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CONCISE REVIEW

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What is Changing in Indications and Treatment of Focal Nodular Hyperplasia of the Liver. Is There any Place for Surgery?

Aristotelis Perrakis, Nikolaos Vassos, Robert Grützmann, Roland S. Croner

Department of Surgery, University of Erlangen-Nuremberg, Krankenhausstr. Erlangen, Germany.
Perrakis A. and Vassos N. contributed equally to this manuscript.

ABSTRACT

Focal nodular hyperplasia (FNH) is a common benign liver tumor, which occurs in the vast majority of the cases in young women. FNH represents a polyclonal lesion characterized by local vascular abnormalities and is a truly benign lesion without any potential for malignant transformation. A retrospective single institution analysis of 227 FNH patients, treated from 1990 to 2016 and a review of studies reporting surgical therapy of overall 293 patients with FNH was performed. Indications for resection with a focus on diagnostic workup, patient selection, surgical mode and operative mortality and morbidity have been analysed. Ninety three patients underwent elective hepatectomy and 134 patients observation alone, where median follow-up was 107 months. Postoperative complications were recorded in 14 patients, 92% of patients reported an improvement with respect to their symptoms. Overall among 293 patients underwent surgery in the series, included to this review, there was a morbidity of 13%, where median follow-up was 53 months. Systematic follow-up remains the gold standard in asymptomatic patients with FNH. However elective surgery should be considered in symptomatic patients, in those with marked enlargement and in case of uncertainty of diagnosis. Surgery for FNH is a safe procedure with low morbidity and very good long term results as far as quality of life after surgery is concerned and surely an integral part of the modern management of FNH.

Key words. Focal nodular hyperplasia. Liver. Surgery. Observation. Follow-up.

INTRODUCTION

Solid benign liver tumors can be classified according to consistency: for example solid versus cystic, radiologic appearance in terms of vascularisation of the lesion (hypervascular versus hypovascular), as well as cell of origin (mesenchymal vs. epithelial).[1-30] Recently, there has been a growing interest in solid benign liver tumors as far as the management of disease is concerned.[30-44] Focal nodular hyperplasia (FNH) is -after liver hemangioma- the second most common benign nodular disease with a prevalence ranging from 0.3 to 3%, and its exact aetiology and pathogenesis are not completely understood.[1-5,30,32] The prevailing theory of the development of FNH is that this tumor arises from a vascular malformation, mediated possibly by the dysregulation of angiopoietin genes (ANGPT1 and ANGPT2)[36] which leads to blood hyperperfusion triggering a secondary hyperplastic/regenerative response in the liver parenchyma. This response is mediated by the increased expression of vascular endothelial and somatic growth factors that trigger an activation of hepatic stellate cells.[37] FNH is considered to be a truly benign formation, which does not undergo a malignant transformation.[2] It appears predominantly in women during their reproductive years (gender bias women:men 80:20). According to the majority of reports about FNH there is a not-well established association between oral contraceptives and FNH.[3-5]

FNH is in the most cases an incidental finding and can cause unspecific abdominal symptoms. Major complications, such as acute bleeding and perforation are rare.[5] Liver function tests are in the most cases normal and alpha fetoprotein is not present.[6] Contrast-enhanced magnetic resonance imaging (MRI) scanning has been shown to be the most sensitive modality for characterising this lesion, while the triple phase spiral computed tomography (CT)

