Benign focal liver lesions
From diagnosis to treatment

Türkan Terkivatan

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Benign Focal Liver Lesions
From Diagnosis to Treatment

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"Amor que no es locura no es amor".
"Love that is not madness is not love".

Pedro Calderón de la Barca.

CONTENTS

Chapter 1

General introduction and outline of the thesis

1.1 A HISTORICAL OVERVIEW

In 1970, Janet Baum of Ann Arbor submitted a paper to the Journal of the American Medical Association suggesting, on the basis of 3 cases, that oral contraceptives might be implicated in the development of benign hepatic tumours in young women. To her annoyance, the editors rejected the paper with the comment that her suggestion was ridiculous. The first two published reports of hepatocellular adenoma in women using oral contraceptives appeared in 1971 and 1972[1,2]. However, in neither case did the author speculate on a possible etiological relationship between oral contraceptives and hepatic tumours, so that the credit must go to Baum and her colleagues for drawing attention to this possibility in their report of seven cases which appeared in Lancet in 1973[3]. This paper excited great interest and touched off an avalanche of similar reports.

After that, Dr. Gerald Klatskin presented a paper at a meeting held at Kurume University in Japan in 1977, where he outlined the possible relationship of hepatic tumours to the use of oral contraceptives, and expressed his concern that "…hepatic tumours may prove to be an even more serious problem than thromboembolic disease as a complication of oral contraceptives"[4]. At this meeting, he gave an overview of the clinical course of benign liver lesions in a group of patients with prolonged follow-up. Once one reads this paper it is remarkable that most insights on nature and clinical course of these benign lesions did, in fact, not change. Nowadays, there is still little evidence on aetiology, pathogenesis, and treatment of these benign tumours. And still, we are confronted with serious complications as haemorrhage and malignant transformation.

The large and confusing terminology that has been used to identify different hepatic lesions, such as hepatic adenoma, hepatoma, adenomatosis, nodular transformation, multiple nodular hyperplasia and focal nodular hyperplasia, has led to an International Working Party on nodular diseases of the liver[5]. The working party was raised and sponsored by the World Congress of Gastroenterology 1994 in order to standardise the terminology applied to diseases of the liver.

Having reached the stage of diagnosis and treatment, there are a lot of controversies in the literature. The increased availability and routine use of highly advanced radiological modalities improved the detection of small hepatic lesions. As a consequence, there is an increased incidence of incidentalomas of the liver that are more often benign than malignant[6,7]. However, an accurate characterisation of these incidentalomas may be impossible with a single imaging modality, especially because of the limited phases due to the routine nature and radiation hazards of the investigation[8]. On the other hand, a lot of nuclear and radiological modalities have been described to discriminate benign and malignant tumours and to obtain a differential diagnosis. The various entities that must be considered in the differential diagnosis creates the need for a clear management strategy.

With concern to treatment of benign liver lesions, one should realise that there is no high level of evidence in the literature. Different treatment or management guidelines have been proposed based on observational reports and personal experiences. This stresses the need for a critical review of these reports and to define criteria for observation, surgery, or other interventional techniques in the management of benign liver lesions. Furthermore, it should be questioned if a world-wide well-organised data-base can be implemented to collect data and experience with benign liver tumors in order to handle with more evidence.

The following personal communication we had with a hepatobiliary surgeon clearly illustrates the low level of evidence concerning a management aspect of hepatocellular adenoma.

"Considering your wide experience with the management of liver tumors, we would like to ask your opinion about a challenge we encountered in our clinic about hepatocellular adenomas. We are wondering what would be your advice to a young female patient who has been operated on a hepatocellular adenoma and wants to use oral contraceptives again. In the literature we could not find any clarifying evidence or case reports that answers this problem. Dou you think it is reasonable that a general sensitivity to steroid hormones do exist in the whole liver?"

"In brief, my colleagues and myself would unequivocally dissuade your young patient from any further use of oral contraceptives. Clearly, even though the incidence of hepatocellular adenomas has been reduced with the current dose of estrogens used, we still believe the risk of recurrence is significant in those women who have developed hepatocellular adenomas on oral contraceptives. Moreover, there is a slight increase in risk of hepatocellular carcinoma with the long-term use of oral contraceptives again, though diminished with current dosages used. Given the nearly equally effective alternatives to contraception compared to oral contraceptives, we would recommend alternative prevention methods. I concur that once present, the sensitivity of that liver to subsequent adenomas is increased. I do not have specific references that I can cite at this time, however, this recommendation is the current recommendation at our Clinic." *D.M. Nagorney. Mayo Clinic, Rochester, Minnesota, USA.*

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1.2 OUTLINE OF THE THESIS

In **chapter 2**, a review of the literature concerning diagnosis and treatment of the most common benign liver lesions is performed. In *part 2.1*, we describe the epidemiology, aetiology, histological and imaging characteristics of these lesions. Furthermore, we discuss the role of state-of-the-art MR imaging versus the role of needle biopsy during differential diagnosis, and formulate the indications for surgery based on recent literature and our own experience *(part 2.2)*.

Chapter 3 of this thesis deals with the management of giant haemangioma. Lesion size and the potential for complications, such as rupture and a consumptive coagulopathy, are still reasons for a surgical treatment of hepatic haemangioma, even when the lesion is an incidental finding. In this part, we report on a study of giant haemangiomas with a long-term follow-up, either after a surgical or conservative treatment.

In **chapter 4**, some specific aspects of hepatocellular adenoma are discussed. In *part 4.1*, we describe a case of hepatocellular adenoma detected during pregnancy and consider the reasons for surgical therapy. In *part 4.2*, we report our own experience with ruptured hepatocellular adenoma, and formulate an algorithm for management of this emergency situation. Another challenge that may be encountered during differential diagnosis of a focal liver lesion is the distinction between a hepatocellular adenoma and a well-differentiated hepatocellular carcinoma, which we line out in *part 4.3*.

In **chapter 5**, focal nodular hyperplasia of the liver is studied in detail. In *part 5.1,* we describe the spectrum of typical and atypical features of focal nodular hyperplasia at state-of-the-art MR imaging, ultrasonography, computed tomography, and histopathology. In *part 5.2,* we performed a prospective cohort study, in which we studied lesion characteristics of focal nodular hyperplasia at state-of-the-art MR imaging including dynamic Gadolinium-enhanced and a tissue specific contrast agent (superparamagnetic iron-oxide). Finally, we report on a treatment modality of focal nodular hyperplasia with transcatheter arterial embolisation in *part 5.3*.

Chapter 2

Benign liver tumors: a general review

2.1

Diagnosis and treatment of benign focal liver lesions.

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DIAGNOSIS AND TREATMENT OF BENIGN FOCAL LIVER LESIONS

ABSTRACT

Background: With the routine use of improved imaging modalities more benign liver lesions are detected nowadays. An accurate characterisation of these incidental lesions may be a challenge, and frequently a biopsy or even unnecessary surgery is being performed. However, these interventions are not always to the benefit of the patient.

Methods: A Medline search of studies relevant to imaging diagnosis and management of the most common, benign, solid and non-solid liver lesions was undertaken. References from identified articles were handsearched for further relevant articles. The authors' own experience with benign liver lesions was also taken into account.

Results: Although atypical imaging features are the exception rather than the rule, it is sometimes difficult to differentiate between benign and malignant lesions and knowledge of their imaging features is essential to avoid unnecessary work-up. The use of tissue specific contrast media, which has clearly improved the accuracy of highly advanced radiological techniques, may be helpful during differential diagnosis. Once having established an accurate diagnosis, it is rarely indicated to perform surgery for a benign liver lesion, because of its asymptomatic nature.

Conclusion: Knowledge of imaging features and a clear management strategy during diagnostic work-up, emphasising the indications for surgery will minimalise the number of patients who have to undergo biopsy or unnecessary surgery.

INTRODUCTION

Solitary focal liver lesions in a noncirrhotic liver often present as incidental finding during routine abdominal imaging as part of a general check-up, or during work-up in case of a known malignancy[1,2]. Only in some cases, liver tumours may be symptomatic[3,4].

The most important diagnostic challenge involves differentiating benign tumours from pre-malignant or malignant lesions. Especially during work-up of a known malignancy a correct diagnosis of a liver lesion is essential for an adequate staging, thereby preventing an over-, or undertreatment of malignant disease. However, there are still patients who do undergo unnecessary biopsy or surgery because of a presumed malignancy or because of uncertainty in the diagnosis despite an extensive work-up[5-7]. Even after having diagnosed a benign lesion, the most appropriate treatment still may remain controversial, as in case of a hepatocellular adenoma.

For these reasons, a clinical review of benign liver tumours that emphasises diagnostic work-up and the indications for surgery is warranted. A Medline search of studies relevant to epidemiology, pathogenesis, diagnosis and management of benign solid and non-solid liver lesions was undertaken. References from identified articles were handsearched for further relevant articles.

SOLID LESIONS

Hepatocellular adenoma

One of the problems that a hepatobiliary surgeon may be confronted with is the presence of a centrally located liver lesion in a healthy young woman, suspected of being a hepatocellular adenoma.

Hepatocellular adenoma is a benign liver tumour that occur more frequently in women in their third and fourth decades[8,9]. Following the introduction of oral contraceptives in the 1960s, reports began to emerge about the association of oral contraceptives and hepatocellular adenoma[10]. Epidemiological studies reported that the relative risk of hepatocellular adenoma was 25.0 for women who used oral contraceptives for more than 9 years compared with those who used oral contraceptives for less than one year[11,12]. An incidence has been calculated of 3 to 4/100,000 in long-term users of oral contraceptives. Recent data do not reveal an increased risk for women using modern low-dose oral contraceptives[13]. Although rare, hepatocellular adenomas are known to occur in patients without a history of hormone use[2,14,15]. Spontaneous development has also been observed in patients with glycogen storage disease, in that case often a precursor of hepatocellular carcinoma[16,17]. The tumour is uncommon in men, but may be associated with the use of anabolic steroids[18,19]. The female: male ratio ranges from 3.9:1 to 11:1[9].

The pathogenesis is speculative but a consensus indicates that this is an end consequence of general vascular ectasia caused by oral contraceptives and related synthetic steroids, which leads to a benign clonal proliferation of hepatocytes[20]. In patients who have been advised to discontinue oral contraception, regression of hepatocellular adenoma has been described within months[21]. However, persistent growth of the tumour after cessation of steroids can occur as well[22].

Especially large hepatocellular adenomas (> 5 cm) do have a potential for spontaneous rupture and bleeding, causing haemoperitoneum and shock[2,23]. Spontaneous rupture occurs more often in steroid users than in nonusers, and is the mode of presentation in 50-65 per cent of patients taking oral contraceptives[24,25]. Especially during pregnancy, and durante- or post-partum there is an increased risk for haemorrhage due to the high levels of sex steroids and increased vascularity of the liver[25].

Foster and Berman have focussed attention on the potential of hepatocellular adenoma for malignant transformation[26]. It might be argued that this malignant transformation merely reflects the incorrect diagnosis of hepatocellular adenoma in cases of well-differentiated hepatocellular carcinoma. However, Tao suggested that hepatocellular adenoma itself is not a premalignant lesion and may undergo reversible changes after withdrawal of causative agents, whereas foci or areas of liver cell dysplasia arising within adenomas are irreversible, premalignant changes and eventually progress to hepatocellular carcinoma[27].

Histology

Grossly, hepatocellular adenoma are very well circumscribed and possess a pseudocapsule that is formed from compressed and collapsed surrounding hepatic parenchyma[28]. There may be focal areas of haemorrhage and degeneration. On histological examination the hepatocytes in the lesion are identical to those in the surrounding liver, but contain a large amount of fat and glycogen, which contribute to the imaging appearance. The hepatic plate may be two or more cells thick, and rosettes may be seen, which suggest increased hepatocyte proliferation in the lesion. The absence of bile ducts and portal triads makes this lesion a pure growth of hepatocytes.

Differentiation of hepatocellular adenoma from a well-differentiated carcinoma may be difficult, or even impossible. Modern cytopathological techniques such as cytophotometric analysis of DNA content underline the correlation of aneuploidy with the presence and grade of differentiation of hepatocellular carcinoma[29]. Analysis of cytogenetic aberrations in hepatocellular carcinoma may also provide a potential solution to problematic histological queries. Comparative genomic hybridisation and fluorescence *in situ* hybridisation revealed typical aberration patterns not only in moderate or poorly differentiated hepatocellular carcinoma but also in well-differentiated samples[30,31]. These aberrations were strikingly different from the low number of aberrations detected in hepatocellular adenoma[30]. Although these techniques may reduce the uncertainty of distinguishing benign lesions from well-differenti-

ated carcinoma, they are based on an elaborate and time consuming procedures of full tissue samples making it difficult to apply in small biopsies in daily routine.

Radiology

Hepatic adenomas lack predictable diagnostic features on ultrasonography (US), which as a sensitivity of about 30%[2]. Although hepatic adenomas are mostly isodense to the surrounding liver on plain computed tomography (CT), they may show variable densities. These smooth well-defined lesions often show a subtle homogeneous blush during arterial phase fastly fading to nearly isodensity during portal or delayed phases[32]. Hepatic adenomas may show intralesional hypo or hyperdensities, depending on the presence or absence of necrosis or haemorrhage. On magnetic resonance (MR) imaging hepatic adenomas have mildly low to moderately high signal intensity on T1-weighted images, and mildly high signal intensity T2-weighted images. A characteristic feature is that of decreased signal intensity on out-of-phase T1-weighted (or fat suppressed) images because of their fat content[33,34]. They may contain areas with high signal intensity on both T1-weighted and T2-weighted images because of intra-tumoural haemorrhage. The typical enhancement features are, according to the hypervascular nature of the lesion, uniform, moderately intense enhancement on immediate post-gadolinium images, and relatively rapid fading to isointensity on subsequent images. It is sometimes difficult to distinguish adenomas from hepatocellular carcinomas, based on the MR imaging features. Clinical history, and the availability of tissue specific MR contrast media targeting either the Kupffer's cells or hepatocytes will improve the specificity of MR imaging[33,35,36].

This same principle was used in nuclear imaging in the past. Hepatic adenomas may lack Kupffer's cells which concentrate colloid used in nuclear HIDA scanning[37]. Consequently, with colloid imaging, 80% of lesions are cold defects[3,38,39]. In case of uptake (20%), excretion of the agent does not occur because hepatic adenomas lack bile ductules for normal excretion.

Treatment

Since the two clinical concerns in a patient with hepatocellular adenoma are bleeding and progression to hepatocellular carcinoma, the discovery of a hepatocellular adenoma is a reason for resection for most surgeons[1,14,40]. 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 (Figure 1)[2,23]. A conservative approach by a radiological follow-up (e.g. 6 monthly) may be justified with smaller hepatocellular adenomas, even in case of bleeding.

Patients have to be advised to stop steroid use and to avoid pregnancy. Ruptured hepatocellular adenoma during pregnancy is associated with a high foetal as well as maternal mortality rate (50-60%)[41,42]. This might be caused by a serious delay in diagnosis because of confusion with other pregnancy related diseases, like preeclampsia or pulmonary embolism,

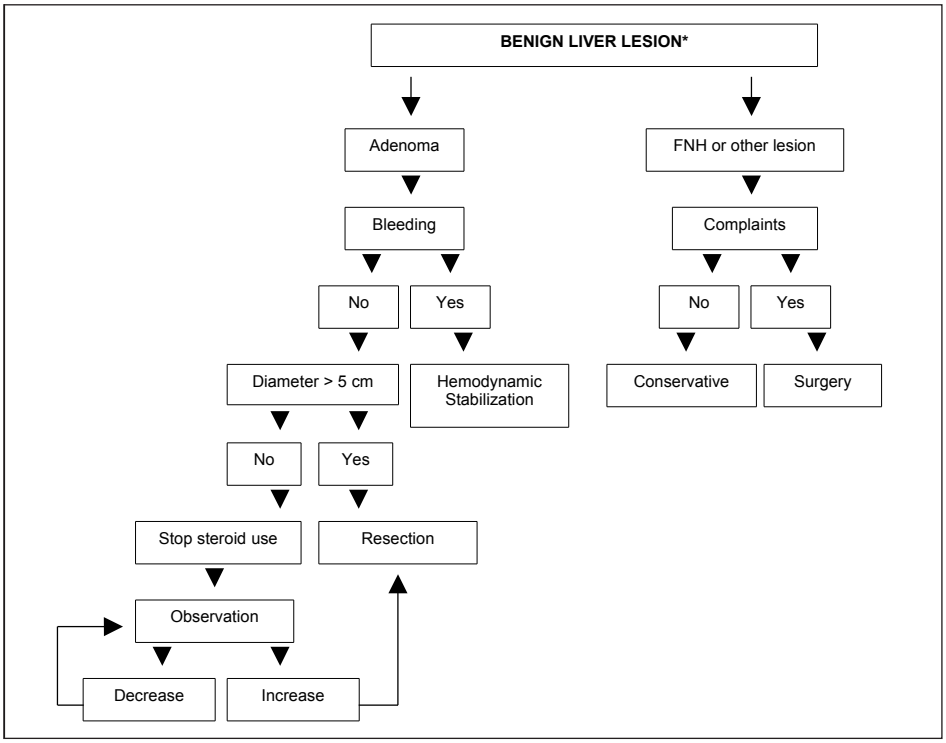

Figure 1. Algorithm for management of solid benign liver lesions.
* There is no sign of liver cirhosis

which leads to a poor general condition prior to surgery. Large hepatocellular adenomas that are detected during pregnancy should be resected because of the high risk of rupture[42]. A surgical procedure can be performed during the second trimester when surgical risks are minimal for both the mother and the foetus[43].

Arterial embolisation should be considered as an alternative to surgical treatment in case of a large and centrally located lesion with a considerable risk of surgery, especially when there is a desire for pregnancy.

Focal nodular hyperplasia

Focal nodular hyperplasia (FNH) is one of the least controversial benign liver lesions for the clinician, and typically is an incidental finding in women during their reproductive years. Cases have been reported in men and children[44]. The female:male ratio ranges between 6:1 to 8:1[45]. Although considered as a rare neoplasm, FNH is the second most common benign liver tumour after haemangioma and has a reported frequency of 3% in adults[46].

There are two theories regarding the pathogenesis of FNH. Congenital vascular malformations as teleangiectasies and arteriovenous malformations, or vascular injury has been suggested as the underlying mechanism for a hyperplastic response of liver parenchyma[47,48].

There is some evidence, however, that FNH is a proliferative lesion with a clonal nature[49]. These data suggest that the cells in the lesion may arise from one pluripotent progenitor cell capable of differentiating into hepatocytes and biliary epithelial cells. Although the relationship between the occurrence of FNH and the use of oral contraceptives has been discussed a long time, this association with steroids has been denied more recently[50]. Compared with hepatocellular adenoma, which was quite uncommon before the introduction of oral contraceptives in 1960, FNH has been frequently described in autopsy series published before 1960[51,52].

Histology

On gross examination, FNH tends to be lobulated and usually has a central stellate scar radiating into nodules of normal hepatocytes, which is histopathologically detected in as many as 83%[3]. The lesion is sharply demarcated from the surrounding liver, but does not have a tumour capsule[53,54]. A pseudocapsule may be prominent as a result of compression of the surrounding liver parenchyma by the tumour, and inflammatory reaction. Microscopically, there are some characteristic features of FNH[53]. First, the central scar contains fibrous connective tissue with inflammatory cells and large tortuous arteries with its sources from the branches of the hepatic artery that provides excellent arterial blood supply in the form of a capillary network to the individual nodules of the lesion. Second, the nodules lack normal lobular architecture and are devoid of portal triads. Within the nodules, relatively large veins drain blood from the sinusoids toward the main hepatic vein. There is no direct connection between the abnormal arteries and the veins[54]. The proliferating cells are practically identical to the surrounding hepatocytes, and Kupffer's cells are identified in the sinusoidal spaces. Third, there are areas of dense bile duct proliferation that do not connect to the biliary tree.

Radiology

On US, FNH is often isoechoic to normal liver and therefore, it may be difficult to detect. The lesion is mostly homogenous (60%) and a large or prominent central scar, which is sonographically detected in 19-40%, is considered as a characteristic feature[55]. As in case of hepatic adenomas, the sensitivity of US is also low for FNH[2]. Most lesions are isodense or slightly hypodense to the liver on unenhanced CT[56,57]. The typical contrast enhancement pattern of FNH, being a hypervascular lesion with its vascularity from the hepatic arterial system, is immediate homogeneous hyperdense enhancement on early phases (arterial and early portal venous) becoming isodense to the liver on late portal venous and delayed images. An enlarged central feeding artery is present in 60%[58]. The absence of contrast retention on late phases is one of the most important characteristics of FNH. The central scar, which is hypodense on unenhanced images, shows a gradual enhancement on portal venous and delayed images[58,59]. This delayed enhancement is caused by the presence of abundant fibrous stroma in the scar. Especially, the presence of a characteristic central scar (20%-65%)[32,58],

which is radiating in a spoke-wheel pattern from the periphery to the centre of the tumour is highly supportive of FNH[58]. However, a central scar may be seen in other lesions such as giant haemangioma, large hepatocellular carcinomas, and fibrolamellar carcinoma[60]. On MR imaging, FNH usually presents as a homogeneous, iso- or hypointense lesion on T1-weighted images, and a slightly hyper- or isointense lesion on T2-weighted images (94-100%)[33,61]. The central scar typically has a low signal intensity on T1-weighted images and a high signal intensity on T2-weighted images. FNH shows an intense uniform enhancement on immediate postgadolinium images and fades rapidly to near isointensity. The central scar, being hypointense on early MR images, shows enhancement on delayed phases. A central scar is visible in up to 85% on T2-weighted images, while contrast enhanced CT scans may detect it in 65% of the lesions[32,56]. The development of tissue-specific contrast agents like mangafodipir trisodium and reticuloendothelial agents such as ferumoxides provide new possibilities for lesion characterisation on the basis of its cellular composition and function rather than its vascularity and diffusion within its extracellular space[33,35]. High accuracy rates of MR imaging has been reported for characterisation of FNH and for differentiation from other focal liver lesions, especially from hepatic adenoma and fibrolamellar carcinoma[62,63].

The ability to show Kupffer's cell activity in FNH has historically made technetium-99m sulphur colloid scintigraphy a diagnostic modality for this lesion[64]. In addition to the Kupffer's cell activity, the vascular supply of the tumour may additionally contribute to its uptake of the sulphur colloid[56]. Overall, 50% of tumours show uptake similar or greater to that of normal liver, and 50% show less uptake than normal liver[3]. Unfortunately, other hepatocellular neoplasms that may contain Kupffer's cells, such as hepatocellular adenoma and hepatocellular carcinoma, can also show sulphur colloid uptake[3,60]. Thus, the uptake of sulphur colloid can suggest the diagnosis of FNH, but is not pathognomonic. At our clinic, we rely on T1- and T2-weighted gadolinium enhanced MR imaging with or without tissue specific contrast agents.

Treatment

When the diagnosis of FNH is certain, treatment is rarely indicated (Figure 1). A conservative approach for asymptomatic lesions is well established because there is no predisposition to haemorrhage or malignant transformation and symptoms may resolve during follow-up[9,14,15,40,46].

Some authors have expressed concern about the progression of FNH during pregnancy. Two recent reports by Weimann et al and Mathieu et al failed to demonstrate any increase in tumour size and any other complications as bleeding during pregnancy[50,65].

Nevertheless, large lesions (>5 cm) may be responsible for abdominal complaints, especially if located in the left liver lobe. In case of a symptomatic lesion, a surgical intervention can be considered.

