and angiography, is reported to be useful for the diagnosis of benign lesions,[5,6] an additive value to preoperative imaging specificity was not shown in our study. The sensitivity rates of imaging methods in the surgically treated population are lower than those reported in the literature.[21-23] This may be caused by a selection bias of more atypical lesions in the group of operated on patients. Furthermore, diagnostic tools and experience have improved during the 20-year period of our study. Nowadays, familiarity with dynamic contrast-enhanced CT and MRI will allow a more accurate diagnosis. Increasingly, MRI is being used to improve the diagnostic accuracy in the case of a liver tumor. Especially when the differential diagnosis includes hemangioma, MRI is a valuable tool, showing a specificity of 90% to 100% and a sensitivity of about 90% (**Figure 2**).[24]

Percutaneous liver biopsy is assumed to be of little value because of the possible lack of specific features in a small specimen and the risk of needle-induced bleeding in hypervascular tumors.[25,26] However, we perform a needle biopsy when doubt remains about the diagnosis and a conservative approach is being considered. The risk of serious hemorrhage during US- or CT-guided needle biopsy in benign liver tumors is reported to be low (0.03%-0.04%),[27,28] and in our series there were no complications with the biopsies performed.

The strategy for management of benign hepatic tumors has ranged from routine resection[7,29,30] to selective observation.[5,6,10,16,31-33] Indications for surgery have been the presence of symptoms, the development of complications, or the need to establish a definite diagnosis when radiological and histological studies were not conclusive. Yet the risk of significant and sometimes uncontrollable intraoperative bleeding in addition to the common risks of any liver resection[17,34,35] should be carefully balanced against the benefit that might be expected from resection. Mortality rates of surgery, which may be underreported in the literature, must be considered as serious, especially taking into account the benign nature and prevalence of the tumor. Observation of the tumor can be used in most patients without risk of significant morbidity and with resolution of symptoms. There is no evidence that FNH lesions can bleed or undergo malignant transformation,[3,16] and the low potential for complications of a liver hemangioma (rupture, growth, mass effect, or Kasabach-Merritt syndrome) does not justify surgery for all detected lesions.[17,36,37] In contrast to FNH and hemangioma, resection of a hepatocellular adenoma is advocated regardless of symptoms.[5,7,30,38-40]

In our clinic, we perform surgery for hepatocellular adenomas with a diameter greater than 5 cm, since lesion size may be an important indicator of malignancy and potential for rupture.[10,38,41] A conservative approach may be justified with smaller hepatocellular adenomas, even in the case of bleeding; patients have to be advised to stop steroid use and to avoid pregnancy. Large hepatocellular adenomas detected during pregnancy should be resected also, since there is an increased risk of bleeding due to high levels of endogenous steroid hormones and the increased vascularity of the liver.[42] Moreover, we advise surgery for any benign liver tumor that causes severe complaints and when there is an uncer-

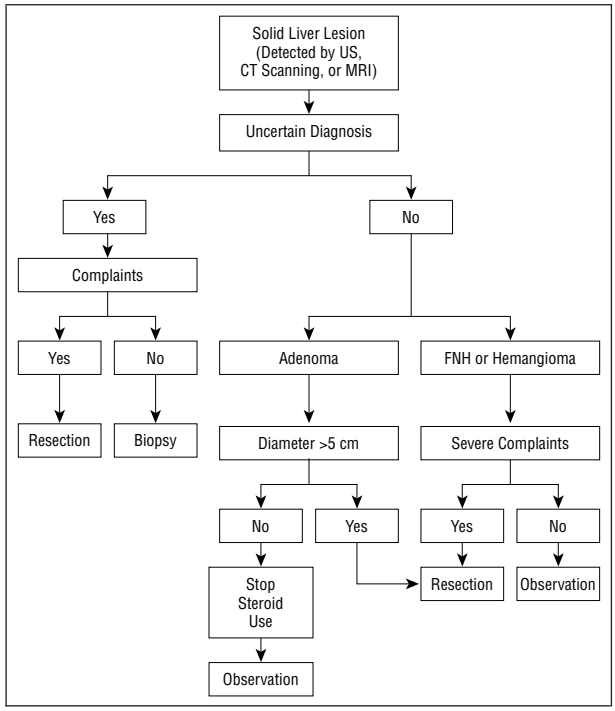

Figure 3. Algorithm for the management of solid liver tumors. US indicates ultrasonography; CT, computed tomographic; MRI, magnetic resonance imaging; and FNH, focal nodular hyperplasia.

tain diagnosis (**Figure 3**). This may explain the fact that we did not find a malignancy during follow-up of our conservatively managed patients.

When considering surgery, patients should be well informed that complaints may persist and that hepatic resection for benign lesions may still be related to serious morbidity and even mortality.

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