Liver: Original Paper

Digestive Diseases

Dig Dis
DOI: 10.1159/000496430

Received: July 4, 2018
Accepted: December 20, 2018
Published online: February 14, 2019

Should Focal Nodular Hyperplasia Still be Operated Upon? Analysis of a Case Series

Enio Campos Amico Izadora K. de Souza Juliana R. Grigório Trigueiro
Fernanda Cunha Miranda Rogério Lacerda Sousa Adriano de Araújo Lima Liguori

Department of Integrated Medicine, Federal University of Rio Grande do Norte/University Hospital Onofre Lopes, Natal, Rio Grande do Norte, Brazil

Keywords
Focal nodular hyperplasia · Imaging · Liver biopsy · Therapy and surgery · Tumors

Abstract
Background: Focal nodular hyperplasia (FNH) is a frequent benign liver lesion. Its course is considered benign, and there is no recommendation for its treatment. Nevertheless, the literature presents a high incidence of surgery. ***Aim:*** To evaluate the results of conservative treatment in a series of patients with presumed FNH. ***Methods:*** The study included patients diagnosed with FNH from May 2007 to July 2017 based on conventional imaging or magnetic resonance imaging with liver-specific contrast (MRI-LSC) or lesion biopsy (histology/immunohistochemical analysis). Patients were followed clinically and using imaging exams. ***Results:*** In a total of 54 patients, the diagnosis was obtained by typical findings on computed tomography scan and gadolinium MRI in 48.1% of the patients, by MRI-LSC in 31.5%, and by histological examination in 20.4% of cases. The mean follow-up time was 35.5 months. The initially asymptomatic patients remained symptom-free, and none of those with HNF-related pain had to worsen of the initial symptom. Conservative treatment was effective in 94.4% of the cases. In only 3 cases, there was a need for some therapeutic approach (5.5%); 2 cases for pain and 1 case for lesion growth during follow-up. ***Conclusion:*** The present study suggests that it is safe to conservatively manage patients with FNH presumed by highly accurate imaging tests. Similar to hepatic hemangiomas, surgery for FNH should be an exception.

Introduction

Focal nodular hyperplasia (FNH) is a benign, solid liver lesion that is diagnosed frequently in liver imaging studies [1]. Its prevalence is estimated between 0.18 and 3.2% in the general population [2]. FNH occurs more frequently in women between 20 and 60 years of age, and its relationship with estrogen is less clear in comparison to liver adenomas [3].

It is not recommended to surgically treat and have a follow-up for FNH, since most patients remain asymptomatic and the lesion remains stable; additionally, there

E-Mail karger@karger.com
www.karger.com/ddi

Izadora Karinny de Souza
Department of Integrated Medicine, Federal University of Rio Grande do Norte/University Hospital Onofre Lopes, Pintassilgos Street, 90, Sun Gardens Condominium 1804 A, Pitimbu, Natal, Rio Grande do Norte, 59067-300 (Brazil)
E-Mail izadoraks@gmail.com

is no risk of rupture, bleeding, or malignant transformation [4, 5]. Nevertheless, many patients with FNH are still operated nowadays.

In a Memorial Sloan-Kettering publication from 2013, although the incidence of resections for benign diseases has declined at that institution, approximately half of the patients with suspected FNH were operated on [6]. Based on data from the literature suggesting that surgical treatment of FNH is an exception [5], the objective of the present study was to analyze a cohort of patients with presumed FNH, with an emphasis on conservative treatment.

Materials and Methods

The study included patients with suspected benign solid liver lesions (BSLLs) from a prospective database from May 2007 to July 2017. All patients were examined at 2 medical institutions in the city of Natal, Rio Grande do Norte, Brazil: Gastrocentro Clinic and Onofre Lopes University Hospital. We evaluated all patients, including physical examination and record of medical history. Patients presented with arterialized lesions greater than 1 cm, which was seen on computed tomography (CT) scan or gadolinium MRI with gadolinium (MRI-G) in a radiologically normal liver. Laboratory diagnoses of viral hepatitis, chronic hepatopathy, or radiological diagnoses of hemangioma, hepatic adenoma, hepatocarcinoma, or hypervascular metastases were considered exclusion criteria.