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(with portal-venous, arterial, venous phase) and contrast-enhanced ultrasonography can be used as further diagnostic tools.[6-17] On gross pathology, FNH is generally a solitary (80% of the cases) 32 coarsely nodular, brown or yellowish-gray lesion of variable size (usually less than 5 cm but can reach up to 20 cm).[20-29] The lesion often has a subcapsular position, is sharply demarcated from the healthy liver tissue, and lacks a true capsule. The hallmark of the lesion is the dense, central stellate scar that contains an inappropriately large artery with arterial branches radiating through the fibrous septa to the periphery. Because of the benign nature of FNH, the observation in a fashion equally to asymptomatic hemangioma[5-12,27] stays on the foreground and the indication for surgical treatment remains controversial. However, the rapid progress of the disease, the occurrence of symptoms, the obstruction of large vessels, jaundice and the uncertainty of the diagnosis - especially in case of an atypical FNH or when there is a difficulty in the differentiation between hepatocellular adenoma (HCA) and FNH can be accepted as indications for surgical treatment. Several studies have reported non-surgical management or observation of FNH.[1-3] However there is an absence of large study-groups with an adequate number of patients, reporting long-term results of both non-surgical and surgical treatment.[5-12] Given that FNH is not a premalignant lesion, it is recommended to perform a non-anatomical wedge resection of the lesion in order to preserve as much normal functional hepatic parenchyma as possible.[5-12,32]

Here, we report our single center experience in the management of the FNH, including patients, who underwent an elective surgical therapy or observation alone. Our aim was to review the long term outcome of these patients and to clarify the indications for surgical treatment. Furthermore we performed a systematic review on high volume studies - including more than 20 patients underwent surgery for FNH - that report outcomes of surgical management of FNH and give details of preoperative diagnostic investigations, stated indications for surgery, operative procedure, mortality, morbidity and patient satisfaction. Thus the indications for conservative *vs.* surgical management of suspected FNH might be more clearly understood.

MATERIAL AND METHODS

After performing a search of the PubMed and MEDLINE databases, including the period 2001 to 2015 inclusive using the MeSH (medical subject headings) terms: focal nodular hyperplasia ; liver resection , surgery and hepatectomy . The search was limited to English-language publications and studies on adult human subjects. All titles and abstracts were reviewed, and appropriate papers assessed for inclusion. The reference sections of all papers initially included were also assessed to ensure the identification of all relevant studies.

Studies were included if they described outcomes following surgery in patients with FNH. Our main focus as far as the data collected and evaluated is concerned, was at preoperative diagnostic methods used, indications for surgery, mode of hepatectomy performed (minor vs. major) and postoperative outcomes. The minimal dataset eligible for inclusion was required to refer to a respectful collective of patients with FNH treated with surgery (≥ 20 patients) and to present diagnostic modality and patient outcome data. All series satisfying these criteria were included. Case series with a "surgical group" under 20 patients, case reports, editorials, unpublished data from conference abstracts and review articles were excluded.

Study population of own series

Between January 1990 and January 2016, 227 patients diagnosed with focal nodular hyperplasia were evaluated in the Surgical Department of the University of Erlangen-Nuremberg.

Table 1. Pretreatment demographic data in current series.

	Surgery (n = 93)	Observation (n = 134)†	p
Age median (years)	42	29	NS
Gender			
Male	15	2	0.003
Female	78	132	0.05
Tumor diameter (cm)	8.5	4.9	NS
Number of lesions			
Solitary	70	115	NS
Multiple	23	19	NS
History of cancer			
No	71	130	NS
Yes	22	4	0.05
Previous hormonal therapy			
No	35	15	0.003
Yes	58	119	0.03
ASAT (U/L)	15.8 (± 1.87)	12.5 (± 1.13)*	NS
ALAT (U/L)	21.1 (± 2.53)	12.3 (± 1.32)*	NS
Gamma-GT (U/L)	63.7 (± 6.72)	29.6 (± 2.65)*	0.003
Bilirubin (mg/dL)	0.71 (± 0.49)	0.73 (± 0.38)*	NS
Alkaline Phosphatate (U/L)	108.8 (± 7.51)	51.1 (± 2.19)*	0.004

*† All patients without surgical therapy. * First ambulant treatment. ASAT: Aspartate-Amino-Transferase. ALAT: Alanine-Amino-Transferase. Gamma-GT: Gamma Glutamytransferase. U/l: units per liter.*

Patients were identified from a prospective database. The patients were analyzed in two groups: Group A (surgical group) (n = 93) included patients, who underwent elective surgical treatment and group B (follow-up group) (n = 134) those, who were observed alone or those, who refused to undergo an operation despite occurrence of symptoms and marked enlargement of the tumour during the follow-up (Table 1).