Transcatheter arterial embolisation has been increasingly useful as a less invasive percutaneous tumour ablation technique in a variety of liver lesions[66,67]. As it has been suggested that

FNH is a hyperplastic response of hepatic parenchyma to a congenital arterial malformation, embolisation appears to be a logical treatment option[68]. Besides, the presence of a central feeding artery makes this method more feasible[69]. Transcatheter arterial embolisation should be considered as a safe and effective alternative to a surgical treatment of symptomatic FNH, especially those with a considerable risk for surgery because of localisation[70].

Angiomyolipoma

Angiomyolipoma of the liver is a rare benign mesenchymal tumour morphologically similar to the more common angiomyolipoma of the kidney. Although the association of renal angiomyolipoma in patients with tuberous sclerosis has been reported in 40-50% of cases[71], this association is less common in case of hepatic angiomyolipomas[72].

There is speculation that all the components of angiomyolipoma may arise from a common precursor cell in the perivascular space, the pericyte; the various morphologic cell types noted in the tumour may, therefore, represent different developmental stages of this precursor cell[73].

Symptoms attributed to a liver mass may be noted in the larger tumours[72,74].

Histology

Grossly, angiomyolipomas are circumscribed, soft masses. Its histological composition, which is characterised by an admixture of mature fat cells, blood vessels, and smooth muscle cells with a large variety in the proportions of the various components in different parts of individual tumours and from case to case, largely determines its radiological appearance.

Radiology

Ultrasonographic examination of the lesion usually shows a hyperechoic mass[75]. On plain CT the lesion commonly appears as a well-defined, heterogeneous hypoattenuating mass. After contrast administration a marked early and prolonged enhancement is usually seen[74,75]. On MR imaging, angiomyolipomas often show high signal intensity on both T1- and T2-weighted images, and a low signal intensity on fat-suppressed images, reflecting their high fat content[33]. They may show diffuse and heterogeneous enhancement on immediate postgadolinium spoiled gradient echo (GRE) images. Common to most reports in the literature is the initial misdiagnosis of this lesion by radiological and histopathological examination, most probably because of the infrequency with which this tumour is encountered[72,76]. The most common errors in diagnosis are other fat-containing liver lesions as lipoma, hepatocellular carcinoma, adenoma, liposarcoma or focal fatty infiltration reflecting the heterogeneity and varying proportions of cell types encountered in the lesion.

Treatment

Surgical resection is not necessary unless there is associated pain, which occasionally results from intratumoural haemorrhage[74]. No malignant counterpart, malignant transformation, or extrahepatic metastases of angiomyolipoma has been reported, although several cases of malignant counterparts of this tumour in the kidney have been reported. Therefore, a conservative approach by follow-up of the lesion is sufficient if the diagnosis of angiomyolipoma is established (Figure 1).

NON-SOLID LESIONS

Simple hepatic cysts

Simple hepatic cysts may be solitary or multiple. They usually are asymptomatic lesions that are detected incidentally, and do not have a clinical significance. However, at the same time, small hepatic cysts are lesions that most commonly cause clinical concern during work-up of an extra-hepatic malignancy.

Epidemiological studies report a prevalence of 0.17-5%, which clearly increases with age[77]. The female:male ratio is approximately 4:1[45].

The pathogenesis of simple hepatic cysts is poorly understood and may be related to congenital lymphatic obstruction, to faulty development or fusion of intrahepatic bile ducts, or to stenosis and obstruction of aberrant bile ducts[78].

Isolated hepatic cysts grow very slowly. Hence, they usually do not cause symptoms in patients younger than 40 years[79]. Solitary hepatic cysts that become symptomatic typically have diameters larger than 5 cm and present as a dull, vague right upper-quadrant discomfort or fullness. Rarely, hepatic cysts present with acute symptoms due to intracystic haemorrhage, or superinfection of the cyst[80,81].

Histology

Hepatic cysts contain various amounts of fluid, which may be clear, mucoid, bloody, or bile stained. Histologically, they are generally lined with flattened cuboidal or columnar epithelium that resembles bile duct epithelium and have a basement membrane surrounded by a fibrous layer.

Radiology

A simple hepatic cyst has to be differentiated from infectious cysts (echinococcal cysts, abscesses), from pre-malignant or malignant cysts as cystadenomas and cystadenocarcinomas, and from metastases of extra-hepatic cancer. On US, the cyst is usually hypoechoic and thin walled with sharp, smooth margins and shows increased transmission of ultrasound through the lesion, resulting in posterior acoustic enhancement[82]. On CT, cysts can be seen

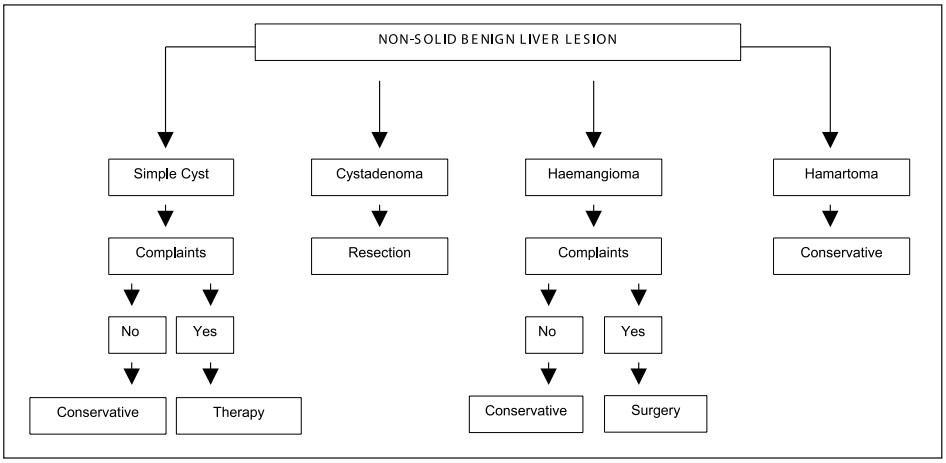

Figure 2. Algorithm for management of non-solid benign liver lesions.

as sharp, smooth-walled, hypodense lesions of homogeneous density that do not enhance after intravenous injection of contrast. Acute intracystic haemorrhage may produce a higher density, whereas older haemorrhage lacks this characteristic feature[62,83]. For small (<1 cm) and complicated cysts MR imaging is superior to CT[63]. On MR imaging, all uncomplicated hepatic cysts, even those with a few millimetres in diameter, have a low intensity on the T1-weighted scans and high signal intensity on the T2-weighted scans[84]. Cysts with intracystic haemorrhage may show high signal intensity on T1-weighted images. At MR imaging cysts are well-circumscribed lesions that do not show enhancement after contrast administration. Therefore, delayed postgadolinium images are useful to differentiate cysts from poorly vascularised metastases, such as mucinous type colorectal metastases, that show gradual, or only septal enhancement[33].

Treatment

Asymptomatic simple hepatic cysts are best managed conservatively (Figure 2). The preferred treatment of isolated symptomatic cysts is US- or CT-guided percutaneous cyst aspiration followed by alcohol (or doxycycline) sclerotherapy, prohibited that the cyst content does not contain bilirubin[85]. This approach is more than 90% effective in controlling symptoms and ablating the cyst cavity[45]. If the radiologically guided, percutaneous approach is ineffective or unavailable, treatment may include either laparoscopic or open surgical cyst fenestration[86,87].

Biliary cystadenoma

Biliary cystadenoma typically are large, bulky masses in middle-aged women (more than 75 per cent) and tend to present as a discomfort in the right upper quadrant of the abdomen[88].

The aetiology of biliary cystadenoma remains largely unknown. One of the proposed theories is that it develops from ectopic remnants of primitive foregut sequestered within the liver[89]. Another theory suggests an origin from ectopic rests of embryonic gall bladder tissue[90]. Malignant degeneration of cystadenoma has been described in as many as 25% of cases[91,92].

Histology

On gross examination, the thick walls, cystic components, and septations within the lesion are remarkable. Microscopically, the tumour is characterised by three layers of tissue: an inner epithelial component, a middle mesenchymal layer with fibroblasts, smooth muscle, adipose tissue, and capillaries, and an outer layer of collagen and mixed connective tissue.

The histological differentiation of benign cystadenoma from cystadenocarcinoma may be difficult. One study suggests that these two lesions can be differentiated by cytokeratin pattern and in situ hybridisation of albumin mRNA[93].

Radiology

US and CT scanning show the cystadenoma as a multiseptal cystic mass that frequently has mural nodules at the periphery[94]. At CT, after contrast administration, enhancement of the septa and mural nodules can be seen. Mural or septal nodules, discrete soft tissue masses and possibly thick or coarse calcifications increase the likelihood of a cystadenocarcinoma[92]. The MR imaging descriptions of biliary cystadenoma or cystadenocarcinoma are limited[38,95,96]. They appear hyperintense on T2- and hypointense on T1-weighted images. Focal areas of haemorrhage or mucinous contents within the locules may have areas of relatively higher signal intensity on T1 weighting than those with purely bilious fluid content. On T2-weighted images, the septations are evident as low signal intensity bands separating the high signal intensity locules[38,95].

Treatment

Malignant degeneration of cystadenoma has been described in as many as 25% of cases, and a reliable pre-operative diagnosis on aspiration of cyst content or biopsy of the cyst wall is not possible[91,92]. Hence, once a cystadenoma is suspected, the lesion should be completely excised even in the absence of symptoms (Figure 2)[78,97]. If the lesion appears to be malignant, which can be assessed by frozen section during surgery, a wider excision should be obtained. These tumours have a relatively low-grade malignant potential and infrequently recur if adequately excised[78].

Biliary Hamartoma

Biliary hamartomas, also called Von Meyenburg complexes, are benign biliary malformations[98,99]. The prevalence of biliary hamartomas has not been precisely established, but they are currently estimated to be present in about 3% of autopsy patients[99]. Biliary hamartomas are typically multiple, small (usually <1 cm), well-circumscribed focal lesions that are scat-

tered throughout both lobes of the liver[95]. They originate from ductal plate malformations of the small interlobular ducts[100].

Biliary hamartomas are generally without clinical manifestation and are usually encountered as an incidental finding at laparotomy or autopsy, more than on imaging studies. They can be mistaken for metastatic lesions, particularly in patients with underlying malignancy[95,99].

Histology

Biliary hamartomas are usually noted as subcapsular white or green nodules. At pathologic analysis, they consist of small irregular, disorderly, sometimes dilated, ducts that do not communicate with the biliary tree and are embedded in an extensive fibrous stroma.

Radiology

On imaging, biliary hamartomas are usually depicted as non-specific hypoechoic and hypodense small foci on US and CT, respectively[101]. Although homogeneous enhancement of the lesions have been noted, they have been described mostly as non-enhancing structures on contrast-enhanced CT[101]. This might be caused by a detection problem of former CT techniques, since enhancement is detected on gadolinium-enhanced MR imaging[33,99]. On MR imaging, biliary hamartomas are typically hypointense on T1- and hyperintense on T2-weighted images, reflecting their high fluid content. Although this appearance resembles that of simple cysts, biliary hamartomas show a thin rim of enhancement that represents compressed hepatic parenchyma, or an inflammatory reaction surrounding the lesion[33,99]. It may be difficult to distinguish biliary hamartomas from metastatic lesions because of the presence of this rim enhancement. Rim enhancement does not spread centrally, whereas enhancement in metastases most often is irregular and spreads centrally. Biliary hamartomas are usually smaller in size, and are very bright at MR imaging, as opposed to most metastases. These imaging features may help to distinguish biliary hamartomas from metastatic lesions.

Treatment

The significance of these lesions lies in their possibility of their being mistaken on gross examination or on imaging studies for malignant lesions, such as cholangiocarcinoma or metastatic disease. There is no risk of malignant degeneration, and hepatic resection is not indicated (Figure 2)[45].

Cavernous haemangioma

Cavernous haemangioma is the most common benign tumour of the liver, with an estimated prevalence of 5-7 per cent[9]. Cavernous haemangiomas occur in all age groups but are more frequently encountered in patients in the third, fourth and fifth decades of life. Published series indicate a female preponderance, with female:male gender ratios up to 6:1[38,102].

The aetiology of liver haemangiomas is still a matter of speculation. It is suggested that haemangioma is probably a congenital abnormality and not a neoplasm[102]. The possibility of a role of female sex hormones in the development of hepatic haemangioma and the effects of pregnancy on growth has been described in the literature[103-105] but these data are most inconsistent.

Although often small, they are capable of reaching enormous size. Traditionally, lesions greater than 4 cm in diameter have been referred to as giant haemangiomas[106]. They are usually solitary, but two or more tumours occur in 10% of patients[45].

The most common clinical presentation of cavernous haemangioma is an incidental finding on hepatic imaging. The lesion is typically small (<5 cm in diameter)[4]. Large cavernous haemangiomas may present with symptoms of abdominal pain or discomfort due to capsular stretch, partial infarction, intralesional haemorrhage, or pressure on surrounding tissues. More rarely, giant haemangiomas may rupture spontaneously or traumatic, be associated with a consumptive coagulopathy with low platelet count and hypofibrinogenaemia (Kasabach-Merritt syndrome), a high output cardiac failure or abscess formation[107-110].

Histology

Cavernous haemangiomas have a dark colour and are readily recognised on gross examination. The cystic spaces are engorged with blood and palpation of the lesion indicates a compressibility that is practically restricted to vascular lesions. Microscopically, cavernous haemangiomas consist of cystically dilated vascular spaces that are lined by a single layer of endothelial cells. These spaces contain either fibrin thrombi or aggregates of red blood cells separated from one another by fibrous tissue.

Radiology

The usual ultrasonographic appearance is a lobulated, predominantly hyperechoic, and sharply marginated lesion in the liver, which is not pathognomonic. The echogenicity of haemangiomas can be variable secondary to internal fibrosis, thrombosis, haemorrhage, and occasionally calcifications[111]. Because primary and metastatic liver tumours may also have a hyperechoic appearance, the diagnosis is usually made in conjunction with other imaging modalities. The sensitivity of US for the diagnosis of cavernous haemangioma ranges from 60% to 70%, and specificity ranges from 60% to 80%[45]. At CT, cavernous haemangiomas have a typical appearance showing a low density without contrast medium[112]. Following intravenous injection of contrast, small haemangiomas may show an hyperdense and homogeneous appearance. Larger lesions (> 3 or 4 cm) show characteristic peripheral nodular enhancement that may or may not progress towards the centre of the lesion. Over time, the lesions usually become more homogeneously enhanced with a density equal to or greater than the surrounding liver parenchyma. Very large haemangiomas with extensive fibrosis or bleeding may show persistent areas of nonenhancement, centrally[113]. A finding of peripheral

nodular, or globular enhancement, or areas of pooling of contrast within the lesion is a sign that has been identified as an enabling distinction of haemangioma from hepatic metastases[113,114]. The overall sensitivity of dynamic CT scans ranges from 75% to 85%, and specificity from 75% to 100%[45]. At MR imaging, haemangiomas are typically very bright on T2-weighted images, and have moderately low signal intensity on T1-weighted images with a homogeneous pattern[33,84]. Large haemangiomas (> 5 cm) tend to have mildly complex signal intensity on T2-weighted images with the frequent presence of low signal strands, which reflects their internal network of fibrous stroma. Haemangiomas typically show peripheral nodular enhancement on immediate postgadolinium images with slow, orderly, complete or nearly complete spread of enhancement to involve the entire lesion. Occasionally, small haemangiomas may show a homogeneous intense enhancement during early phases of the dynamic study, though, haemangiomas, unlike malignant lesions, retain contrast material and stay hyperintense on delayed contrast-enhanced images[33,115]. The overall accuracy of MR imaging for detection and characterisation of haemangioma has been reported to be the highest of all imaging modalities with a sensitivity of 85 % to 95%[63,116], and specificity of 90-100%, especially when T2- weighted MR images with short and long echo-times are combined with the multiphasic dynamic contrast-enhanced images, and delayed contrast-enhanced images.

Scintigraphic imaging with technetium (99mTc)-labelled red blood cells (RBCs), which is reported to be a highly sensitive and specific method for the diagnosis of hepatic haemangioma because of its blood-filled nature, reveals a focal photopenic defect on early phase imaging that fills in centripetally with delayed imaging over a 30- to 50-minute time interval[117-119]. Lesions less than one cm cannot be detected because they are beyond the limit of spatial resolution of the gamma camera[117]. Although the use of this scintigraphic imaging with Tc-99m-pertechnatate-labeled RBCs has been accepted and widely used for diagnosis of haemangioma[14,15], we rely on the state-of-the-art MR imaging, especially, if other imaging modalities, such as US or CT, are non-conclusive, in order to gain a more accurate differential diagnosis (Figure 2)[2,120].

Treatment

Treatment is not indicated for small asymptomatic haemangiomas. Although follow-up with annual ultrasonography has been advised, recent data suggest that this may not be necessary for lesions that appear typical with diagnostic imaging[121].

In case of a large symptomatic lesion surgery can be considered[122]. Indications for excision have been the presence of symptoms, or even a perceived risk of complications as mentioned above. However, the risks of liver surgery in case of a hypervascular lesion must be carefully balanced against the benefit that might be expected from a surgical procedure[123,124]. In a substantial proportion of patients (15-30 per cent) symptoms persist after resection, probably as a consequence of another undiagnosed problem[4,125]. The potential for complications during a conservative approach is minimal and symptoms may even resolve[14,120]. Any risk of

morbidity and mortality must be considered unacceptable, taking into account the benign nature and high prevalence of the tumour. Based on our experience we advocate surgery for cavernous liver haemangioma only in patients with incapacitating symptoms (Figure 2). Size of the lesion, *per se*, is not a criterion for resection.

Surgical options include enucleation or resection[126,127]. Embolisation should be reserved for tumours with extensive hilar involvement that have favourable vascular anatomy, for patients who require haemodynamic stabilisation before surgery, or to reduce blood loss at the time of surgery[128,129]. Transplantation is indicated for large, unresectable or multiple tumours, or when neither surgical resection nor embolisation is feasible[130,131]. Ligation of the hepatic artery[132] and hepatic irradiation[133] have been used in rare cases when surgical resection or transplantation was not feasible.

DISCUSSION

Due to the increased use of imaging modalities as US, CT and MR imaging more incidental liver lesions are discovered that are benign[54,134]. Problems may arise in obtaining a definite diagnosis in case of a solid hepatic tumour in a non-cirrhotic liver. Clinical evidence of malignant disease or a known extrahepatic malignancy in medical history may be helpful during differentiation between benign and malignant tumours. When there is no such evidence, serum tumour markers are normal, and markers for chronic viral infection (hepatitis B or C serology tests) are negative, a benign lesion must be considered in differential diagnosis.

Routine laboratory tests do not contribute to the differential diagnosis in case of a focal liver lesion in a non-cirrhotic liver. Some cases of giant haemangioma complicated by focal thrombosis or haemorrhage within the tumour may show evidence of disseminated intravascular coagulation (Kasabach-Merritt syndrome), such as thrombocytopenia and hypofibrinogenaemia. The only serum tumour markers that are clinically used during work-up of an isolated focal liver lesion, such as alpha-fetoprotein (AFP) carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19-9) may contribute to the differential diagnosis of the tumour[135].

After detection of a focal liver lesion and its segmental extent, characterisation of the lesion will permit an accurate treatment after evaluation. Although atypical imaging features are the exception rather than the rule, it is sometimes difficult to differentiate between benign and malignant lesions, and knowledge of their imaging features is essential to avoid unnecessary work-up.

US is frequently used because of its non-invasive nature and its wide accessibility. With US, mass lesions of the liver can be classified as solid or non-solid lesions. The broad availability of CT as well as the recent development of the faster multirow detector machines makes this modality an excellent technique for detection and characterisation of focal liver tumours.

Currently, the multirow detector CT does allow multiphasic dynamic contrast enhanced imaging in relatively shorter scanning times. The shorter scanning times allow the capture of distinct phases, including the unenhanced phase, arterial phase, portal phase, and venous phase that provide important information for characterisation of a focal liver lesion. In clinical practice however, the number of phases is limited and often kept to a minimum, mainly due to the radiation hazard. At the same time, helical scanning and thinner collimation are used, more often. As a consequence, more smaller hepatic lesions are detected that cannot be characterised with CT scanning after monophasic injection of contrast material[134]. MR imaging, however, may be the most reliable way of detection and characterisation of benign and malignant liver tumours[62,136,137]. The superiority of MR imaging is due to differences in techniques of data acquisition and contrast medium administration, in addition to inherently greater tissue contrast with MR imaging. Although nuclear imaging has been advocated for determination of a liver lesion[56,118,119], the recent availability of tissue specific contrast media such as manganese chelates and reticuloendothelial agents, e.g. ferumoxides targeting either hepatocytes or Kupffer cells, improved the specificity of MR imaging, and its utility above the less specific scintigraphic techniques[138,139].

The role of needle biopsy or aspiration of focal liver lesions remains much debated. Although histological examination is still considered to be the gold standard in the diagnosis of benign and malignant liver tumours, the availability of highly advanced radiological techniques provides a non-invasive diagnostic tool that is being used frequently. It is remarkable that histology and radiological examination almost share the same accuracy rate, and in some

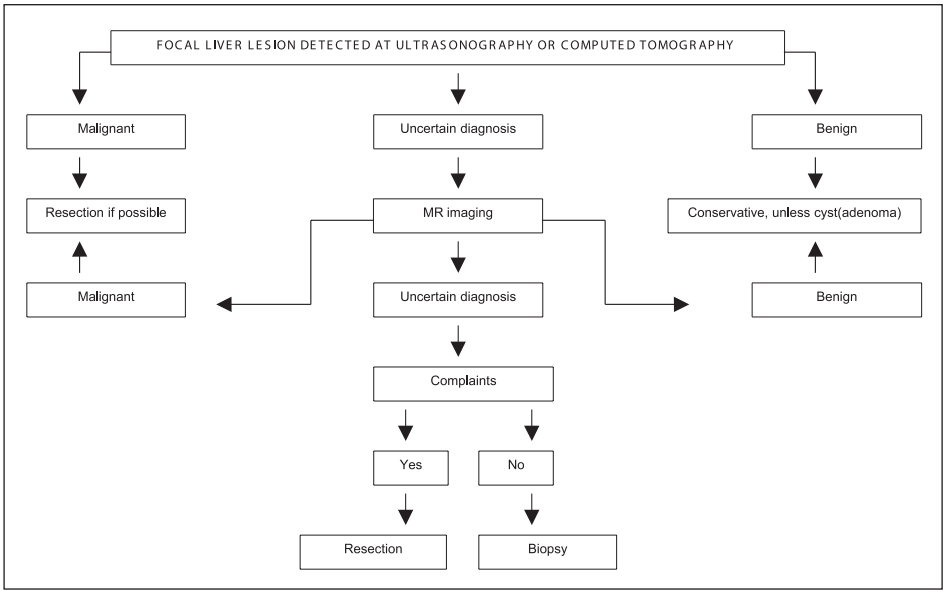

Figure 3. Algorithm for diagnostic work-up in case of a solitary focal liver lesion.

studies even a higher accuracy has been reported for MR imaging[137,140,141]. In addition, small hepatic lesions deemed too small to characterise, are more frequently benign than malignant, even in patients with extrahepatic cancer[134,142]. This may have consequences for the role of histology during work-up of a focal liver lesion, which has its own diagnostic pitfalls. The morphology and immunohistochemical phenotype of liver tumours may overlap, while sampling error and needle-tract tumour seeding can provide another diagnostic problem[143,144].
In our clinic, we recommend to do only a liver biopsy in patients where radiological diagnosis remains unclear and if patients are not eligible for surgery, due to general condition or localisation of the tumour (Figure 3)[2].