Only patients with a presumptive or definitive diagnosis of FNH were included in the study. The authors established the diagnosis by 3 ways: (1) hypervascular lesion without washout and with central scar on CT scan or MRI-G; (2) hypervascular lesion without washout with hyper/isointense signal in the hepatobiliary phase of the magnetic resonance imaging with liver-specific contrast (MRI-LSC); or (3) hypervascular lesion whose histopathological examination combined or not with immunohistochemistry was compatible with the diagnosis of FNH. For patients who did not undergo item 1, MRI-LSC was preferred, and biopsy was indicated when liver-specific contrast was unavailable, or imaging findings were doubtful.

The imaging tests were performed using different devices. Minimum quality criteria for radiological examination were established for inclusion in the study. All patients underwent triple-phase studies with 16-slice or more MDCT scanners and maximum 5 mm slice thickness.

The dynamic study used a T1-weighted sequence with fat saturation before and after intravenous administration of extracellular gadolinium-based contrast medium and through an injection pump in the arterial, portal and equilibrium phases. The hepatobiliary phase was added approximately 20 min after the start of contrast injection with gadoxetic acid (Gd-EOB-DTPA; Primovist®, Bayer-Schering, Berlin, Germany)

Liver biopsy was preferably by laparoscopic access in superficial lesions or by tomography-guided percutaneous access in intraparenchymal lesions with a Tru-Cut 16-gauge needle in a both cases. The slides were stained with hematoxylin-eosin and other similar dye available.

Many cases underwent slide revision and it was necessary that immunohistochemical examinations be conducted for diagnosis complementation. The panel used was based on publications from the Bordoux group [7, 8]. The exam was typical of FNH when showing the presence of radiating fibrous septa with numerous ductules, dystrophic arterial vessels, no portal branches dividing the hepatocytes and no atypias in lobes. Immunohistochemistry was positive when a map-like glutamine synthetase staining pattern was present.

All included patients had to return to the outpatient clinic to undergo control radiological examinations, preferably with MRI-G or CT at 6 months and thereafter annually.

Results

The total number of patients in this study was 54, of which 92.5% were female. The mean age at diagnosis was 35 years (15–65). Regarding symptoms, 55.5% were asymptomatic; 20.37% presented nonspecific symptoms such as nausea, vomiting, malaise, and abdominal discomfort; 24% had pain in the upper abdomen, with only 3 patients having intense pain that required continuous analgesic medication. Only 1 of these patients with severe pain underwent immediate surgery (bisegmentectomy II/III) due to intense and persistent pain on the right hypochondrium and atypical lesion on CT examination. The diagnosis of FNH was confirmed by anatomical-pathological examination with immunohistochemistry. The patient presented symptom relief after surgery.

Patient diagnosis and treatment are outlined in Figure 1. The conventional CT/MRI-G with the presence of a central scar was sufficient for the diagnosis in 48.1% of patients (Fig. 2); by MRI-LSC in 31.5% (Fig. 3); and by histological examination in 20.4% of cases.

In 10 patients, biopsy was necessary for the diagnosis – 8 biopsies via laparoscopic access (80%) and the others by percutaneous access. There were no complications due to the procedure, regardless of the type of access used. In 4 of the 10 patients, it was necessary to use immunohistochemistry.