Our final analysis involved 189 patients, who underwent a complete follow-up until December 2015 or until death.

We analyzed the demographic data, the health status according the EQ5D questionnaire 35, laboratory liver values, number and size of the lesions, diagnostic methods used, mode of surgical treatment and postoperative outcome with peri- and postoperative complications.

Demographic parameters and diagnostic imaging

Median age of the patients was 39 years (range: 19-70). Hundred four patients were female (Table 1). The diagnostic workup included ultrasonography, contrast-enhanced triphasic CT and MRI (Table 2). The imaging findings were compared with the outcome of the histopathological examination of the resected specimen. The latter was taken as the gold standard for confirmation of the diagnosis. Tumour biopsy was performed preoperatively in 10 patients (percutaneously: 6 patients, laparoscopically: 4 patients). Liver serum tests included aspartate-amino-transferase (ASAT), alanine-amino-tansferase (ALAT), bilirubin, gamma-glutamyltransferase (gamma-GT) and alkaline phosphatase (AP) and alpha fetoprotein (Table 1).

Surgical procedures, indication criteria

Indications for surgical treatment included abdominal discomfort (n = 68), marked tumour enlargement with a rate of growth > 0.5 cm per year or > 3 cm in comparison to initial diamater (n = 16) and uncertainty of diagnosis (n = 15) (Table 3). The parameters assessed for the surgical group were blood loss and blood transfusion in the perioperative phase and early postoperative course, hepatic and extrahepatic complications, the 90 day morbidity/mortality, the length of stay in the Intensive Care Unit (ICU) and in hospital and the relief of symptoms after the surgical treatment. The observation parameters for the patients in group B were:

- The improvement of symptoms.
- Symptom progression.
- Tumour enlargement.
- Tumour related morbidity and mortality, and
- Health status according to EQ5D questionnaire.[35]

Statistical analysis

The statistical analysis was performed using statistical software (SPSS for Windows version 17.0; SPSS Inc., Chicago IL and Excel 2007; Microsoft, Redmond,WA) and all data were checked for significance by use of the unpaired Students *t*-test. A p-value < 0.05 was considered statistically significant. Continuous variables are reported as the mean ± deviation.

RESULTS

The sex bias was in group A 84%:16% (female:male) and in group B 98.5%:1.5%. Twenty four percent of the patients in group A had a history of cancer (n = 22) and 58 patients (62%) a hormonal therapy prior to the diagnosis. In the surgical group the mean tumour diameter was 8.5 cm (range 1-20) and in the follow-up group 4.9 cm (range 1-12) (Table 1).

In all patients with the diagnosis FNH there was a cessation of consumption of contraceptives after the first referral in our Department.

Of the studies reviewed, four and the present one focused in high volume fashion on patients with FNH.[9-12]

Table 3. Indication for resection of FNH in current series.

	N*
Abdominal discomfort	68
Uncertainty of diagnosis	15
Tumor enlargement	16
Jaundice	4

*Tumor enlargement: growth rate: 0.5 cm/year or > 3 cm in comparison to initial size. * Multiple answers are permitted.*

Table 2. Imaging modality and the rates of diagnosis in current series.

	N	Correct	Uncertain	Incorrect
US (%)	93	45 (48)	27 (29)	21 (23)
CT (%)	65	50 (77)	12 (18)	3 (5)
MRI (%)	62	55 (89)	5 (8)	2 (3)

In total, these studies involved 293 patients submitted to surgery for FNH (Table 4).