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2.2

Indications and long-term outcome of treatment for benign hepatic tumours: A critical appraisal.

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INDICATIONS AND LONG-TERM OUTCOME OF TREATMENT FOR BENIGN HEPATIC TUMOURS: A CRITICAL APPRAISAL

ABSTRACT

Background: Haemangioma, focal nodular hyperplasia (FNH) and hepatocellular adenoma are benign hepatic tumours that continue to pose diagnostic and therapeutic dilemmas. Till now, the most appropriate treatment for these liver tumours remains undefined and often a primary surgical treatment is being performed. However, the natural history and clinical behaviour of benign hepatic tumours during long-term follow-up may not justify a primary surgical treatment.

Methods: Two hundred and eight patients were diagnosed with a benign liver tumour between January 1979 and December 1999. The medical records were analysed and symptoms and complications were assessed during management and long-term follow-up.

Results: Hepatic surgery was performed in 74 patients, and 134 were managed conservatively by radiological follow-up. In the surgically treated population the liver lesion was symptomatic in 64% and an incidental finding in 36%. Operative morbidity and mortality was 27% and 3%, respectively. Overall, 80% of patients with complaints were asymptomatic after surgery. During observation of the tumour in the conservatively managed group, 39 out of 45 patients (87%) who presented with complaints are currently asymptomatic during a mean follow-up of 45 months; 6 patients have mild abdominal pain considered to be unrelated to the tumour.

Conclusions: A conservative management of solid benign liver lesions as FNH and haemangioma 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 case of severe complaints related to the tumour. Resection is always advocated in case of a large hepatocellular adenoma (>5 cm) to reduce the risk of rupture and malignant degeneration.

INTRODUCTION

In contrast with haemangioma, focal nodular hyperplasia (FNH) and hepatocellular adenoma are uncommon benign liver tumours that are detected more frequently nowadays because of improvements in radiological modalities and the widespread use of ultrasound[1,2]. They are often recognised 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 have documented the cause, differential diagnosis and treatment of FNH, adenoma and haemangioma of the liver[1,3-8]. Although findings in these studies provide a framework for the management of benign hepatic tumours, the most appropriate treatment remains controversial[9-11]. Especially in the case of a hepatocellular adenoma, many prefer surgery to conservative treatment because of the risk of rupture and potential malignancy[5,6,9].

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

PATIENTS AND METHODS

A total of 208 patients with a benign liver tumour were analysed 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 haemangioma, 1:2.8 (Table 1). Seventy-five percent (45/60) of women with FNH used oral contraceptives for a mean±SD of 137 ± 44 months, and 93% 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 serology 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 liver scintigraphy, and cholescintigraphy with the diisopropyl iminodiacetic acid hepatobiliary agent. The tumour was classified using predefined criteria as FNH, hepatocellular adenoma, haemangioma or undetermined (Table 2)[12-14]. Angiography had an additive value for diagnosis when a central feeding artery

was 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 tumours, resection was performed for the largest tumour, unless all tumours were located in the same segment or lobe. When surgical morbidity was calculated, all complications requiring treatment were included in the analysis.

Table 1. Benign liver tumours and patients' characteristics ($n = 208$)

Tumour	Sex, M/F	Age, y*	Patients Who Underwent Surgery	Pateints 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
Haemangioma	27/76	48 (30-77)	25	78	103
Cyst adenoma	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).

Table 2. Lesion characteristics for each imaging modality*

Type of Lesion	US	CT Scanning	MRI
Haemangioma	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 localised 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 haemorrhage	Isointense SI on both 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.

RESULTS

Surgical treatment

In the case of an incidentally detected tumour (32%, or 24 of 74 patients), the inability to differentiate between FNH, hepatocellular adenoma, or carcinoma was an indication for surgery (Table 3). Small tumours 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 haemangioma. The tumour 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). Rupture of the tumour was observed in 8 (42%) of the 19 patients with hepatocellular adenoma.

Table 3. Clinical presentation in 74 patients with a benign liver tumour, treated surgically*

Clinical presentation	Focal Nodular Hyperplasia (n = 26)	Hepatocellular Adenoma (n = 19)	Haemangioma (n = 25)
Incidental	12 (46)	4 (21)	3 (12)
Suspected metastases	1 (4)	0	4 (16)
Abdominal pain	10 (38)	6 (32)	15 (56)
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.

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 work-up usually included US and contrast-enhanced CT (Table 4). Computed tomographic scanning led to the imaging diagnosis in 37% of patients with FNH, in 56% of those with hepatocellular adenoma, and in 70% of those with haemangioma. 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 haemangioma, the diagnosis was established unequivocally.

Table 4. Imaging modality and sensitivity rates for FNH, Hepatocellular adenoma and Haemangioma*

Imaging Modality	FNH	Hepatocellular Adenoma	Haemangioma
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.

Table 5. Surgical procedure in 74 patients*

Procedure	Focal Nodular Hyperplasia (n = 26)	Hepatocellular Adenoma (n = 19)	Haemangioma (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.

The results of a pre-operative needle biopsy, performed in 38 patients, were confirmatory, with the histopathological diagnosis of the resected tumour 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 haemangioma.

In the surgically treated population, 5 patients with FNH and 9 patients with haemangioma had 2 or more tumours 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, and a (bi)segmental resection was performed in 32 cases (Table 5).

The mean±SD greatest diameter of the resected tumour 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 haemangioma.

During the postoperative hospital stay (median, 11days; 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 tumour (14 and 15 cm). One of these tumours, located centrally in the liver, compressed the duodenum from outside and caused gastric outlet obstruction, which necessitated surgical treatment. Six patients required additional surgical intervention during the same period of hospitalisation, 5 patients with secondary bleeding for control of haemorrhage and 1 with thrombosis of the inferior caval vein 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 is shown in Table 7.

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 haemangioma), symptoms persisted. All women with previous hepatocellular adenoma stopped using oral contraceptives. Tumour recurrence was not detected during radiological follow-up of all patients.

Conservative treatment

A total of 134 patients (42 with FNH, 14 with hepatocellular adenoma, and 78 with haemangioma) were managed by observation. In 43% of the patients with FNH, in 43% with a hepatocellular adenoma, and in 78% with a haemangioma the tumour was found incidentally during abdominal imaging or laparotomy for other indications (Table 8). Abdominal pain was noted in 33%, 14%, and 12% of those with FNH, a hepatocellular adenoma and a haemangioma, respectively. Four patients presented with a ruptured hepatocellular adenoma and

Table 6. Surgical morbidity*

Complication	Focal Nodular Hyperplasia (n = 26)	Hepatocellular Adenoma (n = 19)	Haemangioma (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. Long-term morbidity related to surgery*

Complaint	No. of Patients (n = 72)**
Abdominal pain	5
Incisional pain	3
Incisional hernia	2
Fatigue	3
Total, No. (%)	**13 (18)**

*Data are given as the number of patients.

**Two patients who are died are excluded.

were managed conservatively by haemodynamic stabilisation and control of coagulation disorders. When the tumour 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, needle biopsy was performed (in 25 patients with FNH, in 16 with a hepatocellular adenoma, and in 15 with a haemangioma).

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 tumour (mean diameter, 4.7 cm; range, 3.0-5.6 cm) and 6 (14%) had nonspecific complaints of fatigue.

Table 8. Clinical presentation in 134 patients with benign liver tumours, treated conservatively*

	Focal Nodular Hyperplasia	Hepatocellular Adenoma	Haemangioma
Clinical presentation	(n = 42)	(n = 14)	(n = 78)
Incidental	18 (43)	6 (43)	61 (78)
Abdominal pain	14 (33)	2 (14)	9 (12)
Nonspecific complaints	10 (24)	2 (14)	8 (11)
Bleeding	0	4 (29)	0

*Data are given as the number of patients.

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

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

DISCUSSION

The results of our experience indicate that liver surgery for benign liver tumours may relieve complaints in a high percentage of symptomatic patients (80%). However, in many patients, symptoms persist after resection of the tumour 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 haemangioma on the one hand and for hepatocellular adenoma on the other. Focal nodular hyperplasia and haemangioma 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 hepatocellular adenoma, however, have a higher prevalence of symptoms at first presentation, probably caused by the rate of intra-tumoural or intra-abdominal haemorrhage (50%-65%)[3,7,20].

Problems may arise in obtaining a definite diagnosis in the case of a solid hepatic tumour, and in differentiating between benign and malignant tumours. When clinical evidence of malignant disease is absent, serum α-fetoprotein levels are normal and hepatitis B and C serologic tests are negative, a benign lesion must be considered in the differential diagnosis. Because additional laboratory tests are not helpful during diagnostic work-up, 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 haemorrhage 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 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[21,22]. Especially when the differential diagnosis includes haemangioma, MRI is a valuable tool, showing a specificity of 90% to 100% and sensitivity of about 90% (Figure 2)[24].

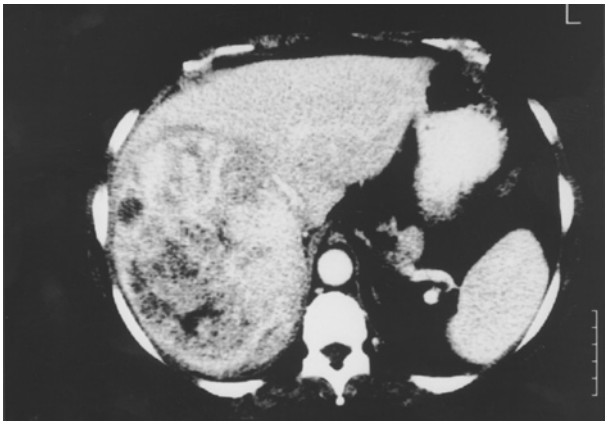

Figure 1. Computed tomographic image of a hepatic tumour with intralesional haemorrhage and necrosis. Typical features of a hepatocellular adenoma. This tumour was resected because of its large diameter.

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

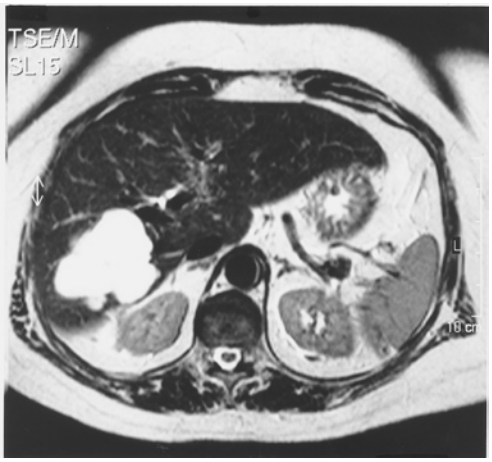

Figure 2. Magnetic resonance image of a conservatively treated patient, showing a typical lobulated hyperdense lesion on T2-weighted sequences, characteristic of a haemangioma.

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 haemorrhage during US- or CT-guided needle biopsy in benign liver tumours 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 tumours 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 tumour. Observation of the tumour 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 haemangioma (rupture, growth, mass effect, Kasabach-Merritt syndrome) does not justify surgery for all detected lesions[17,36,37]. In contrast to FNH and haemangioma, resection of 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 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 tumour which causes severe complaints and when there is an uncertain 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.

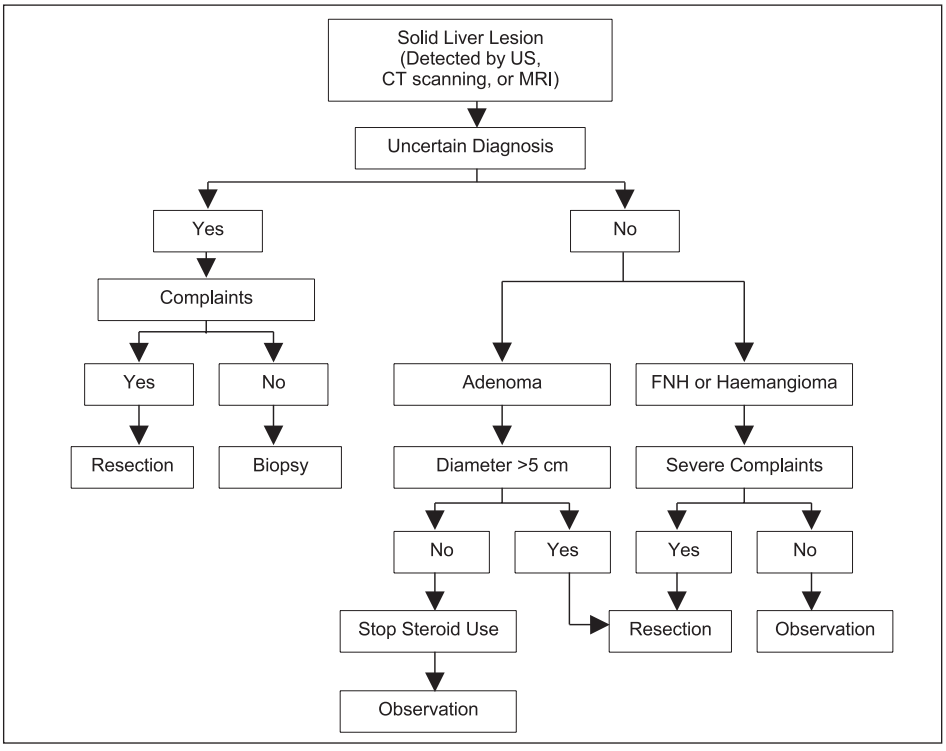

Figure 3. Algorithm for the management of solid liver tumors.
US indicates ultrasonography; CT, computed tomographic; MRI, magnetic resonance imaging; and FNH, focal nodular hyperplasia.

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Chapter 3

Hepatic haemangioma

3

Size of lesion is not a criterion for resection during management of giant liver haemangioma.

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SIZE OF LESION IS NOT A CRITERION FOR RESECTION DURING MANAGEMENT OF GIANT LIVER HAEMANGIOMA

ABSTRACT

Background: The unknown natural course and risk of complications of large haemangiomas may pose therapeutic dilemmas. The authors describe their experience with the management of giant haemangiomas.

Methods: Patients with a giant haemangioma were identified by a survey of the hospital database. Forty-nine patients with a haemangioma of at least 4 cm in diameter presented between January 1990 to December 2000. Medical records were analysed retrospectively.

Results: Eleven patients had surgical treatment and 38 were managed conservatively. The median diameter of the tumours was 8.0 cm in surgically treated patients and 6.0 cm in the group managed by observation. Surgery-related morbidity occurred in three patients, and abdominal complaints persisted in three of ten patients with a symptomatic lesion. During a median follow-up of 52 months, 12 non-operated patients had mild abdominal complaints, considered to be unrelated to the lesion. In these patients symptoms either diminished or became minimal during follow-up. Complications did not occur.

Conclusion: Observation of giant haemangiomas can be performed safely. The authors advocate resection of cavernous liver haemangiomas only in patients with persistent severe complaints.

INTRODUCTION

Cavernous haemangioma is the most common benign tumour of the liver, with an estimated prevalence of 5-7 per cent[1]. The incidental finding of liver haemangioma has increased considerably as many patients undergo modern imaging techniques[2,3]. Although most of these lesions remain asymptomatic, they may be responsible for pain due to capsular stretch, partial infarction or pressure on surrounding tissues. More rarely, haemangiomas may rupture, or be associated with a consumptive coagulopathy (Kasabach-Merritt syndrome) or abscess formation[4-7]. Strategies for the management of liver haemangioma have ranged from selective observation to a variety of radiological and surgical interventions[8-12]. While there is general agreement that small asymptomatic lesions should be managed conservatively, the unknown natural history and the possibility of complications of larger, or giant, haemangiomas (4 cm or more) makes treatment selection difficult[3,9].

The management of large haemangiomas has become increasingly conservative with time. Because serious complications may occur during conservative management of liver haemangiomas, a retrospective review was undertaken to identify the magnitude of these risks.

METHODS

A survey of the hospital database was performed to identify all consecutive patients with a diagnosis of giant haemangioma (at least 4 cm in diameter) who presented at University Hospital Rotterdam-Dijkzigt between January 1990 and December 2000. Forty-nine patients were identified. The diameter of the tumour was 10 cm or more in eight patients. Liver haemangiomas were solitary in 31 of the 49 patients. Bilaterally giant haemangiomas were found in 12 patients (Table 1).

Table 1. Tumour characteristics

	Surgery (*n* = 11)	**Observation (*n* = 38)**
Location		
Right	4	22
Left	5	6
Bilateral	2	10
No. of tumours		
One	9	22
Two	2	8
Three or more	0	8
Diameter (cm)		
Mean	9.5	6.5
Median	8.0	6.0
Range	4.0-20.0	4.0-25.0

There were 33 women (67 per cent) and 16 men, with a mean age of 55 (range 32-89) years. Eleven (22 per cent) of the 49 patients underwent operation and 38 (78 per cent) were managed by observation. The medical records of all patients were reviewed to document clinical presentation, diagnostic strategies, treatment, complications, and follow-up.

Diagnostic investigation included ultrasonography, triphasic spiral computed tomography (CT) and magnetic resonance imaging (MRI). The current MRI protocol for haemangiomas includes T2-weighted images with short and long echo times, multiphasic dynamic contrast-enhanced T1-weighted images, and delayed fat-saturated dynamic contrast-enhanced T1-weighted images. In the first part of this retrospective study, ultrasonographically guided needle cytology or biopsy was performed when there was still doubt regarding the diagnosis after the use of imaging modalities and a conservative approach was being considered. The histological diagnosis of cavernous liver haemangioma was retained if the biopsy specimen demonstrated endothelium-lined spaces containing either fibrin thrombi or aggregates of red blood cells separated from one another by connective tissue septa. More recently, fine-needle aspiration cytology or biopsy has been performed only when MRI is not conclusive.

A variety of surgical procedures were employed (Table 2), designed to minimise the unnecessary loss of normal liver tissue. When feasible enucleation was preferred. In patients with multiple haemangiomas, resection was performed for the tumour that was presumed to be causing symptoms, considering size and localisation.

Follow-up after either surgical or conservative treatment consisted of physical examination and ultrasonographic visualisation of the liver.

Table 2. Surgical procedures undertaken in 11 patients

	n	Diameter (cm)
Right hemihepatectomy	2	7.0, 12.0 (9.5)
Right extended hemihepatectomy	1	20.0
Left hemihepatectomy	2	9.0, 12.0 (10.5)
Segmental resection	3	4.0, 7.0, 9.0 (6.7)
Enucleation	3	5.0, 6.0, 7.0 (6.0)

Values in parentheses are mean.

RESULTS

In 27 (55 per cent) of the 49 patients, hepatic haemangioma was an incidental finding during abdominal imaging for unrelated pathology or during follow-up or staging of an extrahepatic malignancy (Table 3). Symptoms potentially related to haemangioma included upper abdominal pain, fullness and dyspepsia.

Table 3. Clinical presentation of 49 patients with a giant haemangioma

	Surgery (*n* = 11)	Observation (*n* = 38)	Total (*n* = 49)
Abdominal complaints	10	12	22 (45)
Incidental finding	1	22	23 (47)
Suspected metastasis	-	3	3 (6)
Raised γ-glutamyl transferase level	-	1	1 (1)

Values in parentheses are percentages.

Liver function test results were abnormal in 25 patients (51 per cent) but did not contribute to the diagnosis. No patient had thrombocytopenia or anaemia.

Ultrasonography was performed in all 49 patients and demonstrated haemangioma in 30. Twenty-three patients had CT, which was conclusive in 21 patients. In some of the patients with a typical lesion, MRI was performed additionally to increase the level of confidence and experience with this imaging technique; in eight of nine patients, MRI established the diagnosis unequivocally. When fine-needle cytology or biopsy was employed, haemangioma was detected in five of ten and nine of eleven patients respectively.

Surgical treatment

In ten patients an operation was performed where abdominal symptoms were considered to be related to haemangioma (infarction, capsular stretch or pressure on surrounding tissues). One patient underwent operation for an asymptomatic giant haemangioma (diameter 12 cm) with persistent growth (5 cm during radiological follow-up of 36 months). The mean greatest diameter of all resected tumours was 9.5 (median 8.0, range 4.0-20.0) cm (Table 1).

Post-operative complications occurred in three patients. One patient developed secondary bleeding that necessitated relaparotomy; one had a pleural effusion and another had a subhepatic abscess, both of which required drainage. During postoperative follow-up of 24.5 (range 13-110) months, abdominal symptoms persisted in three patients. Two of these symptomatic patients had bilaterally haemangiomas at the time of operation. They have been managed conservatively by radiological follow-up of the contralaterally lesions, which have been left *in situ* (6 and 7 cm). There was no surgery-related mortality.

Conservative management

Thirty-eight patients were managed conservatively. Twelve non-operated patients had mild abdominal pain or discomfort, considered to be unrelated to the lesion (Table 3). The mean greatest diameter of the tumour in these symptomatic patients (6.1 (median 6.0, range 4.0-11.0) cm) was not significantly different from the symptomatic patients who underwent surgery (mean 9.7 cm, median 8.5 cm) ($P = 0.36$).

During a mean follow-up of 59 (median 52, range 12-122) months, symptoms had either diminished or become minimal in all 12 patients with abdominal complaints. None of the

patients who were asymptomatic at the time of first referral developed abdominal pain. In 32 patients the tumour was followed by means of ultrasonography. An increased diameter was observed in only one patient with an asymptomatic haemangioma (5 cm growth over 49 months). Coagulation disorders, other complications or tumour-related death has not occurred.

DISCUSSION

In patients with benign liver tumours, surgery may relieve complaints in a large proportion of those with symptoms. In a substantial proportion of patients (15-30 per cent), however, symptoms persist after resection probably as a consequence of another misdiagnosed problem, such as irritable bowel syndrome, peptic ulcer or reflux disease[8,13]. It is essential to decide whether the mass is indeed the cause of the patient's complaints, as simple observation of a benign liver lesion might be the best clinical approach without the risks of surgery and the potential for symptom resolution. In patients with a haemangioma, it may be even more difficult to correlate symptoms with size and location. Indications for operation have traditionally been the presence of symptoms, the development of complications, and the need to establish a definite diagnosis when radiological and histological studies were inconclusive. Liver haemangiomas have also been resected because of a perceived risk of spontaneous or traumatic rupture, and the possibility of the Kasabach-Merritt syndrome, a consumption coagulopathy with low platelet counts and hypo-fibrinogenaemia[6,9,14,15]. The potential for complications of a liver haemangioma is minimal[4,16] and does not justify, *per se,* resection of all haemangiomas. The risk of significant and sometimes uncontrollable intraoperative bleeding of hypervascular lesions, in addition to the common risks of any liver resection[17-19], should be carefully balanced against the benefit that might be expected from surgery. The reported mortality rate associated with elective liver resection of such tumours ranges from 0 to 4 per cent[8,13,20,21]. The latter figure must be considered unacceptable, taking into account the benign nature and high prevalence of the tumour.