Clinical follow-up was performed in 88.8% of the patients. The mean follow-up time was 35.5 months (1–120 months). During the follow-up, none of the asymptomatic patients started to present symptoms, and none of the patients with specific pain had to worsen of the initial symptom. Two patients with severe pain at presentation underwent conservative treatment. One of the patients, who had a large 13.1-cm hypervascular lesion in the right hepatic lobe, underwent 2 arterial embolizations, obtaining pain relief with a 5-month follow-up. The other patient with a hypervascular lesion (3.5 cm), also with a cen-

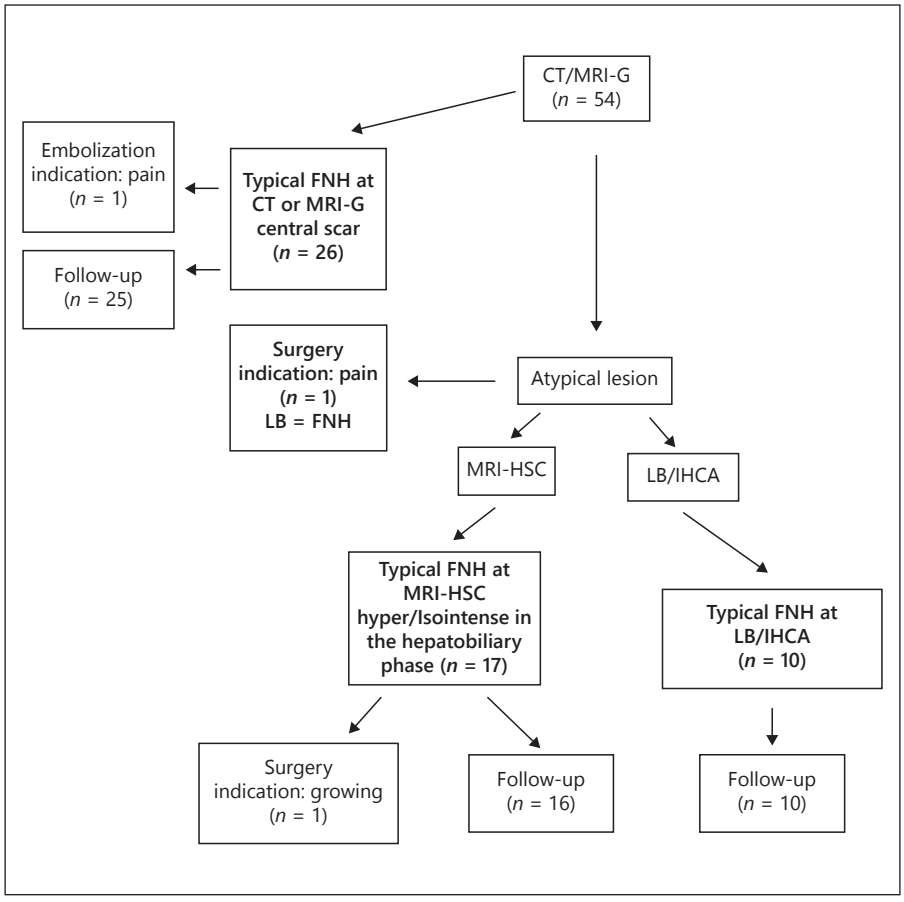

Fig. 1. Diagnostic form of the patients included in the study and the conduct taken. CT, Computed tomography; MRI-G, Magnetic resonance imaging gadolinium contrast; LB, Liver biopsy; MRI-HSC, Magnetic resonance imaging hepatocyte-specific contrast; IHCA, Immunohistochemical analysis.