Diagnostic studies

All patients who were treated surgically underwent abdominal ultrasonography. In 45 of 93 patients (48%) the diagnosis was established correctly. In 27 patients (29%) there was an uncertainty of the diagnosis; while in 21 patients (22%) the ultrasound examination did not offer the correct diagnosis. A contrast enhanced triphasic CT scan was performed in 65 patients (69%) and established the correct diagnosis in 48 patients (77%). In 18% of these patients (n = 12) there was an uncertainty of the diagnosis and in 3 patients (5%) there was an incorrect diagnosis. The vast majority of these patients (n = 43) were referred to our department with abdominal CT already performed. In the rest of the patients a CT was performed because of cancer history or suspected malignancy.

In 62 patients a contrast enhanced MRI examination was performed. The diagnosis was accurate in 55 patients (89%); uncertain in 5 (8%) patients and incorrect in 2 (3%) patients (Table 2).

Four studies -and the present one- provided details of the diagnostic modalities employed preoperatively in a total of 293 FNH patients.[9-12]

The reference-standard method of diagnosis of FNH was the histological analysis of the specimen.

Preoperative biopsy of tumour

Only one study included data on the use of biopsy in the context of the management of presumed FNH.

Descottes, *et al*. reported preoperative liver biopsy performed in 11 patients with FNH (23% of all FNH patients) either percutaneous (n = 3) or laparoscopic (n = 8).[10] The results of biopsy-derived histological diagnoses had a poor accuracy when compared with resection specimen histology. Six (55%) positive results have been registered. The remaining findings included four false positive results referring to the misdiagnosis of three adenomas and one hepatocellular carcinoma (HCC) and one uncertain result.

Ultrasound

Shen, *et al.*[9] reported the application of contrast-enhanced ultrasound (US) in 79 of 86 (92%) patients undergoing resection for FNH. Ultrasound achieved an accurate diagnosis of FNH in 33% (n = 26) of patients. Of the remaining 53 patients, 28 had an uncertain US diagnosis and in 25 there was an incorrect diagnosis, presenting these FNH patients having malignant lesions in terms of hepatocellular carcinoma (HCC).

Descottes, *et al.* reported using US in 85 (98%) patients, but did not present data on its accuracy.[10]

Computed tomography (CT)

Shen, *et al.*[9] reported the use of multiphase computed tomography (CT) in 67% (n = 58) of the patients and Descottes, et al.10 reported using CT in 74 (85%) patients but in both reports information on the diagnostic accuracy of CT is missing.

Magnetic resonance imaging (MRI)

Shen, *et al.* used MRI in 31 patients (36%) with acceptable results as far as the diagnostic accuracy is concerned; in 77% (n = 24) of patients a correct diagnosis has been established.[9] In 22 patients both diagnostic methods, CT and MRI, have been applied. Through this combined approach an accurate FNH diagnosis has been established in 20 (91%) patients.

Descottes, *et al.,* reported the application of MRI in 44 (51%) patients without any further information about the diagnostic accuracy of the diagnostic method.[10]

Table 4. Analysis of the examined studies, reporting FNH patients underwent surgery.

	Patients (n)	Morbidity (n/%)	Indication 1 (n/%)	Indication 2	Follow-up in months (Median)
Descottes, *et al.*[10]	48	N/A	23(45%)	28(55%)	10
Kamphues, *et al.*[11]	45	N/A	N/A	N/A	50
Petri, *et al.*[12]	21	7(33%)	N/A	N/A	N/A
Shen, *et al.*[9]	86	6(7%)	N/A	N/A	45
Perrakis, *et al.*	93	13(14%)	6(73%)	15(16%)	107
Overall	293	26(13%)*	91	43	53

** Concerning 3 studies providing data about morbidity. Indication 1: abdominal symptoms. Indication 2: uncertainty of diagnosis.*