Specific features of cavernous liver haemangioma may be apparent with a variety of imaging techniques such as ultrasonography, dynamic contrast-enhanced CT and MRI. With ultrasonography, a typical haemangioma is characterised as a sharply marginated, lobulated, predominantly hyperechoic lesion[22-24]. Haemangiomas may be complicated by bleeding, scar tissue or calcification[24]. Such lesions have a variable appearance at ultrasonography. In addition, the ultrasonographic appearance of uncomplicated haemangiomas may overlap with those of primary or secondary malignant liver tumours. In patients with an unclear diagnosis and in those with a known (colorectal) malignancy or cirrhosis, the authors recommend MRI because of its high specificity in the diagnosis of haemangioma. At MRI, haemangiomas are typically very bright on T2-weighted images (Figure 1) and show peripheral nodular enhance-

ment on dynamic contrast-enhanced T1-weighted images (Figure 2). Occasionally, small haemangiomas may show a homogeneous intense enhancement during early phases of the dynamic study, although haemangiomas, unlike malignant lesions, retain contrast material and stay hyperintense on delayed contrast-enhanced images[22,24]. The overall accuracy of MRI for the detection and characterisation of haemangioma has been reported to be high, with a specificity of 90-100 per cent and a sensitivity of about 90 per cent[22-24], especially when T2-weighted images with short and long echo times are combined with multiphasic dynamic contrast-enhanced images, and delayed contrast-enhanced images. The results of MRI in the present study, although obtained in only a small number of patients with haemangioma, are in accordance with those reported previously[22,24]. The use of other invasive imaging methods, such as scintigraphy and technetium-99m-labelled red blood cell scanning, has been reported for the diagnosis of benign liver lesions and especially hemangiomas[25,26].

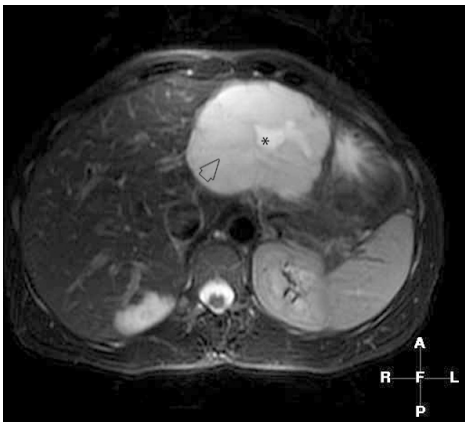

Figure 1. T2-weighted magnetic resonance image with fat saturation showing a typical giant haemangioma (arrowhead) with a central scar (*) on the left side of the liver, and a small haemangioma in the right liver (black arrow). Both lesions are sharply marginated and very bright compared with surrounding liver.

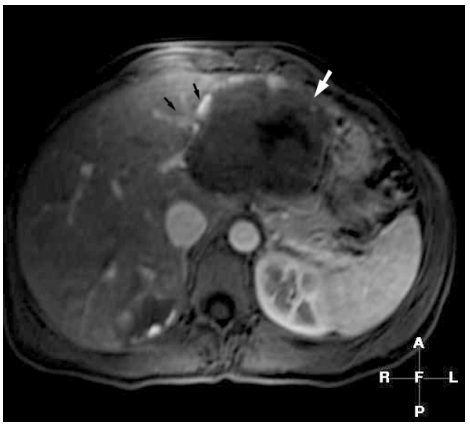

Figure 2. T1-weighted image during the arterial phase of a dynamic study after intravenous injection of magnetic resonance imaging contrast medium (gadolinium-diethylenetriamine penta-acetate), showing typical peripheral nodular enhancement (black arrows) in both lesions (giant haemangioma indicated with white arrow). The presence of a combination of a bright lesion on a T2-weighted image and peripheral nodular enhancement is pathognomic for liver haemangioma.

The risk of needle-induced bleeding during ultrasonographically or CT-guided biopsy in benign hypervascular tumours is reported to be low (0.03-0.04 per cent)[27,28]. In the present series there were no complications following biopsy. A tissue diagnosis is recommended when the radiological diagnosis remains unclear and conservative treatment is being considered.

Conservative management of liver haemangioma is preferred because of the minimal risk of complications. As supported by the present observation, mild symptoms often resolve

spontaneously during follow-up, and operation is not completely successful in terms of symptomatic relief. In addition, this series derives from a tertiary referral centre with a higher proportion of large tumours than is observed in the general population. The study clearly demonstrates that a confident diagnosis may be made using modern recent high-resolution radiological studies, and that conservative management can be undertaken safely. Based on the present experience, surgery for liver haemangioma is advocated only in patients with incapacitating symptoms. The size of the lesion is not a criterion for resection and some exceptional indications or complications which may necessitate liver surgery or even transplantation[12,13,29] confirm the importance of this general guideline for the treatment of liver haemangioma: observe the lesion, unless the patient has severe symptoms.

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CHAPTER 4

Hepatocellular adenoma

4.1

Management of hepatocellular adenoma during pregnancy.

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MANAGEMENT OF HEPATOCELLULAR ADENOMA DURING PREGNANCY

Although the aetiology of hepatocellular adenoma is unknown, these benign tumours seem to be related to the use of oral contraceptives[1,2]. An association with pregnancy has also been described, probably due to increased levels of endogenous steroid hormones[3,4]. During pregnancy the risk of rupture of hepatocellular adenomas exists, and this is associated with high foetal and maternal mortality[3,5-8]. In non-pregnant women, surgical resection is often indicated in larger hepatocellular adenomas because of a proven risk of rupture[1,9,10] or malignant transformation[11,12]. Successful resection of malignant hepatic tumours during gestation has been reported[13,14].

We report a case of 32-year-old pregnant woman with a hepatocellular adenoma, where surgical excision was performed. At 12 weeks' gestation the patient complained of increasing epigastric pain. She had been taking oral contraceptives for 15 years and did not use either alcohol or hepatotoxic medication. Except for an elevated alkaline phosphatase level of 273 (n. 25-75) IU/L and a γ-glutamyl transpeptidase level of 72 (n. 5-35) IU/L, all laboratory results were within normal limits (including alpha-fetoprotein) and actual or past infection with hepatitis B or C was excluded. Ultrasonography followed by computed tomography demonstrated a 7x9 cm tumour in the left hepatic lobe, consistent with either hepatocellular adenoma or focal nodular hyperplasia. Subsequent ultrasonography-guided percutaneous biopsy was consistent with hepatocellular adenoma, but a highly differentiated liver cell carcinoma could not be excluded. Radiological, laboratory, and histological findings, including the patient's history of oral contraceptive use during 15 years, made the diagnosis of hepatocellular adenoma most likely. Considering the risk of rupture in case of a hepatocellular adenoma, a resection of segment II and III was performed at 13 weeks' gestation. Histological study of the tumour revealed free surgical margins of a hepatocellular adenoma in the left liver lobe. The postoperative recovery was unremarkable and the patient was discharged on the 7th postoperative day. There were no other problems during her pregnancy and the delivery was uneventful. Mother and child were in good condition 12 months after surgery.

In the last 40 years an increasing incidence of hepatocellular adenoma has been observed. In women who have never used oral contraceptives, hepatocellular adenoma develops at an annual rate of approximately 0.012 per 10.000[1]. On the other hand, the tumour even appears to be related to the drug exposure time. In women who have used oral contraceptives for more than 9 years, the risk of developing a hepatocellular adenoma is increased 25-fold. The use of oral contraceptives not only increases the risk of developing a hepatocellular adenoma, but it also increases the risk of spontaneous rupture[2,9]. As a consequence, in patients who have been advised to discontinue oral contraceptives, regression of hepatocellular adenoma has been described[15]. However, persistent growth of the tumour after cessation of oral contraception can occur as well[16].

Discussion about the right management of hepatocellular adenoma is still going on. Once the diagnosis of hepatocellular adenoma has been established, we advise patients to discontinue oral contraception and to avoid pregnancy. Asymptomatic tumours with a diameter of less than 5 cm are treated conservatively, i.e. discontinuation of oral contraceptive use and ultrasonographic observation[17,18]. Primary surgical resection is performed in case of an initial diameter of 5 cm or more, or in patients with serious complaints.

It is unknown whether a hepatocellular adenoma found during pregnancy can regress after termination or completion of pregnancy. Stock et al. reported a case in which they performed a therapeutic abortion[19]. Abrupt necrosis occurred and the tumour did not regress in size.

High levels of sex steroids and increased vascularity of the liver during pregnancy increases the chances of liver rupture[3]. Elective resection of hepatocellular adenoma in non-pregnant women has a mortality rate of less than 1%, while the mortality with free rupture is 5% to 10%[1,2]. Rupture of a hepatocellular adenoma during pregnancy carries a much higher mortality rate. In a review by Bis et al. comprising 91 cases, several cases of ruptured hepatocellular adenoma with intraperitoneal haemorrhage during gestation have been described, with a reported 59% maternal and 62% foetal mortality[8]. The reason for this high mortality rate might be a serious delay in diagnosis because of confusion with other diseases, like preeclampsia or pulmonary embolism, which leads to a poor general condition prior to surgery[3,6].

Successful resection of hepatic tumours during gestation has also been described by many other authors. Because of the unpredictable behaviour of hepatocellular adenomas and high maternal and foetal mortality rates in case of a rupture during pregnancy, we recommend resection once a large (≥5 cm) or a growing symptomatic hepatocellular adenoma is diagnosed. When a surgical procedure is performed during the second trimester, operative risks are minimal for both the mother and the foetus[20].

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4.2

Treatment of ruptured hepatocellular adenoma.

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TREATMENT OF RUPTURED HEPATOCELLULAR ADENOMA

ABSTRACT

Background: Emergency resection is suggested as the treatment of choice in patients with ruptured hepatocellular adenoma. As the morbidity and mortality rates associated with emergency resection are high, the authors have favoured initial non-operative management in haemodynamically stable patients.

Methods: A retrospective study was performed to evaluate early management and treatment of ruptured hepatocellular adenoma.

Results: Over a 21-year period, 12 patients presented with a ruptured hepatocellular adenoma. Haemodynamic observation and support was the initial management in all 12 patients. Three underwent urgent laparotomy and gauze packing because of haemodynamic instability; no emergency liver resection was necessary. Eight patients had definitive surgery; three showed post-operative complications but none died. Regression of the tumour was observed in three of four patients treated conservatively.

Conclusion: The initial management of a ruptured hepatocellular adenoma should be haemodynamic stabilisation. Definitive resection is required for rebleeding or for tumours exceeding 5 cm in diameter. A conservative approach may well be justified in case of regression of an asymptomatic adenoma.

INTRODUCTION

Hepatocellular adenoma is a relatively uncommon liver tumour. Since the last 30 years the incidence of this benign lesion has clearly increased, which is partly a result of an increased awareness and improved diagnostic techniques. There also seems to be an association with the widespread use of oral contraceptives since the 1960s[1-4]. The use of oral contraceptives both increases the risk of developing hepatocellular adenoma, as well as the risk of serious complications from this lesion[5,6]. In addition, hepatocellular adenomas in oral contraceptive users tend to be larger, with higher rates of intratumoural and intraperitoneal haemorrhage[5,7,8].

Emergency resection of a ruptured hepatocellular adenoma is associated with high morbidity and mortality rates. While elective resection of a hepatocellular adenoma has a mortality rate of less than 1 per cent, this may increase to 5-10 per cent in those with intra-abdominal haemorrhage[7-10].

In this study the management of 12 patients with a spontaneously ruptured hepatocellular adenoma was reviewed.

PATIENTS AND METHODS

A retrospective study was undertaken of 12 patients with a ruptured hepatocellular adenoma who were managed at University Hospital Rotterdam between 1978 and 1999. Medical records were reviewed with respect to the haemodynamic state on presentation, treatment and outcome. If operation was necessary, a distinction was made between emergency resection within 24 h of admission and (elective) resection after haemodynamic stabilisation.

Shock on admission was arbitrarily defined as a pulse rate of more than 100 beats per min, a systolic blood pressure of less than 100 mm Hg and a decline or low haemoglobin level.

Follow-up was obtained by chart review, and all patients were invited to visit the outpatient department, where an inquiry into complaints, physical examination and radiological investigation of the liver were performed.

There were ten women and two men, with a mean age of 35 (range 20-49) years. All the women had a history of oral contraceptive use with a mean duration of 10.5 (range 5-20) years. Both men had been using anabolic steroids, for 16 and 4 years, respectively.

In ten patients, bleeding was the first presentation of the hepatocellular adenoma, and two patients were known to have a liver lesion. In one patient the liver lesion was misdiagnosed as a focal nodular hyperplasia 6 years before presentation, and one patient was known to have 3 hepatocellular adenomas.

RESULTS

Five patients were in hypovolaemic shock on admission; the remainder were stable (Table 1-2). Acute abdominal pain was the predominant complaint in all 12 patients. Four patients had lower chest pain, which referred to the right shoulder in combination with breathlessness; one of these patients was primarily misdiagnosed and treated as having a pulmonary embolism. Further radiological investigation revealed a bleeding liver tumour in this patient. Two patients had a history of abdominal pain before the onset of the acute moment.

Diagnostic work-up with ultrasonography (US) and computed tomographic (CT) scanning showed imaging characteristics of a hepatocellular adenoma with signs of haemorrhage and necrosis (figure 1a). The lesion was solitary in 10 patients. One patient had two lesions and one patient three. Bleeding was intra-abdominal in five patients, subcapsular in four and intrahepatic in three.

Laboratory tests demonstrated normal α-fetoprotein levels; hepatitis B and C serology (hepatitis B surface antigen, anti-hepatitis B core antigen, anti-hepatitis C virus) was negative in all patients.

Initial management included haemodynamic support. Urgent laparotomy and gauze packing was undertaken in three patients who had persistent bleeding. Eight patients had definitive surgery but no emergency resection was necessary (Table 1).

The median interval between presentation and definitive surgery was 10.5 (range 3-64) days. Resection involved right-sided hemihepatectomy (three patients), wedge resection (one patient), or segmental resection (four patients). Median intraoperative blood loss was 1950 (range 750-5500) ml. There was no surgery-related mortality. Morbidity included a secondary haemorrhage that necessitated relaparotomy, thrombosis of the femoral and iliac vein, and a wound infection. Median hospital stay was 12.5 (range 5-22) days.

The median diameter of the resected tumour was 8 (range 4-20) cm; pathological investigation confirmed the diagnosis of hepatocellular adenoma in all patients.

The median duration of follow-up for the surgically treated patients was 13.5 (range 1-188) months. All patients were alive. Seven patients were asymptomatic; one had complaints of fatigue without any liver enzyme abnormalities. All patients stopped using oral contraceptives and US of the liver showed no recurrence of a hepatocellular adenoma.

Four patients were treated conservatively without resection; two of them were in hypovolaemic shock on initial admission (Table 2). The duration of follow-up ranged from 7 to 15 months; steroids were not used. Three patients showed regression of the tumour and resorption of the haematoma on CT scanning. In two of these patients the tumour was not detectable at the last follow-up (Figure 1). One patient had no sign of regression, and resection was advised.

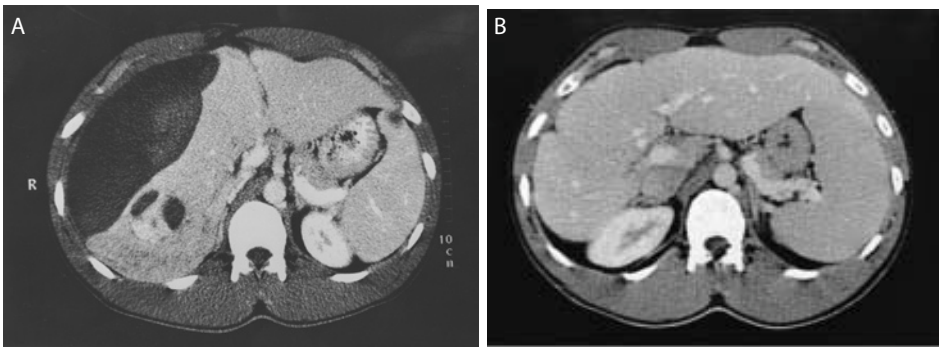


Figure 1. a. Computed tomogram at presentation showing a ruptured hepatocellular adenoma (asterisk) with subcapsular haematoma. The haematoma has displaced the right kidney (not seen in this figure) caudally and the falciform ligament (arrows) to the left. **b.** Computed tomogram at 15 months' follow-up of the same patient, treated conservatively. No adenoma was detectable and total regression of the subcapsular haematoma was noted. The right kidney and falciform ligament have been replaced.

DISCUSSION

Hepatocellular adenoma may present in various ways, including a mild abdominal pain or discomfort in the right upper quadrant, or as an incidental finding at abdominal imaging for unrelated pathology or at laparotomy. These tumours may also rupture and present with limited bleeding, causing acute abdominal pain in the right upper quadrant. On occasion, initial bleeding may be severe enough to produce haemorrhagic shock. Rupture is the mode of presentation in 50-65 per cent of individuals taking oral contraceptives who have a hepatocellular adenoma[2,11].

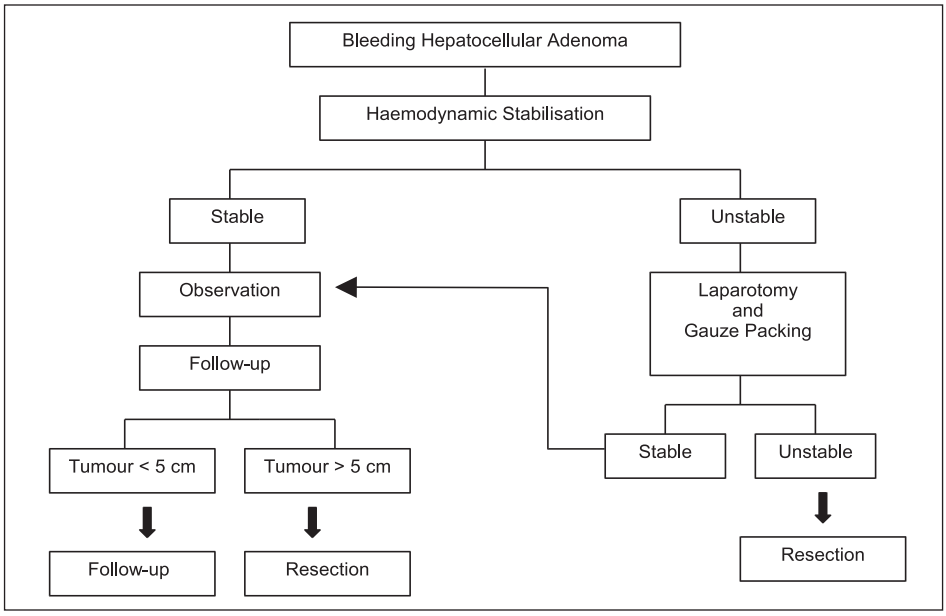
Size of a hepatocellular adenoma seems to be the predominant factor in determining whether bleeding will occur[9,12]. It has been suggested that the high rate of bleeding in case of a hepatocellular adenoma can be explained by their anatomical and pathological characteristics; hepatocellular adenomas are highly vascular tumours containing multiple dilated, thin-walled sinusoids with a high pressure inside, which is caused by an extensive arterial blood supply to the lesion[13,14]. In addition, they lack connective tissue support that allows blood to spread diffusely throughout the tumour. Whether haemorrhage remains confined to the tumour or produces haemoperitoneum depends principally on the distance separating the tumour from the liver surface and the thickness of the capsule.

Management of ruptured hepatocellular adenoma is of major concern. Many authors suggest that emergency resection is the preferred treatment for a ruptured hepatocellular adenoma[12,15-18]. However, high mortality rates and the serious morbidity after emergency resection[7-10] argue for a more conservative approach. Alternative approaches include hepatic arterial embolization to control bleeding[19-21]. A primary, non-operative management with or without arterial embolization is currently the preferred treatment for blunt liver injury, as

well[22,23]. Although spontaneous bleeding of a hepatocellular adenoma is an intrinsic process, the severity of liver injury may be equivalent to that sustained in major blunt trauma.

For this reason, a primary non-operative treatment with haemodynamic stabilisation and control of coagulation disorders is recommended. Even the possibility of malignancy is not an argument for acute resection, because intra-abdominal rupture of a carcinoma has to be considered as disseminated disease. In case of persistent or recurrent haemorrhage, laparotomy and abdominal packing is an option. In patients treated conservatively, subsequent management could include CT scanning at 3 and 6 months' follow-up, stopping oral contraceptives and avoiding pregnancy (Figure 2). Definitive resection should follow if the tumour diameter exceeds 5 cm after 6 months of follow-up or if rebleeding occurs. This distinction of 5 cm as an indication for resection is in accordance with series described in the literature[13,24], where data suggest that lesion size may be an important indicator of malignant transformation and rupture. If regression is noted, a conservative approach is justified in patients with an asymptomatic adenoma. One exception to these rules is when markers of chronic viral infection (hepatitis B or C) are positive or α-fetoprotein levels are high. In these patients it is virtually impossible for the pathologist to discriminate between adenoma and highly differentiated hepatocellular carcinoma. If there is no regression or even growth of the lesion, resection has to be preferred to prevent rebleeding or malignant transformation.

Figure 2. Algorithm for the management of bleeding hepatocellular adenoma.



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4.3

Work-up of focal liver lesions: Is there still a place for liver biopsy in the era of contrast MRI?

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Submitted.

WORK-UP OF FOCAL LIVER LESIONS: IS THERE STILL A PLACE FOR LIVER BIOPSY IN THE ERA OF CONTRAST MRI?

ABSTRACT

During differential diagnosis of a focal liver lesion most patients are subjected to an extensive work-up with different radiological modalities and multiple needle biopsies of the tumour. While liver biopsy is considered to be the gold standard during differential diagnosis of focal liver lesions, it is questionable if it still has an additional value in the era of improved radiological modalities, such as MR imaging.

We performed a review of the literature assisted by our own experience of three female patients who underwent surgery because of a focal liver lesion. In this report, we describe the diagnostic challenges that we encountered during differential diagnosis of these lesions and emphasise the improving role of the state-of-the art contrast MR imaging, which may equal or even exceed the value of needle biopsy.

INTRODUCTION

Although histological examination by fine needle biopsy is still considered to be the gold standard in the diagnosis of benign and malignant liver tumours[1,2], the availability of highly advanced radiological techniques provides a non-invasive diagnostic tool that is frequently being used. It is remarkable that needle biopsy and radiological examination share almost the same accuracy rate, and in some studies even a higher accuracy has been reported for magnetic resonance imaging (MRI)[3-6]. The availability of MRI sequences that allow faster imaging of the entire liver with much thinner slices, and tissue specific magnetic resonance (MR) contrast media clearly improved the sensitivity and specificity of MRI, while needle biopsy of focal liver lesions does have its own diagnostic pitfalls[7-9]. The morphology and immunohistochemical phenotype of liver tumours may overlap and sampling error can provide another diagnostic problem. In addition, precise histological criteria of liver cell dysplasia or atypia are not well described causing high interobserver variation and controversy concerning its diagnostic utility.

We report three cases of young female patients who underwent surgery for large liver lesions and the difficulty we encountered during the differential diagnosis of these tumours.

Case 1

A 29-year-old woman was referred to our hospital for evaluation of a hepatic mass, which was detected elsewhere. Her complaints consisted of diarrhoea without blood loss that started during her visit to a Latin American country. Intermittently, she experienced nausea and vomiting. Her complaints had been self-limiting at the time of first presentation in another clinic. She denied fever, jaundice or a history of intravenous drugs or alcohol abuse. She had used an oral contraceptive for the last 10 years.

Physical examination revealed normal vital signs. The abdomen was soft and non-tender. There was no palpable mass, nor signs of liver insufficiency. The initial analysis consisted of viral serology tests (hepatitis B and C, cytomegalovirus and Epstein-Barr virus) and repeated stool microscopy for cysts or trophozoites; no infectious disease could be detected. Laboratory values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, γ-glutamyl transferase, and α-fetopotein were within the normal range.