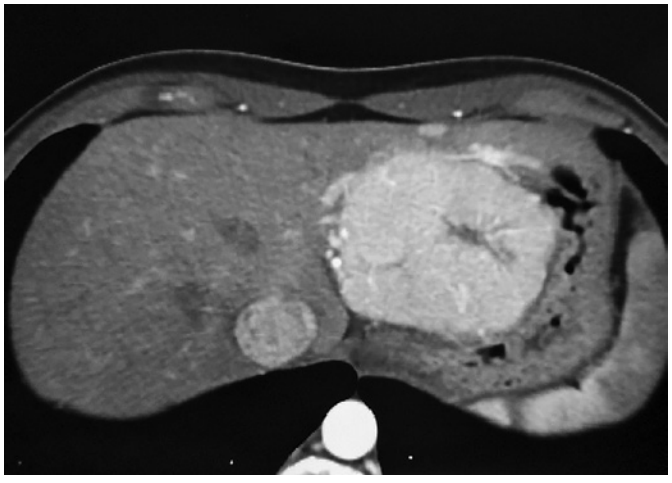

Fig. 2. Abdominal multislice computed tomography on arterial phase. Arterially enhancing lesion on the left liver lobe with stellate hypo-enhancing central area, suggesting a central scar (Typical FNH).

tral scar in liver segment V, had a diagnosis of cervical and lumbar degenerative disc disease with disc protrusion, obtaining abdominal pain relief with the treatment of this pathology.

Radiological follow-up was performed with CT or MRI scans, at least 6 months apart, in 79.6% of the patients. The mean follow-up time was 33.2 months (6–95 months). Eighty-seven exams were performed in 43 patients during follow-up (mean of 2.0 exams/patient).

In 19 patients (44.2%), there was stabilization of the lesion; at 15 (34.9%), there was an increase in the lesion, in 8 (18.6%) there was injury reduction, and in 1 patient (2.3%), the lesion disappeared. The variation of the size in the group of patients who had an increase and reduction of the lesion was, respectively, 1.19 (0.3–2.2) and 1.38 cm (0.3–3.7 cm). None of the patients in the group who had increased lesion became symptomatic in the follow-up.

During follow-up, 2 patients underwent percutaneous biopsy. In both cases, the presumed diagnosis had

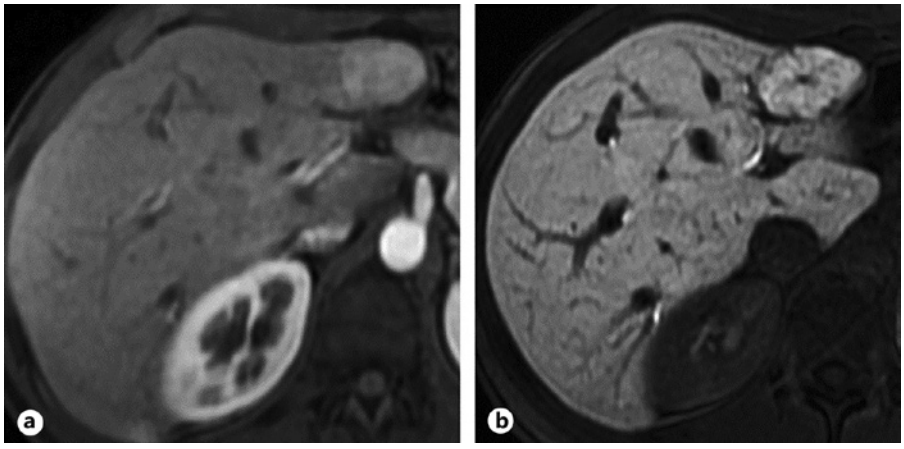

Fig. 3. Magnetic resonance 3D gradient-echo T1 fat saturation sequence after the injection of hepato-specific contrast on arterial phase (**a**) and hepatobiliary phase (**b**). **a** Unspecific arterially enhancing liver lesion on segment II. **b** typical FNH enhancing pattern, without enhancement on central scar.

been given by the presence of the central scar; the lesions initially measured 8.1 and 10.6 cm each and maintained proximity to vascular structures, with subsequent growth rates of 25.9 and 27% respectively. In both cases, the results of the anatomical-pathological examination confirmed the diagnosis of FNH, but there was a need to perform immunohistochemistry in only 1 of these cases.