Surgical treatment

All patients in the surgical group (group A) underwent an elective liver resection. A minor hepatectomy in terms of segmentectomy or bisegmentsectomy[34,45] was performed in 52 (67%) patients. Six of these patients in the time frame from 2014 to 2016 underwent a minimal invasive minor liver resection, either laparoscopically or robotic-assisted by use of DaVinci. A major hepatectomy in terms of a right/left hemihepatectomy and an extended right/left hemihepatectomy has been performed in 18 (33%) patients. Temporal occlusion of the hepatoduodenal ligament (Pringle maneuver) was performed in 31 patients. Perioperative blood loss of more than 500 mL was registered in 22 (28%) patients. The remaining patients in group A (n = 56, 72%) had a blood loss less than 500 mL. Intra- or postoperative blood transfusion was required in 10 patients (1-3 erythrocyte concentrates in 9 patients [13%], > 4 erythrocyte concentrates in 1 patient) (Table 5).

The reviewed studies presented data on the mode of hepatectomy performed for FNH in a total of 293 patients.[9-12] Five studies provided data on the sizes of the hepatic lesions removed and the anatomical extent of resection.[9-12] Major versus minor hepatic resection was inferred from the data presented, and the techniques employed are reviewed where presented.

Descottes, *et al.* reported 48 minor laparoscopic liver resections in patients with FNH. The procedures performed included 14 (27%) left lateral hepatectomies, 12 (24%) segmentectomies and 25 (49%) non-anatomic (wedge) resections. In six (12%) patients, a laparoscopic procedure has been converted to conventional hepatectomy because of significant bleeding (n = 2, 33%) and due to technical reasons (n = 4). The median diameter of the resected lesions was larger in the symptomatic group than in the asymptomatic group [5 cm (range: 2-11 cm) *vs.* 4 cm (range: 1-6 cm)], but the difference was not significant.[10]

Shen, *et al*. performed liver resections in 86 patients with FNH between 1996 and 2006. Seventeen patients (20%) underwent a major hepatectomy in terms of hemihepatectomy and most patients underwent non-anatomic wedge resection of FNH lesions (n = 68, 79%). The mean diameter of resected lesions in all patients was 3 cm (range: 0.3-15 cm).[9]

Across the rest of the studies reviewed minor resections of three or fewer Couinaud segments 45 were performed in 209 patients. Major hepatectomy (≥ 3 Couinaud segments) has been performed in 39 patients. One patient underwent a liver transplant. In the series of Kamphues et al there was no FNH specific data regarding mode of resection.[9-12]

Outcome

Patient follow up as of January 2016 or till time of death ranged from 0 to 248 months (median follow-up: 109 months). None of the patients who underwent surgery were lost from follow-up. These patients underwent follow-up examinations every 6 months: clinical examination, imaging modalities (US and/or MRI) and a face to face interview on their health status after surgery or during observation by using the EQ5D health questionnaire 35 (Table 6).

There was no peri- or postoperative mortality in our series. Postoperative complications were recorded in 12 (15%) patients. One patient had biliary leakage, which was treated through ERCP, placement of a nasobiliary tube and a biliary stent. Extrahepatic complications: pleural effusion (n = 2), pneumonia (n = 3), wound infection (n = 4), seroma (n = 2) occurred in 11 patients (14%) and were treated conservatively (Table 4). All recorded complications according to the Dindo Clavien classification46 were graded mild or moderate (Table 7).

Mean hospital stay was 9.8 days (range 4-25 days) and mean length of stay in the intensive care unit was 0.8 days (range 0-8 days). None of the patients who underwent operative treatment developed late postoperative complications or a disease recurrence. Symptom relief occurred in 92% of the patients in group A.

In the observation group (group B) 96 of 134 patients (72%) underwent a complete follow up. The remaining patients declined follow-up or were referred to another

Table 5. Intraoperative features and postoperative outcome after liver resection for FNH in current series.