Abdominal ultrasound (US) showed a large solid lesion in the liver, situated in the right lobe with only a subtle change in echogenecity compared to the surrounding normal liver parenchyma. A contrast-enhanced dynamic CT scan revealed a well-defined lesion in segment V of the liver, which was hypodense to the surrounding liver on plain CT, and showed a very slight inhomogeneous increase in density after delivery of contrast. At MR imaging the lesion measured 7.8cm in largest diameter and had a well circumscribed, inhomogeneous appearance. On T1-weighted MR images, the tumour was composed of several nodules that

were surrounded by a low signal intensity tumour capsule. After intravenous administration of Gadolinium (a non-specific MR contrast agent), the lesion showed arterial enhancement of some nodules, with enhancement of the tumour capsule during the delayed images (Figure 1). To assess the Kupffer cell activity of the lesion, an additional MRI after administration of a superparamagnetic iron oxide (SPIO) (a specific MR contrast medium) was performed; there was no change in signal intensity at all, indicating the absence of Kupffer cells. The multinodularity of the lesion in combination with a differential enhancement of these nodules, the enhancement of a fibrous capsule, and the absence of Kupffer cells were consistent with a malignant nature of the tumour.

An ultrasound-guided percutaneous fine needle aspiration biopsy, which was performed before this patient presented in our clinic, showed foci of hepatocytes with a disturbed architecture within an irregular reticulin framework. Cytologically, the hepatocytes appeared uniform and normal. There were no mitotic figures, fatty change, or bile stasis. Multiple dilated, blood-filled spaces were observed. Portal tracts or ductular proliferation were not present. Based on these histological findings, a differential diagnosis of hepatocellular adenoma or focal nodular hyperplasia was made.

Considering the size of the tumour and the uncertain diagnosis, resection was recommended. At the time of operation, there was a well-circumscribed, non-compressible liver mass in segment V, which was surrounded by a firm fibrous capsule. The remainder of the liver was grossly normal. An enucleation of the tumour was performed.

The surgically enucleated tumour consisted of a 7.0 x 4.5 cm firmly encapsulated, well-circumscribed, solid tumour, which weighed 105 g (see Figure 1c). At microscopic examination, the tumour consisted of cells of hepatocellular origin that varied in size and were organised in groups, trabeculae and rosettes (see Figure 1d). The variation in nuclear and cellular size with hyperchromasia and prominent nucleoli was interpreted as mild to moderate atypia. No mitotic figures were present. Multiple arteries and veins were observed diffusely, but signs of vascular invasion were absent. A mildly to moderately increased mononuclear infiltrate was present in the tumour. Some connective tissue trabeculae with focal areas of haemorrhage and degeneration were seen. Portal zones with cholangioles, proliferating and reactive bile ductules were occasionally present. Because of the presence of areas with obvious atypia, the difficulty of differentiating between a hepatocellular adenoma, and a well-differentiated hepatocellular carcinoma persisted.

After a clinical and radiological follow-up of 28 months, no signs of tumour recurrence were detected in this patient.

Case 2

A 44-year-old woman was admitted to our hospital for the evaluation of multiple liver lesions that had been discovered by ultrasound elsewhere. The patient complained of an abdominal discomfort and had taken oral contraceptives continuously for 20 years until a few months

before admission. She denied alcohol or drugs abuse, and had no previous medical history. Physical examination revealed no abnormality, except obesity with a Body Mass Index of 28. Routine laboratory investigations and all tested tumour markers, e.g. alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen (CA19-9), and cancer antigen 125 (CA 125) were normal. Hepatitis serology tests were negative.

An abdominal US was performed, and showed multiple hyperechogeneous lesions scattered throughout the liver. After having been transferred to our institution, MRI was performed which illustrated a diffuse fatty liver (steatosis hepatis) with focal non-fatty areas. These areas were round or nodular in shape, creating "pseudotumours", and appeared as heterogeneous and slightly hyperintense on fat-suppressed T2-weighted images. Two larger solid lesions (largest diameter 6.2 cm and 2.4 cm, respectively) were identified in segment VI and VII and appeared inhomogeneous and hyperintense on T2-weighted and isointense on T1-weighted images. On out-of-phase T1-weighted MR images these solid lesions had a high signal due to the absence of fat within the nodules. After intravenous administration of Gadolinium, all lesions showed an immediate, intense arterial blush; on delayed images they were isointense to the surrounding liver. During arterial phase, there were additional multiple small lesions that were not seen on plain series; in delayed phase images some of these lesions remained visible. An additional MRI with a SPIO-agent was performed; seventeen minutes after contrast administration most of the "pseudotumours" became isointense to the surrounding liver, while the two larger lesions in segment VI and VII remained somewhat inhomogeneous. The MR imaging findings were consistent with the diagnosis of multiple hepatocellular adenomas.

Fine needle biopsy of the largest lesion that was performed elsewhere and revised in our clinic confirmed the outcome of MR imaging; normal hepatocytes with foci of double cell plates and steatosis were seen while there was an absence of bile ducts and portal triads. Using these morphologically diagnostic criteria, the lesion was diagnosed as a hepatocellular adenoma.

Because of the size of the largest adenoma, surgery was advised and the patient was operated on by an enucleation of the tumour.

The histopathologic examination of the resected specimen showed a normal background liver parenchyma with an extensive macrovacuolar pericellular steatosis. The lesion consisted of hepatocytes with normal nuclear/cytoplasmic ratios, and without mitotic figures. They were arranged in trabeculae of one or two cells thick. An irregular distribution of portal zones and dilated sinusoids were seen. No cholangioles or proliferating ductules were present, which has been confirmed by cytoceratin 19 immunostaining. Occasionally, septae of connective tissue were present containing some inflammation and thin-walled vessels. Centrally within the lesion, areas of haemorrhage and necrosis were detected.

Case 3

A 23-year old woman was referred to our clinic because of multiple liver lesions that were detected incidentally by an abdominal US, which was performed because of continuous left flank pain. There was no nausea, fever, or jaundice. The patient denied the use cigarettes, alcohol, or drugs, and she had no past medical history. At admission she had already stopped using oral contraceptives, which she had taken for a few years.

During physical examination, her obesity was remarkable (Body Mass Index: 30). There were no palpable masses in the abdomen, nor signs of liver insufficiency. Routine laboratory tests were normal and viral serology tests negative.

In our clinic, MRI was performed, which showed four well circumscribed lesions in the right liver lobe; in segment VI and VII (largest diameter 8.0 cm), in segment V and VI (largest diameter 4.0 cm), in segment VII and VIII (largest diameter 2.6 cm), and the final one in segment IVa (largest diameter 2.2 cm). All lesions had high signal intensity on T2- and low signal intensity on T1-weighted images, containing areas with low signal intensity on both T1- and T2-weighted sequences. There was no central scar. The post-Gadolinium images showed a moderate enhancement of all lesions with less enhancing areas in the largest lesion, which gained slight peripheral hyperintensity in the portal phase. On delayed images the lesions became isointense. On out-of-phase sequences the lesions showed a high signal on T1-weighted images, which is characteristic for adenosis hepatis.

A fine needle biopsy of the largest lesion was performed elsewhere and revised in our clinic. The lesion was of hepatocellular origin and contained some worrying morphological features, such as nuclear polymorphism and hyperchromasia, but no clear evidence for malignancy was found. Adenosis hepatis was considered in the differential diagnosis. Considering the uncertain diagnosis and the diameter of the largest lesion, a right hemihepatectomy was performed.

Histopathology showed a non-cirrhotic and remarkably steatotic background liver. The larger lesion with a maximum diameter of 8.0 cm consisted of a predominantly hepatocellular tumour, which was in some places circumscribed from the adjacent liver tissue, but had a microscopically blending border in other areas. There was a heterogeneous intralesional appearance; in certain places there were thin trabeculae with normal hepatocytes, and elsewhere there were foci of moderate pleomorphism with some areas of ballooned hepatocytes which contained usually small Mallory bodies. There was no mitosis or intralesional bile. In other places, often in the periphery of the lesion, there was more inflammation and ductular proliferation. Although the lesion had a merging border in places, neither definite invasion, nor vascular invasion was seen. An increase of solitary arterioles was present, but there were no abnormal vessels of the type that assist in the identification of focal nodular hyperplasia. There also was intralesional haemorrhage in some places. The smaller lesion with a maximum diameter of 2.5 cm was less variegated and consisted almost entirely of a well-differentiated hepatocellular lesion with ductular proliferation and inflammatory cell infiltration resembling

the peripheral parts of the larger lesion. There was no loss of reticulin in either of the lesions, but the CD34 immunostaining pattern was diffuse and in some places corresponded to the more pleomorphic areas in the larger lesion. Regarding the above called histological features of both lesions, the smaller one was classified as a focal nodular hyperplasia, and the larger one as an "atypical adenoma", indicating that histopathologically a relative benign prognosis was expected, but a careful clinical follow-up of the patient might be justified.

After a follow-up of 18 months, no tumour recurrence or extra-hepatic metastases were detected in this patient.

DISCUSSION

Fine needle biopsy is still accepted as the gold standard for diagnosing tumours in various organs. In focal lesions of the liver the specificity and the positive predictive value is very high, however, the sensitivity of the procedure widely ranges between 67% to 93%[6,10]. Whereas the identification of moderate and poorly differentiated hepatocellular carcinoma is easily achieved by histopathology, identification of well-differentiated hepatocellular carcinoma is more difficult. Distinction from hepatocellular adenoma, and in some cases from focal nodular hyperplasia remains a diagnostic challenge, particularly in small biopsies[11,12]. Besides, needle biopsy of hepatic tumours is associated with the known hazards of haemorrhage, needle-tract tumour seeding, sampling error, and misdiagnosis[13]. If liver cell dysplasia is diagnosed by liver biopsy, the question remains how to classify the degree of dysplasia because of lacking histological criteria of liver cell dysplasia. Another issue is the therapeutic implication of histological dysplasia. Is hepatocellular carcinoma preceded by liver cell dysplasia or should liver cell dysplasia be considered as a risk factor for development of hepatocellular carcinoma[14,15]? Another important subject is how much atypia is permissible within an adenoma before carcinomatous change should be considered. Modern cytopathological techniques such as cytophotometric analysis of DNA content underline the correlation of aneuploidy with the presence and grade of differentiation of hepatocellular carcinoma[10]. Other molecular genetic techniques, such as detection of loss of heterozygosity in hepatocellular carcinoma may also provide a potential solution to problematic histological queries[16]. Comparative genomic hybridisation and fluorescence *in situ* hybridisation revealed typical aberration patterns not only in moderate or poorly differentiated hepatocellular carcinoma but also in well-differentiated samples[17-19]. These aberrations were strikingly different from the low number of aberrations detected in hepatocellular adenoma[17]. Although these techniques may reduce the uncertainty of distinguishing benign lesions from well-differentiated carcinoma, they are based on an elaborate and time consuming procedures making it difficult, and mostly impossible to apply in small biopsies in daily routine.

During radiological investigation of a focal liver mass, MR imaging may be the most reliable way of differentiating malignant lesions from benign liver tumours[4,7,8] (Figure 2a, 2b). The superiority of MR imaging is due to differences in techniques of data acquisition and contrast medium administration, in addition to inherently greater tissue contrast with MR imaging. Firstly, in most centres, dynamic gadolinium-enhanced MR imaging is performed with multislice two-dimensional or three-dimensional breath-hold and breathing-independent sequences that allow faster imaging of the liver with much thinner slices and have several intrinsic features that render them superior to CT[20]. Secondly, fast MR imaging sequences allow the use of timing bolus or automated contrast detection techniques to determine the contrast arrival time within the aorta. Finally, in MR imaging, a small amount of contrast medium is injected. This allows a short injection time with a compact bolus. This facilitates the acquisition of truly distinct phases of dynamic contrast-enhanced MR imaging examination of the entire liver. The recent availability of tissue specific contrast media such as manganese chelates and reticuloendothelial agents, e.g. ferumoxides targeting either hepatocytes or Kupffer cells, provide new possibilities for lesion characterisation on the basis of its cellular composition and function rather than its vascularity and diffusion within its extracellular space[21-23] (Figure 2c, 2d).

In all three cases presented in this report, a pre-operative needle biopsy was performed during work-up in another clinic before the patients were referred to our clinic. In case one, MR imaging could not exclude a malignant lesion, which should be reason to operate on a lesion at all times. The fact that needle biopsy showed benign morphological features did not change our decision for surgery. In the second and third case, MR imaging showed characteristic features of adenosis hepatis. Apart from the outcome of pre-operative needle biopsy, surgery was decided upon the diameter of the lesions, since in our clinic, we follow an operative approach to large hepatocellular adenomas (>5 cm), due to the risk of haemorrhage and malignant degeneration.

By means of this report we would like to underline the improving role of radiology in the diagnosis of focal liver lesions. Although it is impossible to differentiate all focal liver lesions, the use of a state-of-the-art pattern recognition approach and the combination of various MR sequences and contrast enhancement techniques makes it possible to diagnose most hepatic tumours with confidence[7,24]. This may have consequences for the role needle biopsy during work-up of a focal liver lesion. Considering the advantages and disadvantages of both diagnostic modalities, it may be questionable if radiology has equalled or even exceeded the value of needle biopsy as the gold standard. The accuracy rate of these modalities seems to be similar, and it should be questioned if an additional pre-operative needle biopsy will have therapeutic implications after having performed state of the art MR imaging of the liver.

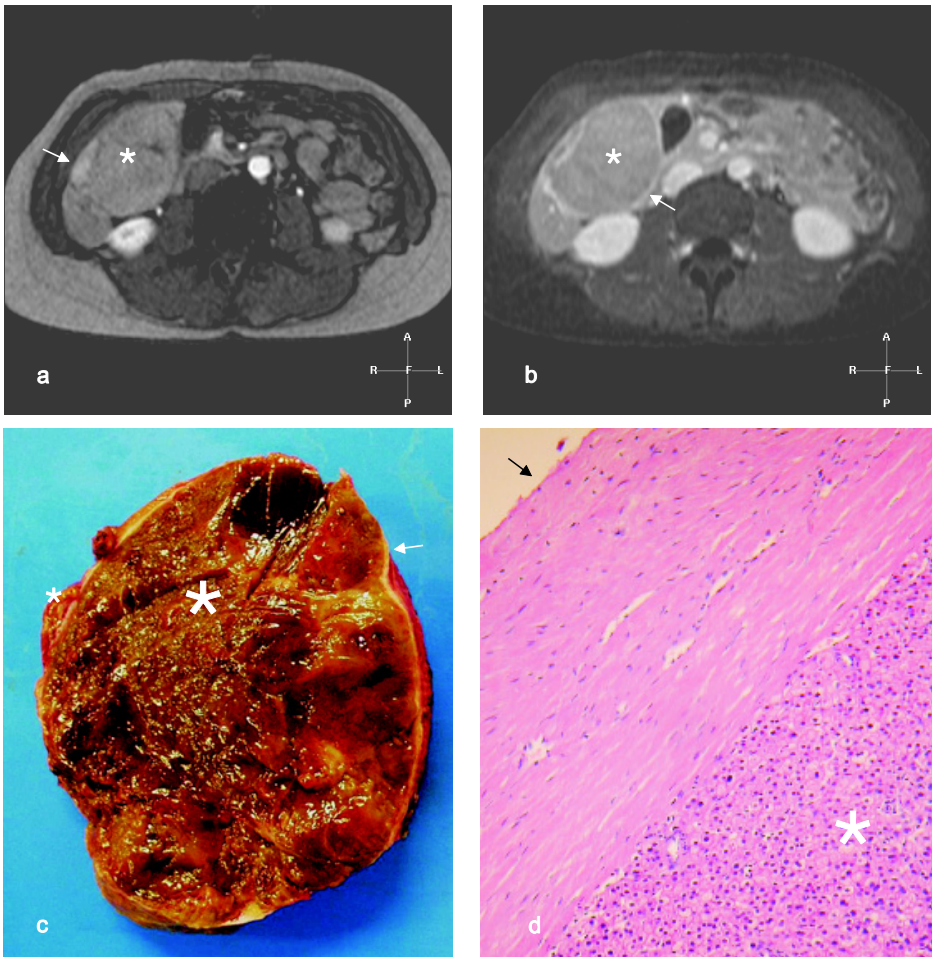

Figure 1. A 26-year-old woman (case 1) with a tumour of hepatocellular origin, with signs of malignancy at MR imaging and gross pathology, and predominantly adenoma-like histology. **a.** A T1-weighted MR image during the arterial phase after intravenous Gadolinium injection shows a tumour composed of several nodules with variable enhancement. One nodule enhances more (arrow) than the other (*). The nodules are surrounded by a dark capsule. These findings suggest malignancy. **b.** A T1-weighted MR image with fat-suppression during the delayed phase after the injection of Gadolinium shows the tumour (*) that is surrounded by a thick enhanced fibrous tumour capsule (arrow), a classic sign of large hepatocellular carcinomas at MR imaging. **c.** Photograph of the resected specimen (*) confirms the MR imaging findings of multi-nodularity and the thick fibrous tumour capsule (arrow). Both findings are often seen in hepatocellular carcinoma. **d.** Photomicrograph (hematoxylin & eosin stain; 100x) through the periphery of the tumour shows the fibrous tumour capsule (arrow) that contains cells of hepatocellular origin organised in groups, trabeculae and rosettes (*).

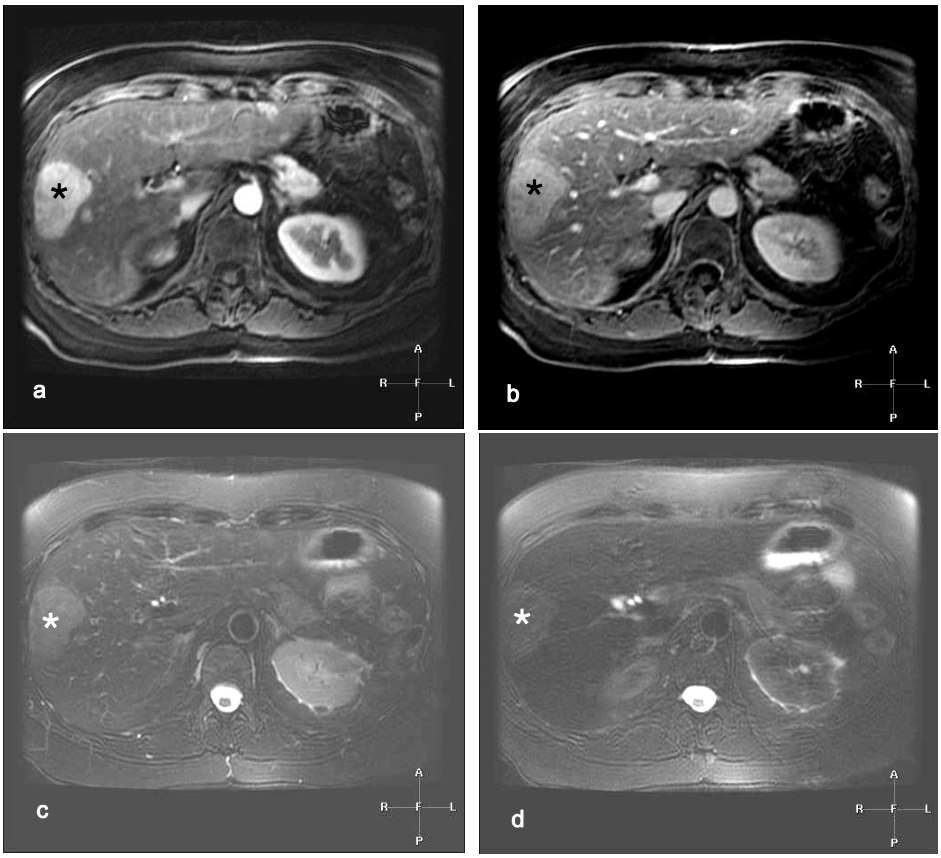

Figure 2. A 30-year-old woman (not described in this manuscript) with a tumour that shows MR imaging findings of a typical hepatocellular adenoma. **a.** A T1-weighted MR image during the arterial phase after intravenous Gadolinium injection shows a tumour with homogeneous enhancement of the entire nodule (*). **b.** A T1-weighted MR image with fat-suppression during the delayed phase after the injection of Gadolinium shows the tumour (*) that has become almost isointense with the surrounding liver, without any evidence of a tumour capsule. **c.** A T2-weighted MR image with fat-suppression before the intravenous injection of superparamagnetic iron oxide (SPIO) contrast agent that is specifically taken up by the Kupffer cells. The tumour (*) is slightly brighter than the surrounding liver, a typical sign of a benign hepatocellular tumour like adenoma. **d.** A T2-weighted MR image with fat-suppression after the intravenous injection of superparamagnetic iron-oxide contrast agent. Note that the liver has become substantially darker compared to the image shown in c) due to the SPIO uptake. In addition, the tumour (*) also shows homogeneous decrease in signal intensity indicating that the tumour contains Kupffer cells with homogeneous distribution, suggesting the primary and benign nature of this lesion.

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CHAPTER 5

Focal nodular hyperplasia

5.1

Focal nodular hyperplasia: Findings at state-of-the-art MR Imaging, US, CT, and pathologic analysis.

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FOCAL NODULAR HYPERPLASIA: FINDINGS AT STATE-OF-THE-ART MR IMAGING, US, CT, AND PATHOLOGIC ANALYSIS

ABSTRACT

Focal nodular hyperplasia (FNH) is the second most common benign liver tumor after hemangioma. FNH is classified into two types: classic (80% of cases) and nonclassic (20%). Distinction between FNH and other hypervascular liver lesions such as hepatocellular adenoma, hepatocellular carcinoma, and hypervascular metastases is critical to ensure proper treatment. An asymptomatic patient with FNH does not require biopsy or surgery. Magnetic resonance (MR) imaging has higher sensitivity and specificity for FNH than does ultrasonography or computed tomography. Typically, FNH is iso- or hypointense on T1weighted images, is slightly hyper- or isointense on T2-weighted images, and has a hyperintense central scar on T2-weighted images. FNH demonstrates intense homogeneous enhancement during the arterial phase of gadolinium-enhanced imaging and enhancement of the central scar during later phases. Familiarity with the proper MR imaging technique and the spectrum of MR imaging findings is essential for correct diagnosis of FNH.

INTRODUCTION

Edmondson[1] introduced the term focal nodular hyperplasia (FNH) in 1958. In 1995, the International Working Party classified FNH with other regenerative lesions, in contrast to adenoma, which is known as a neoplastic lesion[2]. FNH is defined as a nodule composed of benign-appearing hepatocytes occurring in a liver that is otherwise histologically normal or nearly normal[2].

The pathogenesis of this lesion is not well understood[3-7]. Vascular malformation and vascular injury have been suggested as the underlying mechanism[3]. An association with steroids has been denied more recently[5]. FNH is the second most common benign liver tumor after hemangioma and has a reported prevalence of 0.9%[6]. The male-to-female ratio is 1:8, and the tumors occur in relatively young patients[6]. Approximately 20% of the patients have multiple FNH lesions[6]. The combination of multiple FNH lesions and hemangiomas is considered to be multiple FNH syndrome[3,6].

FNH is often an incidental finding at imaging[8-10]. Distinction between FNH and other hypervascular liver lesions such as hepatocellular adenoma, hepatocellular carcinoma (HCC), and hypervascular metastases is critical to ensure proper treatment. FNH is asymptomatic in most patients, and in such cases no treatment is necessary. In symptomatic or ambiguous cases, transarterial embolization or surgical resection may be considered.