Of all cases, only 5.5% (3/54) of the patients received some type of treatment. One patient underwent surgical treatment at inclusion in the study, 1 underwent arterial embolization during follow-up, and 1 underwent laparoscopic enucleation (liver segment VI) due to a history of colon cancer and typical FNH lesion on MRI-LSC with significant growth (from 2.0 to 3.2 cm) of the lesion in 2 years. Intraoperative biopsy confirmed the diagnosis of FNH.

Discussion/Conclusion

The diagnosis of BSLLs has changed substantially in recent years. Twenty years ago, for example, an FNH diagnosis consisted mainly of a combined analysis of ultrasound, CT scan, nuclear medicine exams and, in those undergoing biopsy, routine pathology examination was done. At that time, due to the low accuracy levels of these methods, many asymptomatic patients underwent surgical treatment due to diagnostic doubt [9]. In particular, in the last 10 years, considerable progress has been made in the diagnosis of BSLLs, in particular, FNH.

The following are the two most significant factors associated with an important gain in accuracy in the diagnostic certainty of FNH: (i) the clinical use of liver-specific contrast, associated with MRI, which has the capacity to be excreted in the bile duct [10]; and (ii) the description of the map-like pattern of glutamine synthetase expression in the immunohistochemical study of lesion biopsy, described by the Bordeaux group [7, 8].

Nevertheless, although some authors have observed a reduction in the number of surgeries performed in patients with FNH, many patients with FNH are still operated upon [6]. In fact, currently, there are no studies with a good level of evidence that can clearly define the best management course for FNH [5, 11].

The present study was conducted with the intention of offering additional exams with high diagnostic accuracy (MRI-LSC and biopsy with immunohistochemical examination) to a group of patients with suspected FNH and doubtful diagnosis on conventional CT and MRI scans, and the goal was to reduce diagnostic doubt as a surgical indication for FNH significantly.

With this goal and based on our personal experience of the good clinical evolution of FNH patients with conservative treatment, we propose that only a tiny portion of these patients have a surgical indication. Of a total of 54 patients with a mean follow-up time of 35.5 months and an average of 2 CT/MRI exams performed sequentially, only 2 patients (3.7%) were treated due to abdominal pain, and in many cases, there were no additional symptoms or other complications during follow-up.

Classically, the incidence of surgery in patients with presumed FNH remains approximately 21.6–51.4% [6, 11–15]. There are 2 main reasons for this high incidence. First, in a significant portion of patients, the difficulty in differentiating FNHs from adenomas and malignant le-

sions with routine exams – ultrasound, CT and MRI – is quite variable in the various types of studies and is inversely related to the use of specific exams for diagnostic investigation.

In contrast, in case series using conventional exams, Perrakis et al. [12], Mezhir et al. [6] and Hau et al. [11] indicated surgery due to diagnostic doubt in 16.1, 38.2, and 47.8% of patients, respectively; in the study of Bieze et al. [13], a large number of patients (66.1%) combined with MRI-LSC in which liver biopsy with immunohistochemistry was used, this incidence was zero. With the incorporation of these tests with higher diagnostic accuracy, a progressive and noticeable reduction of this type of surgical indication is expected.

The second and primary reason for the surgical indication is more complex and related to the presence of clinical symptoms. In this case, there is an even greater discrepancy between studies. While Dardenne et al. [14] observed an incidence of 23% of patients with surgical indication due to symptoms in their series, Bieze et al. [13] observed that the presence of symptoms was responsible for all surgical indications in his series.

If there is difficulty in grading a subjective symptom such as pain, there may be concern and fear that the patient has a malignant disease that may be contributing to the intensification of the pain perceived by the patient, an aspect discussed in Hau et al. [11]. Although these authors reported that the presence of symptoms was the primary cause for surgical indication in their series (46%), when the operated patients themselves retrospectively filled out a form indicating the cause for the surgery, only 12% cited impaired quality of life, whereas other causes, such as fear of malignant disease, fear of complications without treatment, doctor's recommendation and other concerns, were cited by 82, 19, 43, and 23%, respectively.