	Surgery (n = 93)
Mode of operation (%)	
Segmentectomy/Bisegmentectomy	75 (81)
Right/left hemihepatectomy	10 (10)
Extended right/left hepatectomy	8 (9)
Blood loss (%)	
< 500 mL	71 (76)
≥ 500 mL	22 (24)
Blood transfusion (%)	
No substitution	83 (89)
1 - 3	9 (10)
≥ 4	1 (1)
Complications (%)	
Biliary leckage	1 (1)
Extrahepatic complications	12 (13)
Perioperative death	0 (0)
Relief of symptoms (%)	86 (92)
Length of in hospital stay (days, range)	9.8 (4-25)
Length of in ICU stay (days, range)	0.8 (0-8)

centre and were lost to follow-up. All patients underwent an ultrasonography and/or MRI every 6 months. Twelve patients (13%) had an improvement of their symptoms. In 12 patients (12%) additional symptoms were noted. Tumour enlargement was registered in 3 patients (4%). Despite symptoms, these patients declined surgical treatment. Neither a tumour related major complication such as rupture nor disease-related mortality were recorded (Table 8).

We used the EQ5D questionnaire in order to evaluate the health status of patients after surgery and during follow up (Table 6).

Table 6. EQ 5 D quality of life after surgery in current series.

	Surgery (n = 93)	Observation (n = 96)	p
Mobility			
No problems	93 (100%)	96 (100%)	NS
Moderate	0 (0%)	0 (0%)	
Immobility	0 (0%)	0 (0%)	
Self-reliance			
Full	93 (100%)	96 (100%)	NS
Moderate	0 (0%)	0 (0%)	
No	0 (0%)	0 (0%)	
Pain / Discomfort (scale: 0-10)			
No	86 (92%)	85 (89%)	NS
Moderate (1-5)	7 (8%)	11 (11%)	NS
Extreme (6-10)	0 (0%)	0 (0%)	NS
Health status (mean)	95%	92%	NS

(0-100). 0: Worst health status. 100: Best health status.

Table 7. Postoperative complications according to the Dindo Clavien classification in current series.

	Surgery (n = 93)
Grade I	8 (8%)
Grade II	15 (16%)
Grade IIIa	1 (1%)
Grade IIIb	0
Grade IV	0

Table 8. Course of disease of patients with FNH and observation alone in current series.

	Observation (n = 96)
Improvement of symptoms (%)	12 (12)
Additional symptoms (%)	12 (12)
Tumor enlargement (%)	3 (4)
Tumor-related complications (%)	0 (0)
Death (%)	0 (0)

Five studies included follow-up data for 293 patients with FNH and FNH-specific morbidity and mortality statistics (9-12) (Table 4).

Shen, *et al.* reported a morbidity rate of 7% (n = 6) in their series. All of the reported complications were fluid collections (hematoma, bilioma) with associated right-sided pleural effusions.[9] During the follow-up period (mean: 45 months), neither recurrence of symptoms nor mortality were reported.

In the series reported by Petri, *et al.* morbidity was reported in 29% (n = 6) of patients underwent a liver resection for FNH: postoperative bleeding (n = 2, 10%), postoperative jaundice (n = 2, 10%), fever of unknown origin (n = 1, 5%) and cerebrovascular insult (n = 1, 5%). In the series of Petri, et al. there was also mortality registered in one patient (5%), which underwent liver transplantation (LT).[12]

Kamphues, *et al.* used the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QLQ) C30 questionnaire to evaluate patients' outcome and quality of life after liver resection for benign disease at a median of 50 months after surgery.11 Patients underwent surgery because of FNH made up 33% (n = 27) of the collective. However a subgroup analysis was not performed. Results from all patients underwent surgery for benign liver lesions demonstrated highly significant improvements in global health status (p = 0.001), social functioning (p = 0.03) and emotional functioning (p = 0.007) after surgery. No significant improvement in physical status or cognitive functioning was seen. Significant impact was also seen in terms of pain (p = 0.001) and fatigue (p = 0.004). The vast majority of patients being questioned (n = 78, 96%) stated that they did not regret their decision to undergo surgery.