Distinction of FNH from other hepatic abnormalities at ultrasonography (US) and computed tomography (CT) may be difficult because these modalities, unlike magnetic resonance (MR) imaging, do not provide information concerning the tissue characteristics of the lesions. Currently, CT is increasingly being used for assessment of liver lesions. Therefore, it should be kept in mind that if triphasic CT is not performed or the timing of the arterial phase is incorrect, FNH can be misdiagnosed and many patients may be exposed to unnecessary biopsy or even surgery.

Based on our experience in more than 60 patients with FNH, this article describes the most recent concepts about the pathologic features of FNH including its angioarchitecture and demonstrates the full spectrum of findings in FNH at state-of-the-art MR imaging in comparison with US and CT.

CLASSIFICATION

Currently, FNH is divided into two types: classic and nonclassic. The nonclassic type contains three subtypes: (a) telangiectatic FNH, (b) FNH with cytologic atypia, and (c) mixed hyperplastic and adenomatous FNH (Table)[6].

Classic FNH is characterized by the presence of (a) abnormal nodular architecture, (b) malformed vessels, and (c) cholangiolar proliferation. Nonclassic FNH lesions lack one of the

following classic features - nodular abnormal architecture or malformed vessels - but always show bile ductular proliferation[6].

Table 1. Current pathologic classification of FNH

Type or Subtype	Percentage of Cases
Classic FNH	80
Nonclassic FNH	20
Telangiectatic FNH	15
FNH with cytologic atypia	3
Mixed hyperplastic and adenomatous FNH	2

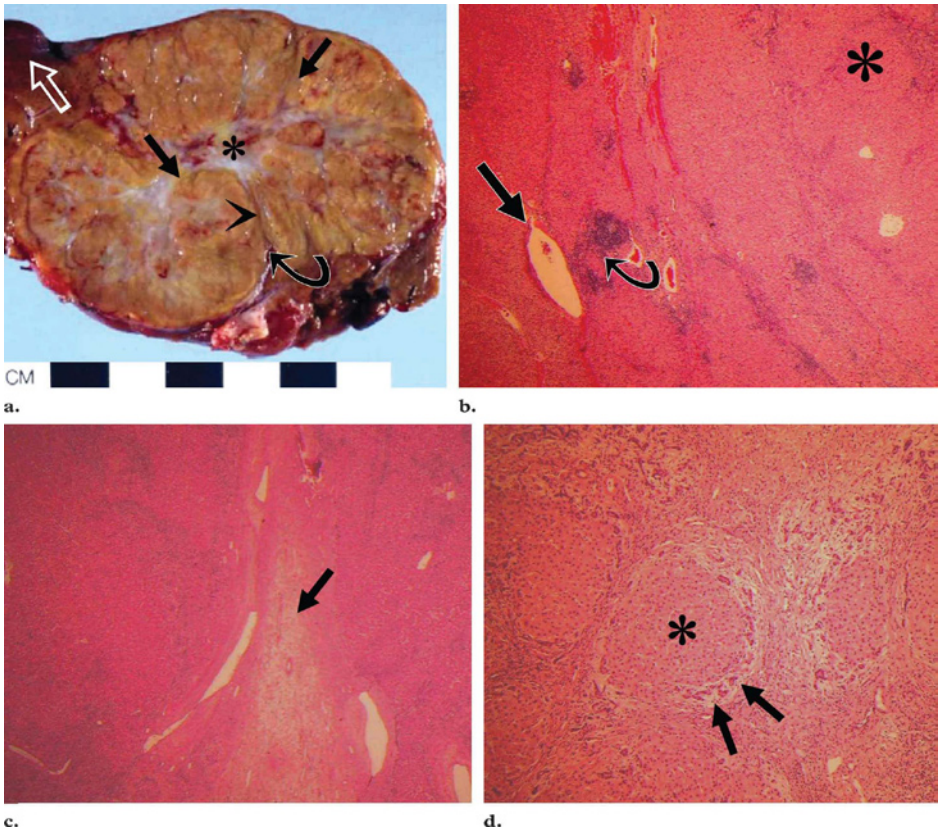


Figure 1. Gross pathologic and histologic features of classic FNH. a. Cross section of a resected specimen of classic FNH shows yellowish nodules of variable size (straight black arrows) surrounded by multiple septa (arrowhead) and a central scar (*). The central scar contains large vessels (curved black arrow). Normal liver tissue (white arrow) surrounds the FNH. Note that there is no fibrous capsule at the interface of the lesion and the liver. b. Photomicrograph (original magnification, x40; hematoxylin-eosin [H-E] stain) shows the interface of the FNH (*), which contains multiple nodules and septa, and the surrounding normal hepatic parenchyma, which contains large vessels (straight arrow) and portal vein tracts with inflammatory infiltrates (curved arrow). c. Photomicrograph (original magnification, x40; H-E stain) shows a septum (arrow) dividing two neighboring nodules. The septum contains connective tissue and multiple arteries. d. Photomicrograph (original magnification, x100; H-E stain) shows a typical FNH nodule (*) surrounded by septa. At the interface of the nodule and the septa, ductular proliferation can be seen (arrows).

GROSS PATHOLOGIC AND HISTOLOGIC FEATURES

The gross appearance of classic FNH consists of lobulated contours and parenchyma that is composed of nodules surrounded by radiating fibrous septa originating from a central scar (Figure 1).

The central scar contains malformed vascular structures (Figure 2). Among classic FNH lesions, one or more macroscopic central scars are present in most cases. At histologic analysis, classic FNH shows nodular hyperplastic parenchyma. These nodules are completely or incompletely surrounded by circular or short fibrous septa. The hepatic plates may be moderately

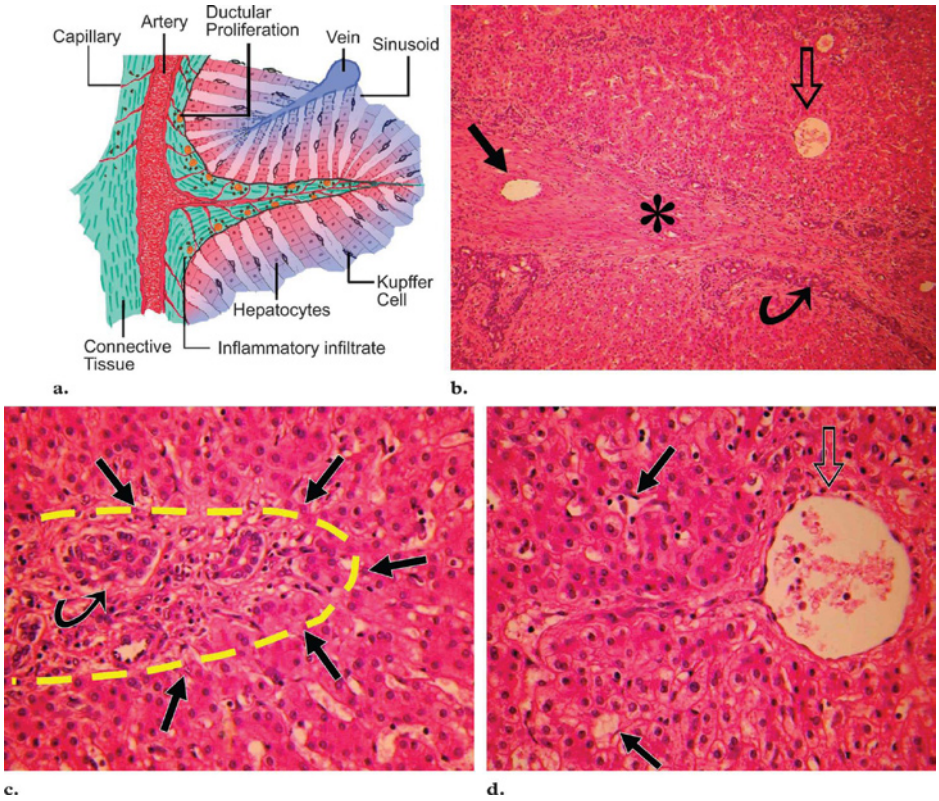


Figure 2. Vascularity of FNH. **a.** Drawing of part of an FNH lesion shows a septum that contains connective tissue, a large thick-walled artery and numerous capillaries, and ductular proliferation with inflammatory cells. The rich network of capillaries, which provides arterial blood to the hepatocytes and sinusoids, is responsible for the highly hypervascular nature of most FNH lesions at imaging. The sinusoids drain into veins. The malformed arteries of FNH arise from the hepatic artery, and the vein of FNH eventually drains into the hepatic vein. Note that FNH does not contain portal vessels. **b.** Photomicrograph (original magnification, x200; H-E stain) shows a fibrous septum (*) that contains a thick-walled artery (straight solid arrow). Note the ductular proliferation (curved arrow) at the interface of the septum and the parenchyma. The vein (open arrow) is located within the parenchyma. **c.** Photomicrograph (original magnification, x400; H-E stain) shows details of the end-artery (dashed line), which is divided into numerous small capillaries that are connected to the sinusoids (straight arrows). Curved arrow = ductular proliferation. **d.** Photomicrograph (original magnification, x400; H-E stain) shows details of the vein (open arrow). Note that numerous sinusoids (straight arrows) drain into a venule and eventually into the vein.

thickened (two or three cells in thickness) with normal-appearing hepatocytes. The central scar contains fibrous connective tissue, cholangiolar proliferation with surrounding inflammatory infiltrates, and malformed vessels of various caliber, including tortuous arteries with thickened walls, capillaries, vascular channels of undetermined type, and veins[3,6]. The afferent artery branches into the hierarchy of vessels, and the smallest arteries supply the mononuclear nodules of approximately 1 mm in diameter[3,6]. The arterial blood in FNH, as opposed to that in adenomas, flows centrifugally from the anomalous central arteries. Approximately 50% of lesions show some degree of fatty infiltration, as opposed to the surrounding liver, which shows signs of steatosis in less than 20% of classic FNH lesions. Both the classic and nonclassic types contain variable amounts of Kupffer cells (Figure 3)[3,6].

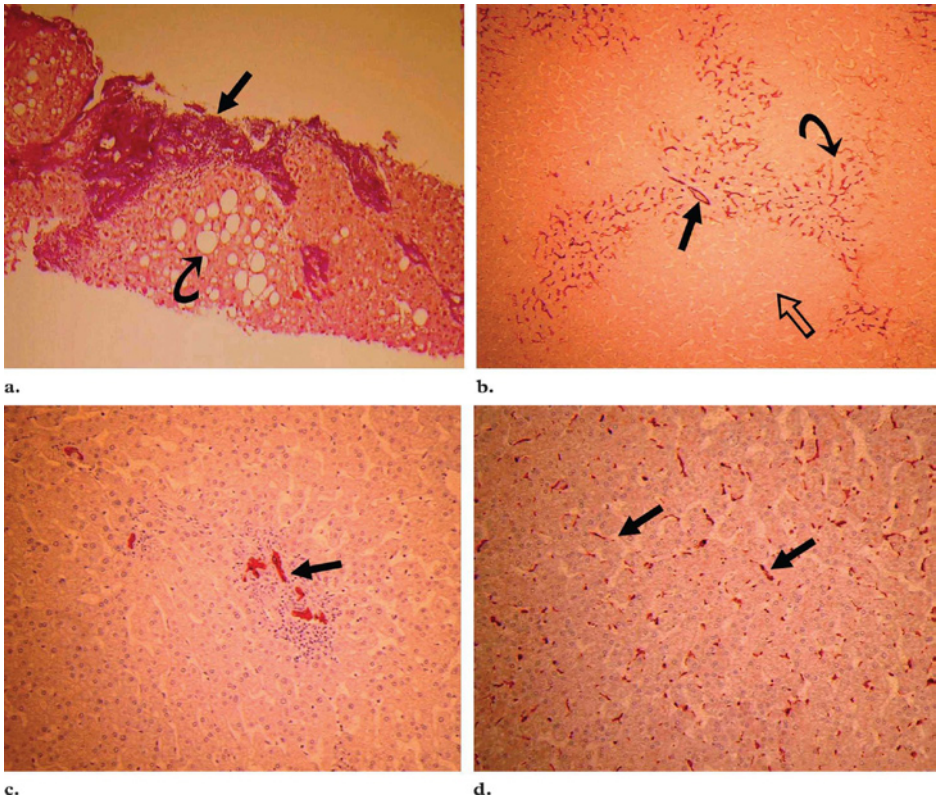


Figure 3. Important tissue components of FNH as shown with specific histologic stains. **a.** Photomicrograph (original magnification, x100; elastica van Gieson stain) of a biopsy specimen shows the fibrous septa (straight arrow) and hepatocytes of FNH, which contain steatosis (curved arrow). **b.** Photomicrograph (original magnification, x200; CD 34 stain) shows the epithelium of the arteries (straight solid arrow) and capillaries (curved arrow) fading into the sinusoids of FNH (open arrow). **c.** Photomicrograph (original magnification, x200; keratine 19 stain) shows ductular proliferation within a short septum of FNH (arrow). **d.** Photomicrograph (original magnification, x200; CD 68 stain) shows numerous Kupffer cells lining the sinusoids of FNH (arrows).

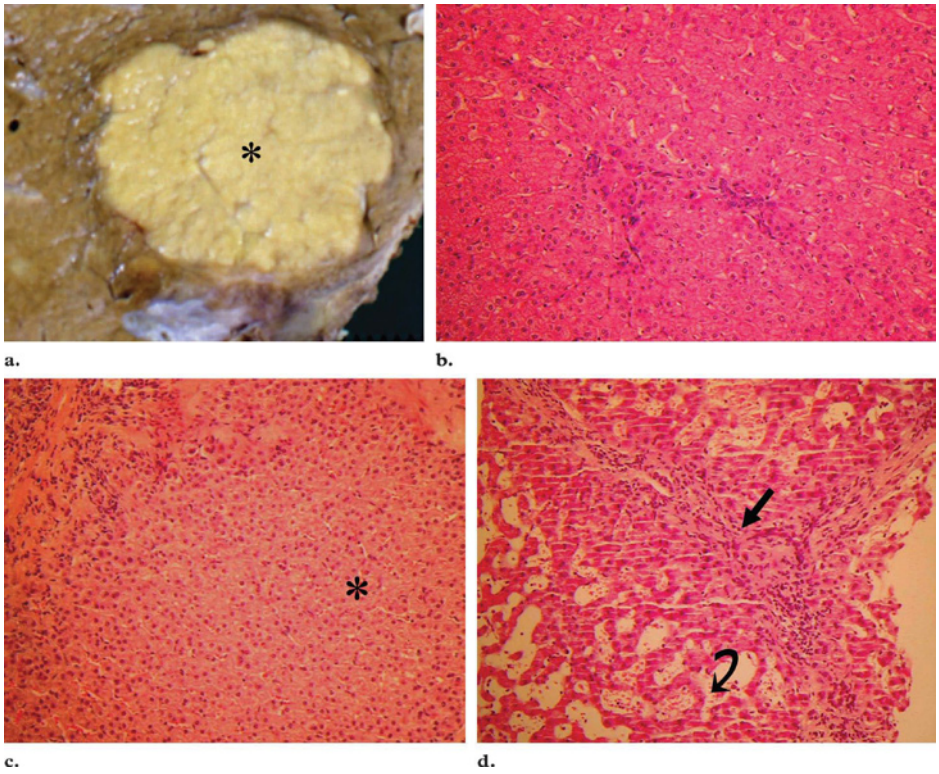


Figure 4. Gross pathologic and histologic features of nonclassic FNH. **a.** Cross section of a fixed resected specimen shows a nonclassic FNH (*). The lesion contains neither prominent septa nor a central scar. Normal liver tissue surrounds the FNH without a fibrous capsule. **b.** Photomicrograph (original magnification, x200; H-E stain) of the FNH shows a short septum containing a small amount of connective tissue and ductular proliferation. (Figure 3c shows ductular proliferation in the same slide.) **c.** Photomicrograph (original magnification, x200; H-E stain) of a specimen from another patient shows a small area of FNH containing monotonous hepatocytes (*), an appearance that resembles that of adenoma and suggests a mixed type of FNH. **d.** Photomicrograph (original magnification, x200; H-E stain) of a specimen from another patient shows telangiectatic FNH, which is composed of a relatively short septum (straight arrow) and atrophic hepatocytes with wider sinusoids than those normally present in classic FNH (curved arrow).

The gross appearance of nonclassic FNH is heterogeneous and globally resembles that of adenomas in most cases, with vaguely lobulated contours and lack of a microscopic central scar in almost all cases. The histologic features of nonclassic FNH depend on the subtype. The telangiectatic type consists on hepatic plates that are one cell thick and frequently appear atrophic. The plates are separated by dilated sinusoids. A few fibrous septa, which are shorter than in classic FNH, can be found in all cases of telangiectatic FNH. The telangiectatic type always contains some degree of bile ductular proliferation. The mixed hyperplastic and adenomatous form of FNH has two alternating aspects: one resembling the telangiectatic type, the other simulating adenomas. FNH with cytologic atypia contains areas of large cell dysplasia. Except for the dysplastic areas, most of these lesions have the gross and histologic features of classic FNH (Figure 4).

IMAGING OF FNH

At imaging studies, typical and atypical lesions can often be distinguished on the basis of morphology, the appearance of the lesion relative to the surrounding liver on unenhanced images, the vascularity of the lesion, and the presence of any diffuse parenchymal liver disease[8-10]. US may often be the initial imaging modality that indicates a focal liver lesion. Typical FNH can be diagnosed by confidence at CT or MR imaging. Atypical FNH may appear as a large lesion, which is sometimes multiple in location. The tumor may show less intense enhancement, unusual appearance or nonenhancement of the central scar, and pseudocapsular enhancement on delayed images. In these cases, it may be difficult to differentiate atypical FNH from benign and malignant lesions such as hepatocellular adenoma, HCC, fibrolamellar carcinoma, and hypervascular hepatic metastases.

ULTRASONOGRAPHY

At US, typical FNH is often not well visualized. There may be only a subtle change in echogenicity compared with the surrounding normal liver parenchyma. The conspicuity of the lesions at US may improve with a relatively large or prominent central scar[8]. The lesions may be slightly hypo-echoic, isoechoic, or slightly hyperechoic. Some lesions may show a hypoechoic halo surrounding the lesion. This halo most likely represents compressed hepatic parenchyma or vessels surrounding the lesion. The halo may be more prominent around FNH with fatty infiltration that is located within a liver with steatosis as well. In such cases, the compressed liver parenchyma surrounding the lesion is devoid of fat and has relatively low echogenicity compared with the liver and the lesion. The outer contours of the lesions may be well defined, although the internal structure of FNH, including the central scar, is often not

well visualized (Figure 5). Use of color and power Doppler US may add information concerning the vascularity of the suspected FNH. In addition, use of US contrast media to characterize FNH has been reported[7,8]. Despite these possibilities, US is currently not considered the modality of choice for characterization of focal liver lesions.

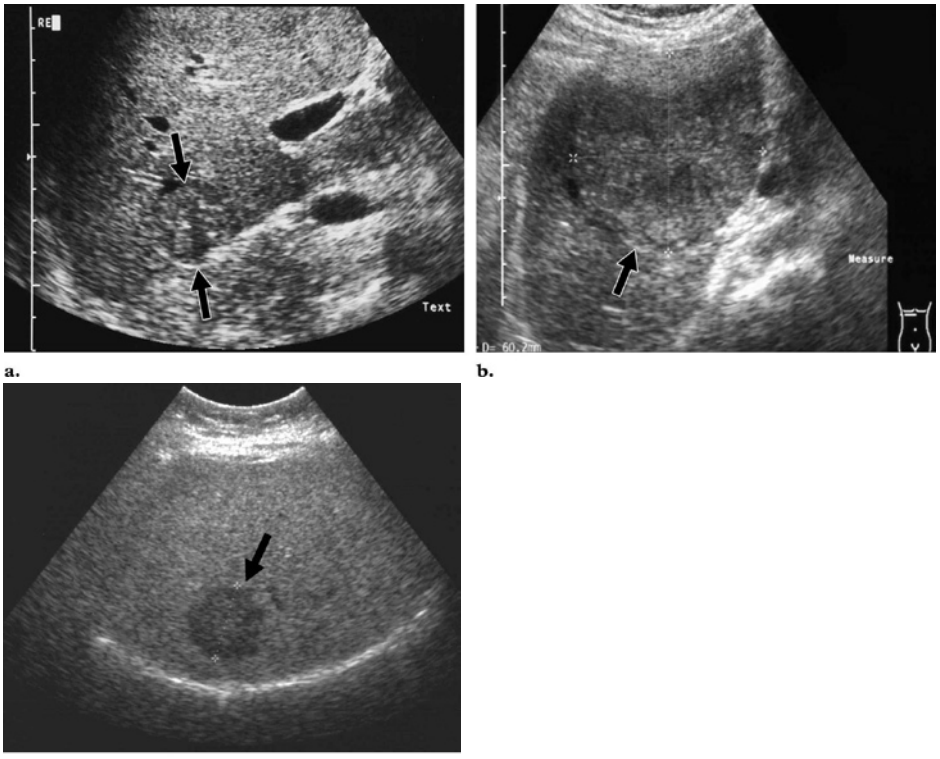


Figure 5. US appearance of FNH. **a.** Sagittal US scan shows FNH that is slightly hypoechoic relative to the surrounding liver tissue (arrows) and causes slight distortion of the outer liver contour. **b.** Sagittal oblique US scan of another patient shows FNH that is well differentiated from the surrounding liver tissue (arrow). There is a suggestion of radiating septa within the lesion. **c.** Axial US scan of another patient shows FNH that is profoundly hypoechoic (arrow) due to diffuse fatty infiltration of the surrounding liver tissue.

COMPUTED TOMOGRAPHY

The broad availability of CT as well as the recent development and implementation of the faster multirow detector machines make this modality an excellent tool for detection and characterization of focal liver lesions, including FNH[9,10]. Currently, multirow detector CT does allow triphasic or even multiphasic dynamic contrast material–enhanced imaging in relatively shorter scanning times. The shorter scanning times allow the capture of distinct phases, including the unenhanced phase, arterial phase, portal phase, and venous phase. These phases provide important information concerning the enhancement patterns and hence offer the possibility of characterizing focal liver lesions. In clinical practice, the number of phases that are usually imaged with CT is limited and often kept to a minimum, mainly due to the radiation hazard. The issue of radiation is even more important in relatively young and otherwise healthy patients with an incidental liver lesion that needs characterization or follow-up, such as FNH.

Typical FNH may have lobulated contours at CT[8-10]. At unenhanced CT, the lesions are either hypoattenuating or isoattenuating to the surrounding liver. In the arterial phase, the lesions become hyperattenuating due to the homogeneous intense enhancement of the entire lesion, except the central scar. In the portal and later phases, the lesions become more isoattenuating with the surrounding liver and the central scar may show some enhancement (Figure 6).