Another curious fact is that a portion of the patients, if not all, who initially present with symptoms and underwent conservative treatment, experienced pain resolution. Ramírez-Fuentes et al. [16] studied 30 patients with 44 presumed FNHs and observed that all 8 patients who initially had pain symptoms had spontaneous resolution unrelated to changes in lesion size. Similarly, Dardenne et al. [14] also observed complete resolution of pain in all patients undergoing conservative treatment who, at the time of study inclusion, reported mild and nonspecific symptoms. These findings suggest the inaccuracy of the causal relationship between pain and FNH.

The first study to report a very low incidence of surgery in presumed FNH and very close to that found by us was conducted by Bröker et al. [17]. In a retrospective study published in 2017, the authors evaluated 162 patients and established the diagnosis of FNH by the combined analysis of at least two imaging exams among contrast enhanced MRI, enhanced CT scan and contrast enhanced USG. In 11.1% of the patients, lesion biopsy was necessary. With a minimum follow-up of 6 months, only 9 patients (5.5%) required surgical treatment: 5 due to symptoms and 4 because of uncertain diagnosis (lesion growth). Only 1 of the patients operated on for pain experienced symptom relief.

The developments in laparoscopic hepatectomy in recent years have been engaging. Laparoscopic resection for benign tumors is associated with less blood loss, less need for analgesics, more rapid feeding after surgery, shorter hospital stays and reduced incidence of complications, according to the recent first European consensus on laparoscopic liver surgery [18].

Excellent results have been used as an argument for some authors to more liberally indicate surgery for patients for this type of tumors [12]. We agree that surgery plays a vital role in patients with unclear diagnostic or symptoms related to FNH. The question that still remains is as follows: which patients fall under these categories? It does not seem conceivable to us to consider that liver lesions are indeterminate and to indicate surgical treatment – as low as its morbidity may be – for an innocuous lesion such as FNH when new exams with high diagnostic capacities are currently available.

Moreover, it seems appropriate to us to reassure patients – with symptoms that often only appear after the incidental diagnosis of the lesion or with non-disabling symptoms – and to follow them up no less than 6 months. This period is sufficient for a careful investigation of other pain causes, and it is also useful for evaluating the progression of the patient's pain complaint. Moreover, it seems appropriate to patients with symptoms that often only appear after the incidental diagnosis of the lesion or that with non-disabling symptoms, to follow them up no less than 6 months. This period is sufficient for a careful investigation of other pain causes, and it is also useful for evaluating the progression of the patient's pain complaint.

The present study has some limitations: first, the series consists of a small number of patients; second, the diagnosis of FNH was only presumed from an analysis of the surgical specimen removed, which could have allowed the inclusion of non-FNH cases in the series. Although

possible, this is very unlikely to have occurred, since we use very specific and highly accurate diagnostic tests. Finally, a longer follow-up time would have been valuable in the validation of our conclusions.

The present study suggests that it is safe to manage patients with FNH presumed by highly accurate imaging tests conservatively, with a low rate of surgical treatment required (3.7%). As with hepatic hemangiomas, surgery for FNH should be an exception.

Ethics Statement

We conducted this study after obtaining the approval of the Ethics Committee of University Hospital Onofre Lopes.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