In summary, the rate of morbidity experienced by patients submitted to resection for FNH was 13% (n = 26). Only two studies -the present one and the series of Descottes, et al.- provide specific information about indication of surgery: The main indication for FNH resection was a symptomatic FNH (n = 91), followed by uncertainty of diagnosis (n = 43). The overall follow-up accounting 53 months was acceptable. No cases of mortality following hepatic resection of FNH lesions alone were reported. One case of 30-day mortality (0.03%) was observed; this occurred in a patient submitted to LT for FNH.

DISCUSSION

FNH is the second most common benign focal lesion of the liver. FNH is characterised as a nodular, hyperplastic lesion and is not a true neoplasm, but a local hyperplastic response to increased blood flow within an intrahepatic arteriovenous malformation.[17] The predominant symp-

toms are abdominal pain and discomfort in the right upper abdominal quadrant.

The aim of this review and the comparison of our long term results with these of other authors were to evaluate if there is an indication change in the management of a purely benign liver lesion, such as FNH and if surgery does still play a role in the modern management of FNH. Diagnostic tools used for the determination of such a lesion are US, CT and MRI.[9-12,32] Many authors have demonstrated that MRI scan and multiphase dynamic CT scans have currently a high diagnostic accuracy for identifying FNH. The diagnosis of a FNH is based in MRI on imaging the central scar, which demonstrates a delayed enhancement and increased signal intensity on T2-weighted imaging, while an accurate differentiation between FNH and a hepatocellular adenoma (HCA) can be achieved on the delayed T1-weighted imaging after administration of hepatobiliary MRI contrast medium. The complementary use of contrast-enhanced ultrasound could play a role in the further differentiation between HCA and FNH.[14-16]

Some authors consider the risk of a major complication triggered by FNH[38,39] as minimal and discourage surgical treatment emphasizing the potential risk of peri- and postoperative complications and suggest a conservative treatment and observation.[2,3] We can present the results of the present review and of our single center experience as counter evidence to this argument.[32] Although 39 patients (Table 8) underwent an advanced hepatectomy, the rate of morbidity was low and the outcome of these patients was excellent.

Generally and due to the lack of randomised clinical trials assessing the possible benefits of a surgical treatment in terms of absence of clinical symptoms and patients' satisfaction after surgery, the therapeutic algorithm of FNH remains controversial.[7-10,22,26,27,32] It is generally accepted that small, asymptomatic FNH without a tendency for enlargement should be managed conservatively. On the other hand, liver lesions where uncertainty of diagnosis is present, especially in those with a cancer history should be treated surgically; even if small in size.[9-12] In particular, the development of symptoms or marked tumor enlargement (> 3-4 cm, 0.5 cm per year) during the follow-up are indications for surgical treatment.[32] In the present review and as far as the indication spectrum for surgery is concerned the uncertainty of diagnosis -after FNH-related abdominal symptoms- has been one of the main indication criteria for surgery in the studies included in this review. This matter is a contradiction to the availability of better imaging, such as MRI, but not surprising, because the largest series consider outcomes and indications over the last 20 years, where the imaging quality was not on the highest level. Nevertheless it is critical to offer the option of surgery in patients, where uncertainty of diagnosis and/or history of cancer are present. However, we believe that the standard use of contrast-enhanced MRI might result in a significant reduction of patients with asymptomatic FNH patients undergoing unnecessary resection, because of initial uncertainty of diagnosis.

Of great importance in the current analysis was also the negative impact of the biopsy of lesion, for example in the series of Descottes, *et al.*[10]: Only in 55% of the patients underwent biopsy because of uncertainty of diagnosis, the right diagnosis could be established. Concerning this matter and the established difficulty of distinguishing large FNH lesions from well-differentiated or fibrolamellar HCC on biopsy histology[26,27,29,32,38-41] the biopsy of such a lesion remains controversial. Furthermore, it is also worth mentioning that several authors demonstrate that the coincidence of portal vein malformation and hepatitis B might play a role in the development of HCC with FNH.[47]

In our series and in the present review we were able to demonstrate that surgery for benign liver lesions is associated with low morbidity. Of great importance was the fact, that no mortality had been registered among patients underwent liver resection.