MR IMAGING

MR imaging has higher sensitivity (70%) and specificity (98%) for FNH than US and CT[10]. The central scar was more often detected with MR imaging than with CT (78% and 60%, respectively). The higher sensitivity and specificity of MR imaging may be due to the fact that state-of-the-art MR imaging provides information concerning the soft-tissue characteristics as well as the vascularity of the lesions. In addition, on the basis of the physical principles, MR imaging provides a number of unique possibilities concerning the technique of data acquisition and contrast medium administration[11-13]. First, in most centers, dynamic gadolinium-enhanced MR imaging is currently performed with multisection two-dimensional (2D) or three-dimensional (3D) gradient-echo (GRE) sequences. With such sequences, the central k-space profiles, which determine the image contrast in all individual sections, are acquired in less than half the total duration of one breath-hold sequence (5 seconds). Second, fast MR imaging sequences allow use of a timing bolus, automated contrast detection techniques, and time-resolved scanning to determine the contrast material arrival time within the aorta. Finally, in MR imaging, a small amount of contrast medium (15-20 mL of gadolinium contrast material) is injected. This allows a short injection time with a compact bolus. This facilitates the imaging of truly distinct

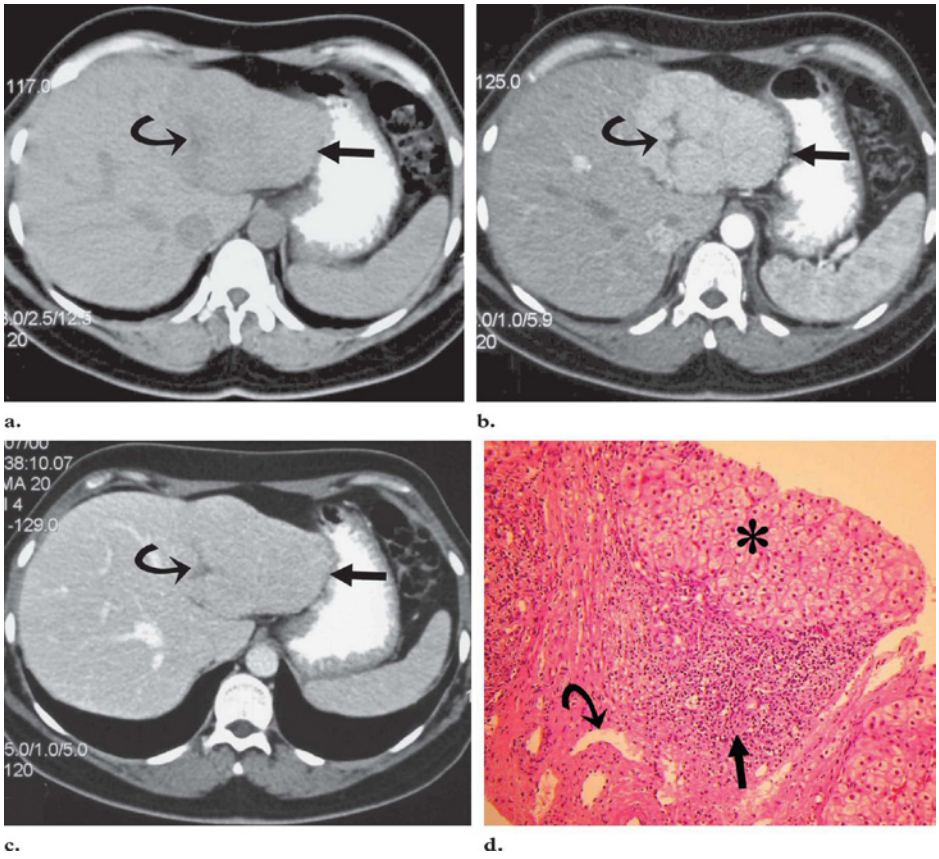


Figure 6. CT appearance of typical FNH with pathologic correlation. **a.** Precontrast CT image shows a large lesion (straight arrow) that is only slightly hypoattenuating relative to the surrounding liver tissue. Within the lesion, a central scar (curved arrow) can be seen. **b.** Contrast-enhanced CT image obtained during the arterial phase shows intense homogeneous enhancement of the lesion (straight arrow), except for the central scar (curved arrow). **c.** Contrast-enhanced CT image obtained during the portal phase shows that the lesion (straight arrow) has become isoattenuating relative to the liver. The central scar (curved arrow) has not yet fully enhanced. **d.** Photomicrograph (original magnification, x200; H-E stain) of a biopsy specimen shows classic FNH composed of nodules (*) surrounded by septa (straight arrow), which contain ductular proliferation, inflammatory infiltrates, connective tissue, and large vessels (curved arrow).

phases in dynamic contrast-enhanced MR imaging of the entire liver. Lack of radiation allows multiphasic gadolinium-enhanced MR imaging in combination with multiple other sequences that facilitate detection and characterization of diffuse and focal liver lesions.

Typically, FNH is iso-or hypointense on T1-weighted images (94%–100%), is slightly hyper- or isointense on T2-weighted images (94%–100%), and has a hyperintense central scar on T2-weighted images (84%)[10]. FNH shows intense homogeneous enhancement in the arterial phase and enhancement of the central scar in the later phases of gadolinium-enhanced imaging (Figure 7). Hepatocellular adenomas show less intense enhancement and lack a central scar.

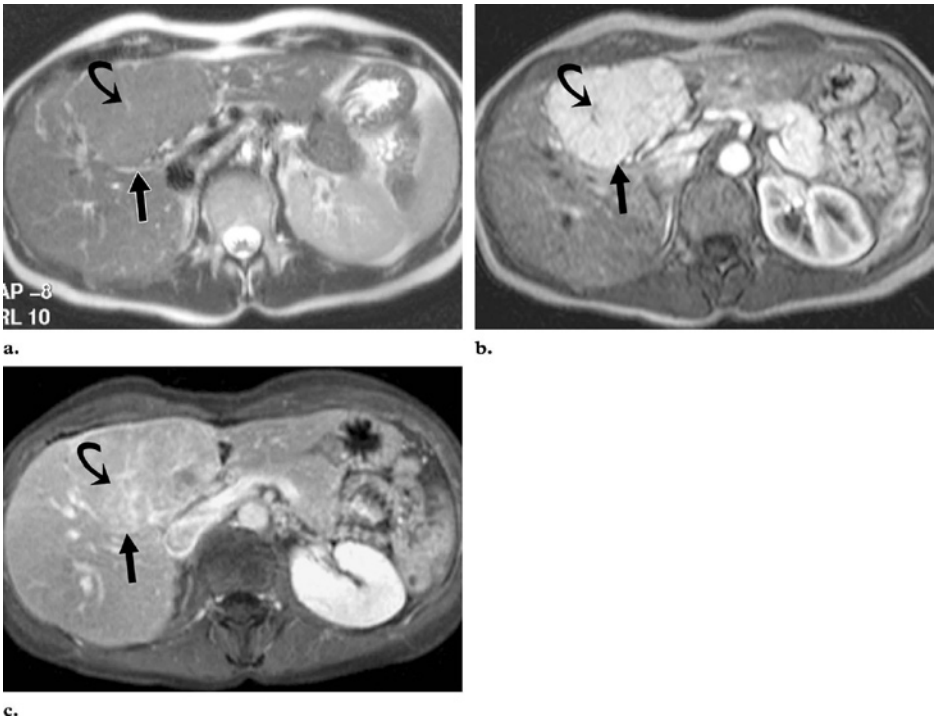
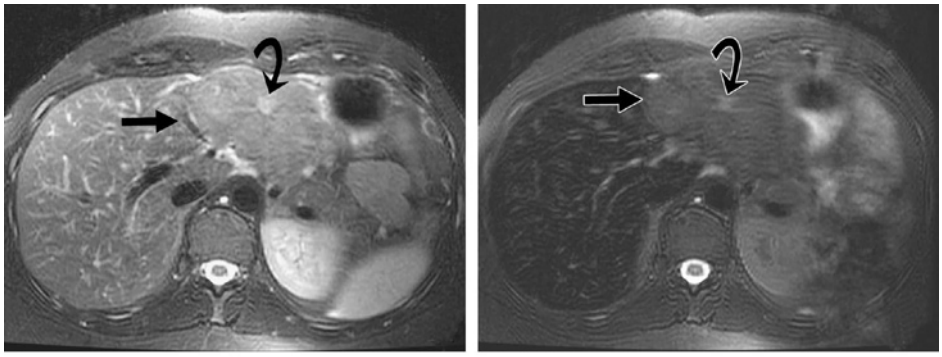


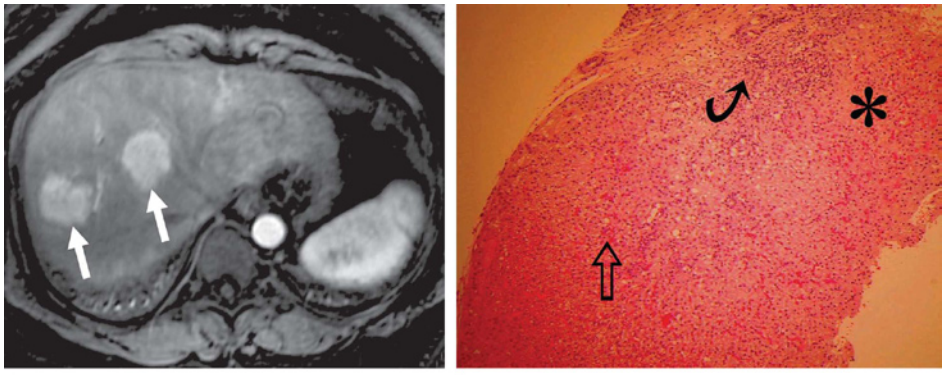
Figure 7. MR imaging appearance of typical FNH. **a.** Axial T2-weighted single-shot fast spin-echo (SE) image shows a large FNH lesion (straight arrow) that is isointense relative to the surrounding liver parenchyma. The central scar (curved arrow) has slightly higher signal intensity than the lesion. **b.** Axial gadolinium-enhanced 2D T1-weighted GRE image obtained during the arterial phase shows intense homogeneous enhancement of the entire lesion (straight arrow), except for the central scar (curved arrow). **c.** Axial gadolinium-enhanced 2D T1-weighted GRE image obtained during the portal phase shows that the lesion (straight arrow) has become isointense relative to the surrounding liver parenchyma, and the central scar (curved arrow) has enhanced.

Specific contrast media such as superparamagnetic iron oxide–based (eg, ferucarbotran [Resovist; Schering, Berlin, Germany]) and manganese-based (ie, mangafodipir trisodium [Tesla-scan; Nycomed Amersham, Oslo, Norway]) media are targeted at the Kupffer cells and hepatocytes, respectively[12-15]. These contrast media can be used to demonstrate the hepatocellular origin of the lesions. The Kupffer cells show uptake of ferucarbotran and lower the signal intensity of the lesions as well as the surrounding liver on T2- and T2*-weighted images (Figure 8).



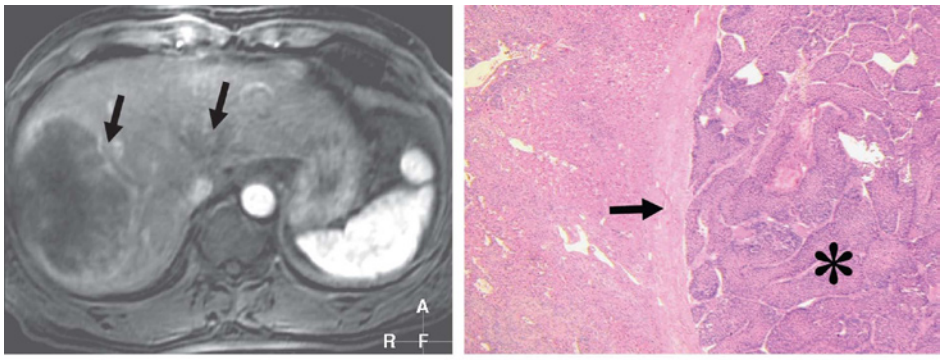
a. b.

Figure 8. Appearance of typical FNH at superparamagnetic iron oxide (ferucarbotran)–enhanced MR imaging. **a.** Axial unenhanced T2-weighted fast SE image shows a large FNH lesion (straight arrow) that is isointense relative to the surrounding liver parenchyma. The central scar (curved arrow) has slightly higher signal intensity than the lesion. **b.** Axial contrast-enhanced fast SE image shows that the lesion (straight arrow) as well as the liver and spleen have decreased signal intensity due to the uptake of ferucarbotran into Kupffer cells. The central scar (curved arrow) does not contain Kupffer cells and has relatively increased signal intensity.



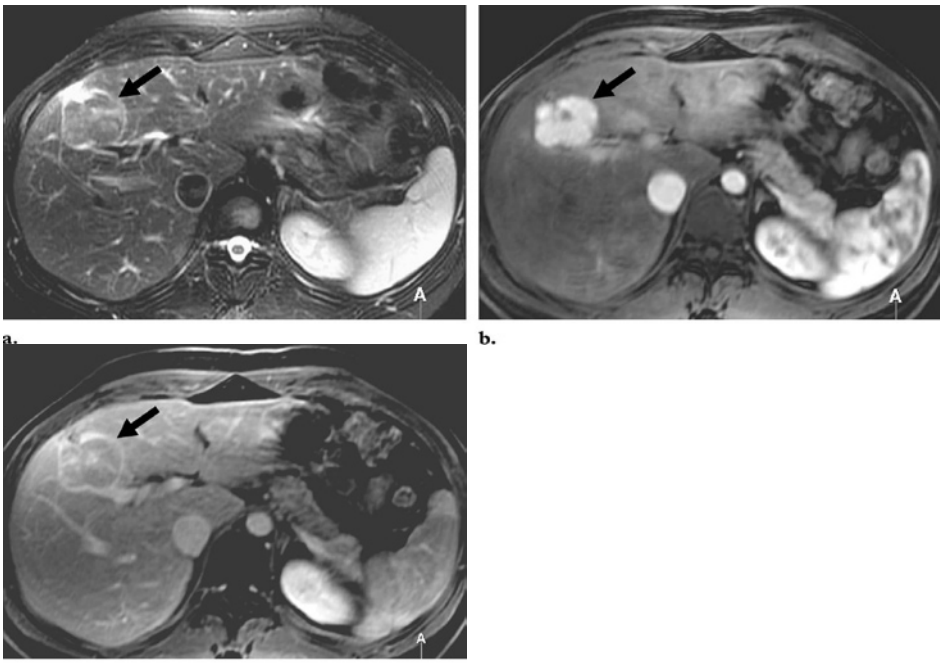
a. b.

Figure 9. MR imaging appearance of multiple FNH lesions. **a.** Axial gadolinium-enhanced fat-saturated 3D fast GRE image obtained during the arterial phase shows intense homogeneous enhancement of two lesions (arrows). This finding is compatible with FNH. **b.** Photomicrograph (original magnification, x200; H-E stain) of a biopsy specimen from one of the lesions shows classic FNH composed of nodules (*) with fatty infiltration (open arrow). Septa (curved arrow) surround the nodules and contain ductular proliferation, inflammatory infiltrates, connective tissue, and vessels.



a. b.

Figure 10. MR imaging appearance of multiple HCCs in a noncirrhotic liver. **a.** Axial gadolinium-enhanced fat-saturated 3D GRE image obtained during the arterial phase showes heterogeneous enhancement of two lesions (arrows). **b.** Photomicrograph (original magnification, x 100; H-E stain) of a resected specimen from the larger lesion shows an HCC (*) surrounded by a fibrous tumor capsule (arrow).



a. b.

c.

Figure 11. MR imaging appearance of an FNH lesion with a prominent pseudocapsule. **a.** Axial fat-saturated T2-weighted fast SE image shows a medium-sized FNH lesion (arrow) with a central scar, a pseudocapsule, and septa, all of which are prominent and have high signal intensity. **b.** Axial gadolinium-enhanced 3D GRE image obtained during the arterial phase shows intense homogeneous enhancement of the lesion (arrow), except for the central scar and septa. **c.** Axial gadolinium-enhanced 3D GRE image obtained during the delayed phase shows enhancement of the central scar as well as the pseudocapsule (arrow).

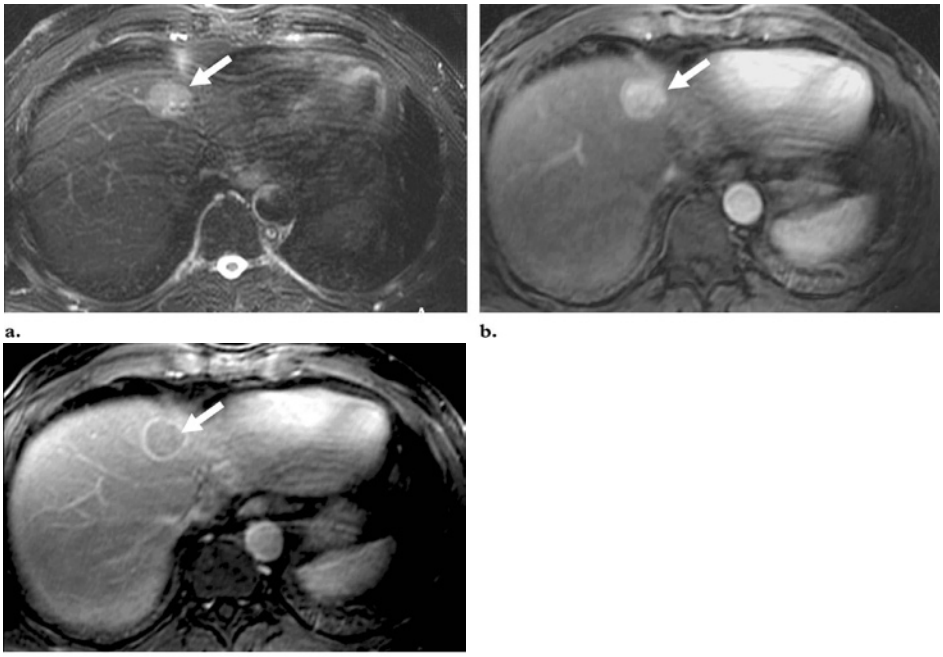


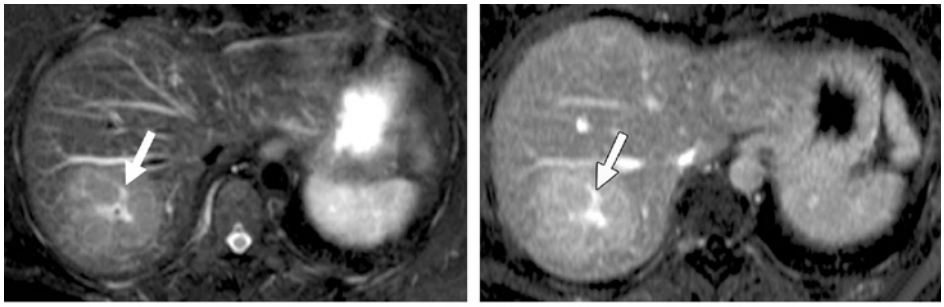
Figure 12. MR imaging appearance of an HCC with a tumor capsule in a noncirrhotic liver. **a.** Axial fat-saturated T2-weighted fast SE image shows an HCC with predominantly high signal intensity (arrow). Owing to its fibrotic nature, the tumor capsule has low signal intensity on T2-weighted images and therefore is not visible. **b.** Axial gadolinium-enhanced 3D GRE image obtained during the arterial phase shows intense, nearly homogeneous enhancement of the lesion (arrow). This appearance may simulate FNH. **c.** Axial gadolinium-enhanced 3D GRE image obtained during the delayed phase shows enhancement of the tumor capsule surrounding the lesion (arrow), which demonstrates complete washout.

Multiple FNH lesions occur in approximately 20%–25% of patients with FNH (Figure 9)[6]. Multiple FNH lesions are more often of the non-classic type and may contain atypical features at imaging. In addition, multiple FNH lesions can be associated with other benign lesions, such as cysts, hemangiomas, and adenomas. Distinction from multiple adenomas and multifocal HCC, particularly in noncirrhotic livers, may be challenging (Figure 10)[12,13,16].

FNH does not have a tumor capsule, although the pseudocapsule surrounding some FNH lesions may be quite prominent. The pseudocapsule of FNH results from compression of the surrounding liver parenchyma by the FNH, perilesion vessels, and inflammatory reaction (Figures 1b, 4a). The pseudocapsule is usually a few millimeters thick and typically shows high signal intensity on T2-weighted images. The pseudocapsule may show enhancement on delayed contrast-enhanced images (Figure 11). A tumor capsule is a characteristic sign of HCC and is present in 60%–80% of cases[12]. This capsule mainly consists of fibrosis and has low signal intensity on both T1- and T2-weighted images; it shows persistent enhancement on delayed contrast-enhanced images (Figure 12).

A central scar is present at imaging in most patients with FNH[10,13]. The amount of scar tissue within FNH and the size of the central scar may vary. The central scar is typically high in signal intensity on T2-weighted images and low in signal intensity on T1-weighted images. It shows visible enhancement on delayed contrast-enhanced images (Figure 13). High signal intensity of the central scar may be caused by the inflammatory reaction around the ductular proliferation as well as the vessels within the septa and central scar. The central scar is not a specific finding of FNH and can be seen in a variety of other focal liver lesions such as giant hemangiomas (Figure 14) and HCCs (Figure 15). The central scar in giant hemangiomas is typically larger and brighter on T2-weighted images. In addition, the lesions have homogeneous high signal intensity on T2-weighted images and show peripheral nodular enhancement in most cases. Some HCCs may contain a central scar. Owing to the presence of scar tissue, calcifications, or necrosis, the central scar in HCC shows low signal intensity on T2- and T1-weighted images and does not enhance much on contrast-enhanced images. Although HCCs occur in noncirrhotic livers, the lesions show quite a different type of enhancement than FNH (Figure 15).

Rarely, FNH may show more than one atypical feature at MR imaging and cause difficulty in diagnosis. Such lesions may have exceptionally high signal intensity on T2-weighted images with a suggestion of lamellae, a central scar with low signal intensity on T2-weighted images, a prominent pseudocapsule, and incomplete intense enhancement of the lesion (Figure 16). In such cases, application of a specific type of contrast medium, such as ferucarbotran or mangafodipir trisodium, may demonstrate the hepatocellular origin of the lesion. When there is homogeneous uptake of such an agent in combination with a normal α-fetoprotein level and normal results at viral serologic analysis, the patient may be safely followed up with imaging. If any doubt remains, one or more biopsies should be performed within the lesion as well as the surrounding liver to exclude malignancies, such as fibrolamellar carcinoma and HCC in a noncirrhotic liver[12-18].



a. b.

Figure 13. MR imaging appearance of an FNH lesion with a prominent central scar. **a.** Axial fat-saturated T2-weighted fast SE image shows a large FNH lesion with a prominent central scar (arrow), which has high signal intensity. A pseudocapsule is not visible. **b.** Axial gadolinium-enhanced fat-saturated 2D T1-weighted GRE image obtained during the delayed phase shows that the lesion has become isointense relative to the liver and the central scar has enhanced (arrow).

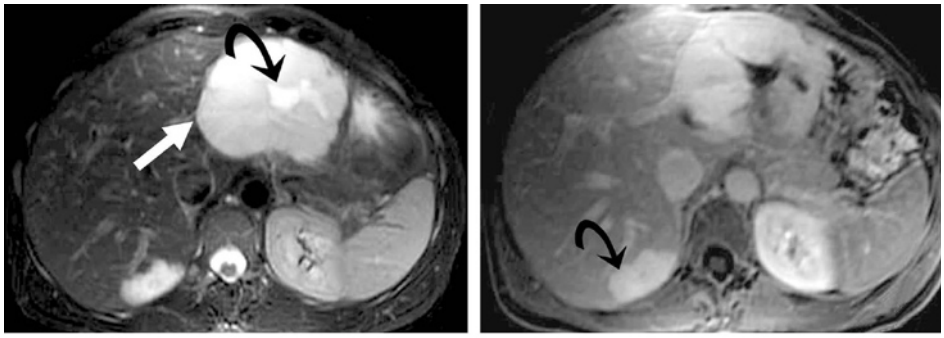


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Figure 14. MR imaging of a giant hemangioma with a prominent central scar. **a.** Axial fat-saturated T2-weighted fast SE image shows a high-signal-intensity giant hemangioma (straight arrow) with a prominent central scar (curved arrow), which has even higher signal intensity than the lesion. Note the smaller hemangioma without a central scar. **b.** On an axial gadolinium-enhanced fat-saturated 3D GRE image obtained during the delayed phase, the smaller lesion (arrow) has completely filled in, whereas the central scar within the larger lesion has not enhanced.