References

1 Amico EC, Alves JR, Souza DLB, Salviano FAM, João SA, Liguori AAL: Hypervascular liver lesions in radiologically normal liver. Arq Bras Cir Dig 2017;30:21–26.
2 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.
3 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.
4 Marrero JA, Ahn J, Rajender Reddy K; Americal College of Gastroenterology: ACG clinical guideline: the diagnosis and management of focal liver lesions. Am J Gastroenterol 2014; 109:1328–1347.
5 European Association for the Study of the Liver (EASL): EASL clinical practice guidelines on the management of benign liver tumours. J Hepatol 2016;65:386–398.
6 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.
7 Bioulac-Sage P, Laumonier H, Rullier A, Cubel G, Laurent C, Zucman-Rossi J, Balabaud C: Over-expression of glutamine synthetase in focal nodular hyperplasia: a novel easy diagnostic tool in surgical pathology. Liver Int 2009;29:459–465.
8 Bioulac-Sage P, Cubel G, Taouji S, et al: Immunohistochemical markers on needle biopsies are helpful for the diagnosis of focal nodular hyperplasia and hepatocellular adenoma subtypes. Am J Surg Pathol 2012;36:1691–1699.
9 Weimann A, Ringe B, Klempnauer J, Lamesch P, Gratz KF, Prokop M, Maschek H, Tusch G, Pichlmayr R: Benign liver tumors: differential diagnosis and indications for surgery. World J Surg 1997;21:983–990.
10 Merkle EM, Zech CJ, Bartolozzi C, Bashir MR, Ba-Ssalamah A, Huppertz A, Lee JM, Ricke J, Sakamoto M, Sirlin CB, Ye SL, Zeng M: Consensus report from the 7th iInternational forum for liver magnetic resonance imaging. Eur Radiol 2016;26:674–682.
11 Hau HM, Kloss A, Wiltberger G, Jahn N, Krenzien F, Benzing C, Schmelzle M, Seehofer D, Atanasov G, Bartels M: The challenge of liver resection in benign solid liver tumors in modern times – in which cases should surgery be done? Z Gastroenterol 2017;55:639–652.
12 Perrakis A, Demir R, Müller V, Mulsow J, Aydin Ü, Alibek S, Hohenberger W, Yedibela S: Management of the focal nodular hyperplasia of the liver: evaluation of the surgical treatment comparing with observation only. Am J Surg 2012;204:689–696.
13 Bieze M, Busch OR, Tanis PJ, Verheij J, Phoa SS, Gouma DJ, van Gulik TM: Outcomes of liver resection in hepatocellular adenoma and focal nodular hyperplasia. HPB (Oxford) 2014;16:140–149.
14 Dardenne S, Hubert C, Sempoux C, Annet L, Jouret-Mourin A, Horsmans Y, Van Beers BE, Zech F, Gigot JF: Conservative and operative management of benign solid hepatic tumours: a successful stratified algorithm. Eur J Gastroenterol Hepatol 2010;22:1337–1344.
15 Bonney GK, Gomez D, Al-Mukhtar A, Toogood GJ, Lodge JP, Prasad R: Indication for treatment and long-term outcome of focal nodular hyperplasia. HPB (Oxford) 2007;9: 368–372.
16 Ramírez-Fuentes C, Martí-Bonmatí L, Torregrosa A, Del Val A, Martínez C: Variations in the size of focal nodular hyperplasia on magnetic resonance imaging. Radiologia 2013;55: 499–504.
17 Bröker MEE, Klompenhouwer AJ, Gaspersz MP, Alleleyn AME, Dwarkasing RS, Pieters IC, de Man RA, IJzermans JNM: Growth of focal nodular hyperplasia is not a reason for surgical intervention, but patients should be referred to a tertiary referral centre. World J Surg. 2018;42:1506–1513.
18 Abu Hilal M, Aldrighetti L, Dagher I, Edwin B, Troisi RI, Alikhanov R, Aroori S, Belli G, Besselink M, Briceno J, Gayet B, D'Hondt M, Lesurtel M, Menon K, Lodge P, Rotellar F, Santoyo J, Scatton O, Soubrane O, Sutcliffe R, Van Dam R, White S, Halls MC, Cipriani F, Van der Poel M, Ciria R, Barkhatov L, Gomez-Luque Y, Ocana-Garcia S, Cook A, Buell J, Clavien PA, Dervenis C, Fusai G, Geller D, Lang H, Primrose J, Taylor M, Van Gulik T, Wakabayashi G, Asbun H, Cherqui D: The southampton consensus guidelines for laparoscopic liver surgery: from indication to implementation. Ann Surg 2018;268: 11–18.