Additionally an important quality factor in favour of surgery was that in both series, this of Kamphues, *et al*. and the present one, there was a marked benefit due to the relief of symptoms in the vast majority of the patients. These results confirm the opinion of other authors, who believe that a relief of symptoms and the patient satisfaction justify (major) liver resection for symptomatic benign focal lesions of the liver.[18,32]

Based on the results of the current review and the opinion of other authors[27] we firmly believe that FNH should be managed according to an algorithm similar to hepatic hemangioma and consequently surgical treatment is an integral part of this workflow, while the initial size of the lesion must not be the major indication criterion for surgery. Once symptoms appear, abnormal behaviour of the lesion is demonstrated, uncertainty of diagnosis and/or a marked enlargement of the lesion are present, and surgery should be considered.

According to our results and in the era of laparoscopic liver surgery, which offers potential operative and postoperative benefits[48,49] the optimal management of FNH management could be reconsidered in favour of elective minimal invasive surgery. As a result, many centres will feel comfortable in performing large numbers of minor resections for benign disease and to avoid unnecessary biopsies of the lesion. Our early results about the advantages and outcome of laparascopic/robotic liver resection, especially of benign lesions, such as less operative blood loss, less postoperative pain and a shorter length of hospital stay 50 add meaningful information to the debate about optimal management of patients with benign liver lesions,

such as FNH, and need to be investigated in large randomised prospective studies.

The existing literature concerning the management of FNH is definitely not sufficient enough. In the last 10 years, few series, focusing on the surgical management of FNH have been published.[9-12,32] Our first results about FNH management and the series of Shen, *et al*. have been the largest series to date.[9,32] The majority of studies reporting the management of FNH retrospectively are in their vast majority only a part of single-centre case series about benign liver lesions, usually without sufficient subgroup analysis.

The aim of this review was to assess the indications for and outcomes of the operative treatment of FNH. Other potential therapeutical such as embolization and radiofrequency ablation (RFA) have not been included in this review, because these do not represent primary modalities for the management of FNH and are an alternative part of the therapeutical algorithm, if patient declines surgery.[41-43]

The evidence base for the management of FNH is weak, because of absence of multicenter randomized clinical trials (RCT) comparing the available treatment modalities in the different collectives. On this matter Navarro, *et al.,* suggests for symptomatic patients, a multicentre RCT comparing operative with conservative management would provide the first level I evidence for the effect of surgery on symptoms presumed to be caused by a benign liver lesion, such as FNH.[30]

CONCLUSION

FNH is often an incidental finding, since such a lesion remains asymptomatic for a long time. The most reliable imaging methods are: MRI (sensitivity over 95%), triple phase spiral CT (with portal-venous, arterial, venous phase) and US/contrast enhanced US. However, despite detailed radiological workup and high sensitivity of MRI, the diagnosis of FNH remains unclear usually in presence of several subtypes of FNH, such as inflammatory and teleangiectatic FNH.[40] This uncertainty of diagnosis, especially in patients with cancer history together with the symptomatic FNH and the significant enlargement of the tumour(s) during follow-up, should be considered as indication criteria for surgery in modern algorithm for FNH management.

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CONFLICT OF INTEREST

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Correspondence and reprint request:
Aristotelis Perrakis, M.D.
Department of Surgery, University of Erlangen-Nuremberg,
Krankenhausstr. 12, 91054 Erlangen, Germany.
Ph.: +49 1723796295, Fax: +49 9131 85 36294.
E-mail: aristotelis.perrakis@uk-erlangen.de