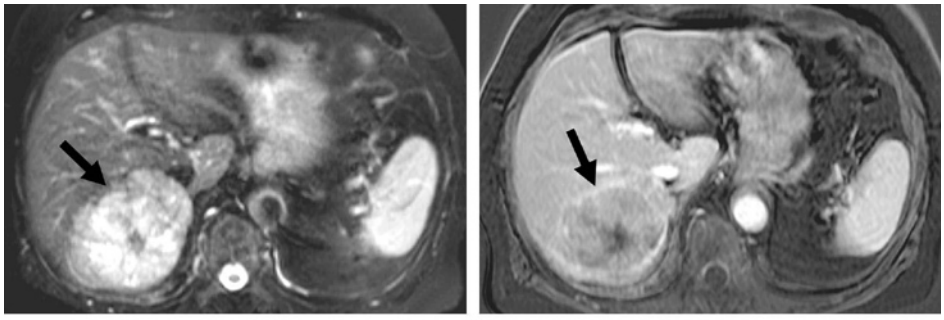

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Figure 15. MR imaging appearance of an HCC with a central scar in a patient who was not cirrhotic but who had extremely high levels of α-fetoprotein. **a.** Axial fat-saturated T2-weighted fast SE image shows a predominantly high-signal-intensity lesion (arrow) with a low-signal-intensity central scar. **b.** Axial gadolinium-enhanced fat-saturated 2D T1-weighted GRE image obtained during the delayed phase shows washout of contrast material in most of the lesion and an enhanced tumor capsule (arrow). The central scar remains mainly unenhanced.

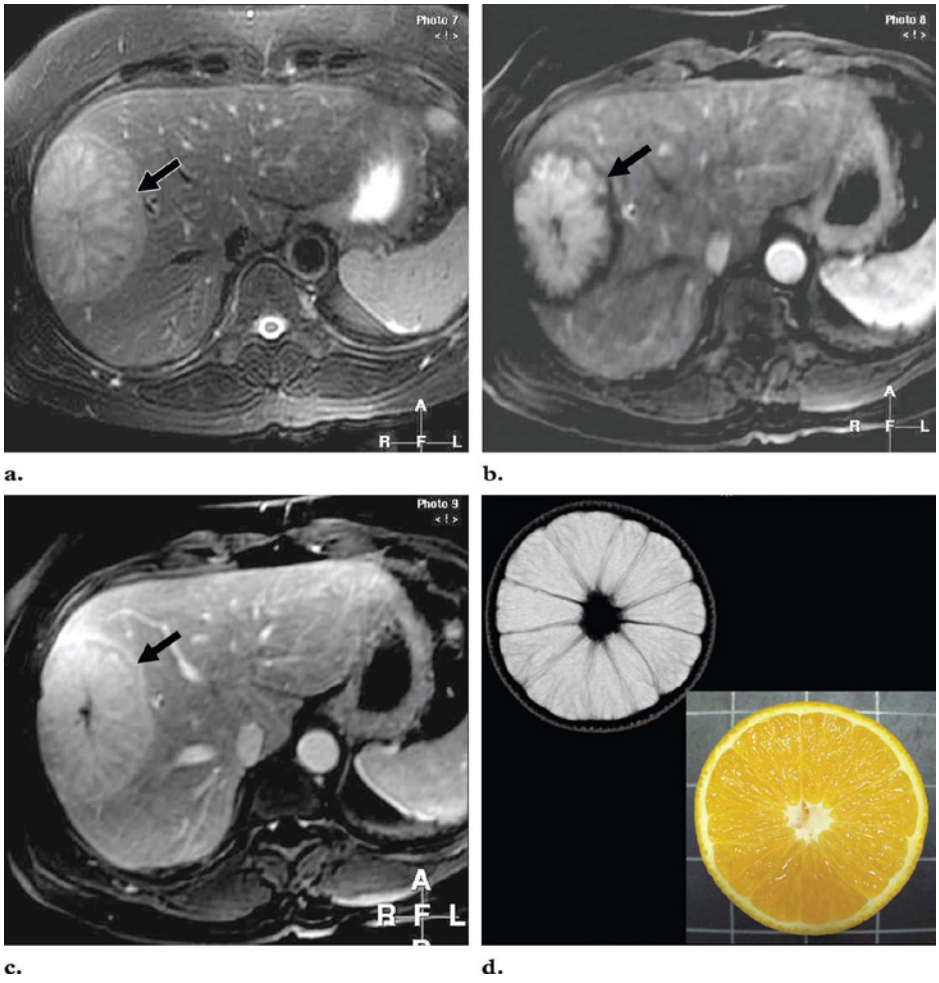

Figure 16. MR imaging appearance of an FNH lesion with a low-signal-intensity scar and a pseudocapsule. **a.** Axial fat-saturated T2-weighted fast SE image shows a predominantly high-signal-intensity FNH lesion with a spinning wheel appearance due to the presence of radiating septa and a pseudocapsule (arrow). **b.** Axial gadolinium-enhanced fat-saturated 3D GRE image obtained during the arterial phase shows intense enhancement of most of the central part of the lesion (arrow). **c.** Axial gadolinium-enhanced fat-saturated 3D GRE image obtained during the portal phase shows nearly homogeneous enhancement of the lesion, including the pseudocapsule (arrow). The lesion has becomes nearly isointense relative to the surrounding liver tissue. **d.** Axial T2-weighted fast SE image and corresponding photograph of an orange show a striking similarity to the FNH lesion.

DISCUSSION AND CONCLUSIONS

This article presents the most recent pathologic classification of FNH, its gross appearance, and its histologic features. Currently, FNH is divided into two types, classic (80%) and nonclassic (20%)[6]. Classic FNH contains all of the components, including an abnormal nodular architecture, malformed vessels, and cholangiolar proliferation. The nonclassic type contains two of the three components but always shows bile ductular proliferation[6].

In addition, the results of recent studies reveal a typical angioarchitecture for FNH. Typically, FNH contains one or more thick-walled, large arteries that run within the fibrous septa and divide into numerous capillaries that are connected to the sinusoids. Relatively large veins drain blood from the sinusoids toward the hepatic vein. FNH does not contain portal veins. The delayed enhancement of the central scar at CT and MR imaging relates to increased interstitial space and fluid content with slow diffusion of contrast material into this space.

The imaging modalities, particularly CT and MR imaging, make use of the abundant vascularity of FNH. On the basis of the vascularity as well as the tissue characteristics, MR imaging allows reliable distinction of FNH from other focal liver lesions in most cases. In fact, since the introduction of state-of-the-art MR imaging at our hospital in 1999, FNH has been diagnosed noninvasively. Diagnoses of typical FNH are confirmed with at least one follow-up MR imaging examination at 6–12 months. Atypical cases undergo additional imaging with specific contrast media to rule out malignancy. Before 1999, most patients underwent US-guided biopsies of focal liver lesions, including FNH, at our institution. US was often used for guidance of the biopsy and not for noninvasive diagnostic imaging.

MR imaging is an ideal imaging modality for work-up of lesions in relatively young women suspected of having FNH because radiation and iodine-based contrast media are not used. Based on our experience, this article demonstrates the full spectrum of findings of FNH at state-of-the-art MR imaging.

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5.2

Focal nodular hyperplasia: Lesion characteristics at state-of-the-art MR imaging including dynamic gadolinium-enhanced and superparamagnetic iron-oxide-uptake sequences in a prospective cohort study.

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FOCAL NODULAR HYPERPLASIA: LESION CHARACTERISTICS AT STATE-OF-THE-ART MAGNETIC RESONANCE IMAGING INCLUDING DYNAMIC GADOLINIUM-ENHANCED AND SUPERPARAMAGNETIC IRON-OXIDE-UPTAKE SEQUENCES IN A PROSPECTIVE COHORT STUDY

ABSTRACT

Purpose: To image a cohort of patients with pathology-proven focal nodular hyperplasia (FNH) in order to assess which of the characteristics on state-of-the-art magnetic resonance (MR) imaging of the liver are most useful for improved detection and characterization of FNH.

Materials and Methods: In fourteen patients, pathology-proven FNH (n=33) were prospectively examined with the state-of-the-art MR imaging using Gadolinium (Gd) and superparamagnetic iron-oxide (SPIO) contrast media. All lesions were evaluated for signal intensity, fatty infiltration, central scar, mode of enhancement with Gadolinium and uptake of SPIO. Percentages of dynamic contrast-enhancement in arterial, portal and delayed phases were assessed. Contrast-to-noise ratio (CNR) before and after administration of SPIO contrast was calculated.

Results: Signal intensity of the lesions was intermediate to isointense on T2-weighted and low to isointense on T1-weighted imaging. Fatty infiltration of the lesion was present in 6%. Percentage of enhancement in liver and lesion respectively were 110, 115 and 95% and 151, 182 and 160% ($p<0.0001$). All lesions showed uptake of SPIO with improved conspicuity of central scar and septa. The CNR values pre-contrast and post-Gd/SPIO were significantly different for T1 in- and opposed-phase black-blood echo planar imaging.

Conclusion: Combination of dynamic Gd-enhanced imaging with T1- and T2-weighted sequences after administration of SPIO facilitates comprehensive evaluation of FNH.

INTRODUCTION

Although focal nodular hyperplasia (FNH) of the liver is a well-described lesion in literature, considerable diagnostic problems regarding this lesion still remain. Given the fact that FNH is the second most common benign liver tumor after hemangioma and has a reported prevalence of approximately 1%[1], definitive distinction between this benign liver lesion and other benign and malignant hepatic masses is a common dilemma. Since FNH is usually observed in young to middle-aged women and most often is asymptomatic, the main goal of imaging in these patients is to firmly establish the diagnosis in order to avoid unnecessary biopsy or surgical resection and to suggest a conservative approach to therapy[2,3].

Since morphology and radiological enhancement patterns of a FNH is strongly determined by its histological composition, it is important to realize that this lesion is divided into two types: classic and non-classic[1]. According to one large pathology study, the non-classic type contains three subtypes (a) teleangiectatic FNH, (b) FNH with cytologic atypia, and (c) mixed hyperplastic and adenomatous FNH. More recently, a study based on DNA micro-array analysis suggested that teleangiectatic FNH had more similarities with hepatocellular adenomas than with FNH[4]. Classic FNH is characterized by the presence of (a) abnormal nodular architecture, (b) malformed vessels, and (c) cholangiolar proliferation. Nonclassic FNH lack one of the following classic features – nodular abnormal architecture or malformed vessels – but always show bile duct proliferation.

Typical magnetic resonance (MR) imaging features of FNH – that is iso- or hypointensity on T1-weighted images, slight hyper- or isointensity on T2-weighted images, and a hyperintense central scar on T2-weighted images – are seen in up to 84-100% of these lesions (Figure 1)[5,6]. However, in our experience these imaging features alone are not diagnostic for FNH and have been observed in a number of benign and malignant lesions[7,8].

Dynamic Gadolinium (Gd)-enhanced MR imaging enables evaluation of the hemokinetics of contrast distribution during the first few minutes after injection. Related to the hypervascularity of the tumor, during the arterial phase of hepatic enhancement, FNH typically shows an immediate and intense enhancement, with the exception of the central scar, which has delayed enhancement caused by the presence of abundant fibrous stroma (Figure 1)[9,10]. During portal or delayed venous phases the hyperintensity of the tumor fades, which results in an isointense lesion with gradual diffusion of the contrast material into the fibrous central scar. On delayed phase imaging, the central scar shows high signal intensity because of the accumulation of contrast material.

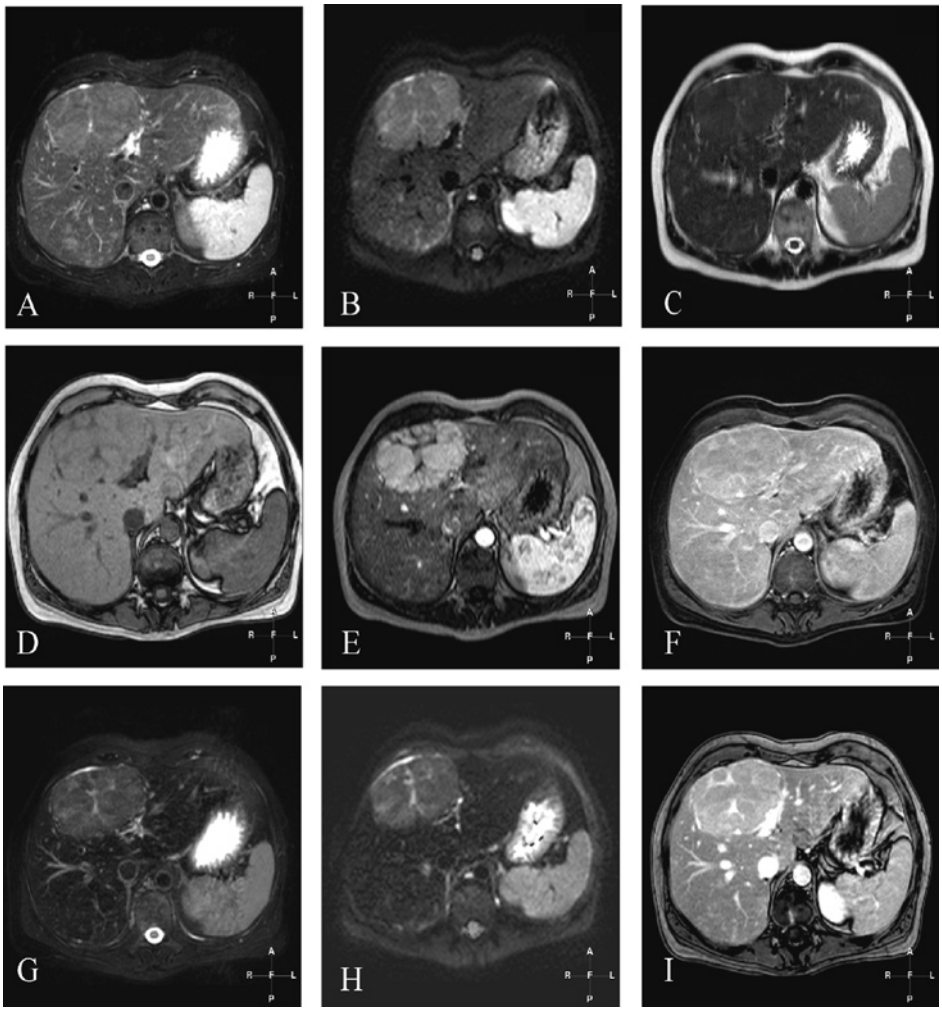

Figure 1. State-of-the-art MR imaging of classical FNH; signal intensity, enhancement patterns and uptake of SPIO. **A.** Fat-suppressed T2-weighted fast spin-echo (FSE): large, well circumscribed FNH in the left liver lobe, just slightly hyperintense to the liver, with a faint hyperintense septa. **B.** Black-blood T2-weighted echo planar imaging (BBEPI): hyperintense signal intensity, with hyperintensity of central scar and septa. **C.** Single-shot T2-weighted fast spin-echo (SSFSE): the lesion is isointense with the liver. **D.** Opposed-phase T1-weighted gradient echo (GRE): the lesion is isointense, with hypointense central scar, septa and pseudocapsule composed of compressed vessels. **E.** Arterial phase Gadolinium (Gd)-enhanced T1-weighted GRE: immediate, homogeneous enhancement with sparing of central scar and septa. **F.** Delayed phase Gd-enhanced 3D T1-weighted GRE: the signal intensity has faded to isointensity with the liver, with faint delayed enhancement of central scar, septa and pseudocapsule. **G.** Post-SPIO fat-suppressed T2-weighted fast spin-echo (FSE): the liver and spleen have dropped in signal intensity after SPIO. The lesion is hyperintense, with slightly improved conspicuity of central scar and septa. **H.** Post-SPIO diffusion T2-weighted black-blood echo planar imaging (BBEPI): better conspicuity of central scar and septa, with high signal intensity. **I.** Post-SPIO opposed-phase T1-weighted gradient echo (GRE): high signal of central scar and septa, especially when compared to delayed phase 3D dynamic Gd-enhanced imaging (F).

Atypically, FNH may present as large lesions, sometimes with multiple localization[5]. Rare imaging features include nonvisualization or nonenhancement of the central scar, and pseudocapsular enhancement on delayed images[9]. In these cases it may be difficult to differentiate an atypical FNH from other benign and malignant hypervascular liver lesions such as hepatocellular adenoma (HCA), hepatocellular carcinoma (HCC) and hypervascular metastases[11-13].

Previous studies have described imaging features of FNH using both non-specific and specific contrast agents such as manganodipir[14] and superparamagnetic iron-oxide (SPIO) particles. In a few studies, uptake of SPIO and imaging characteristics of FNH were assessed using conventional MR sequences[15-19]. To our knowledge, none of the previous studies have evaluated lesion characteristics of pathology-proved FNH using both dynamic Gd-enhanced imaging and multiple T1- and T2-weighted sequences after Gd/SPIO.

At our institute, we apply a state-of-the-art comprehensive MR imaging, which provides information concerning the soft tissue characteristics of the lesion besides the vascularity of the lesion at Gd-enhanced multi-phasic dynamic imaging. In addition, in selected cases specific MR imaging contrast agents such as SPIO particles can provide information concerning the primary nature of the lesion[20,21].

The purpose of our prospective study was to image a cohort of patients with pathology-proven FNH in order to assess which of the characteristics derived from the state-of-the-art comprehensive MR imaging of the liver (including T1-weighted imaging, T2-weighted imaging with short and long TE-values, dynamic Gd-enhanced, multi-phasic imaging, and imaging after SPIO-uptake) would be most useful in the future for improved detection and characterization of FNH.

MATERIALS AND METHODS

Patients

The study was performed in a tertiary referral center with a large experience in hepatobiliary surgery and transplantation. Liver pathology reports of percutaneous needle biopsies that were performed between 1990 and 2003 were reviewed for the diagnosis of FNH. These data were matched with the hospital database to retrieve patients who were managed conservatively by observation of the lesion. Fifty-one patients had been evaluated for therapy by a hepatobiliary surgeon. In none of these patients a surgical treatment was indicated because of the absence of complaints. All of these 51 patients were contacted to take part in this prospective cohort study with the state-of-the-art MR imaging. Of those patients, 14 replied and provided informed consent. Approval for the study was granted by the local ethics committee.

A total of 33 lesions were detected in 14 patients. All patients were women with a mean age of 45 years (range, 30-68 years). Analysis of data was based on evaluation of each lesion

individually. The mean size of all lesions was 2.6 cm (range, 0.6-10.0 cm). Twenty-two lesions were located in the right lobe and 11 in the left lobe. A single lesion was depicted in 7 patients, and multiple lesions were present in the other 7 patients (two lesions in two patients, three in three patients, four in one patient, and nine in one patient).

Histologic proof of FNH was obtained in 14 of the 33 lesions (14 patients). In case of multiple lesions, a percutaneous needle biopsy was performed in the largest one. Nine-teen lesions not confirmed at histology were identical at (follow-up) MR imaging to the biopsy-proved FNH. This is a common clinical practice, and it would have been unnecessary and unethical to biopsy all those lesions. The appearance of the lesions without biopsy remained unchanged at imaging for a period of at least 12-months.

MR imaging technique

The MR examinations were performed using a 1.5-T unit (Philips Medical Systems, Best, The Netherlands). Scan sequences included single-shot fast spin-echo (SSFSE) with varying TE values (short and long TE), fat-suppressed T2-weighted fast spin echo (FSE), diffusion T2-weighted black-blood echo planar imaging (BBEPI) and T1-weighted in- and opposed-phase gradient echo (GRE) sequences. After administration of an intravenous bolus of 30cc of non-liver specific Gadolinium chelate (Magnevist [gadopentetate dimeglumine], Schering, Berlin, Germany), dynamic imaging with 2D or 3D T1-weighted sequences in at least 4 phases (pre-contrast, arterial, portal and delayed phases) was performed. In each patient, a timing bolus technique was used to capture the arterial phase after the administration of Gadolinium. The portal phase was acquired 45 seconds, and delayed at least 120 seconds, after the acquisition of the arterial phase.

After completion of the Gd-enhanced imaging, a SPIO contrast agent (Ferrocarbutan, Schering AG, Berlin, Germany) was administered intravenously as a bolus of 1.4cc (>60 kg body weight). Ten minutes after the administration of SPIO imaging was performed using fat-suppressed T2-weighted FSE, BBEPI, and T1-weighted in- and opposed-phase GRE sequences were performed. No adverse reactions were reported during the study.

The MR scan sequences, including SSFSE with short and long TE values, fat-suppressed T2-weighted FSE, diffusion T2-weighted BBEPI and T1-weighted in- and opposed-phase GRE sequences were complete for at least 29 lesions. In the following sequences, a few lesions were too small to visualize: 2 lesions on SSFSE sequences with short and long TE values (n=31) and 2 lesions on T1-weighted in- and opposed-phase GRE sequences (n=31). Because of technical problems with data acquisition, the following lesions were excluded for the following sequences: SSFSE with long TE values in one patient (2 lesions, n=29), fat-suppressed T2-weighted FSE sequence in 1 patient (3 lesions, n=30) and diffusion T2-weighted BBEPI in 2 patients (with 1 and 2 lesions, respectively; n=30). The dynamic series were available for 28 of 33 lesions after contrast enhancement with Gadolinium and for 30 lesions after enhancement with a SPIO contrast agent. For post-enhancement evaluation of signal intensities of

both the liver and the lesion, analysis was based on 30 lesions for T1-weighted in- and opposed-phase GRE sequences, 27 lesions for fat-suppressed T2-weighted FSE, and 23 lesions for BBEPI sequences.

Image Analysis

All MR imaging exams were transported digitally to a viewing station, using a picture archiving and communication system. The analysis of all liver lesions was performed by two radiologists in consensus and with the knowledge of the diagnosis of FNH.

The following MR items were assessed qualitatively and/or quantitative: 1) liver surrounding the focal lesions (presence or absence of normal parenchyma, 2) diffuse and focal fatty infiltration, 3) focal non-steatosis, 4) iron deposition); 5) lesion localization according to the hepatic segment numbering system of Couinaud; 6) number and diameter of lesions; 7) signal intensity of lesions compared with normal parenchyma before and after intravenous administration of Gadolinium and SPIO at T1- and T2-weighted images; 8) signal intensity characteristics of the lesions at unenhanced and contrast-enhanced T1-weighted images with regard to the surrounding liver parenchyma; 9) homogeneous or heterogeneous appearance; 10) presence of fatty infiltration within the lesion (in and opposed phase); 11) presence of a central scar, 12) presence of a pseudocapsule; 13) the uptake of SPIO, and 14) the conspicuity of the central scar and septa after the uptake of SPIO.

For quantitative image analysis, the signal intensity of the lesion and liver parenchyma were measured using operator-defined regions of interest (ROI). For the lesions, the largest possible region of interest in the lesion that excluded fibrotic areas was selected for measurement of signal intensity. For the liver, a region of interest that excluded vessels and artifacts was used to measure the signal intensity of the liver adjacent to the tumor. The ROI's were placed identically for both the unenhanced and contrast-enhanced images.

In dynamic Gd-enhanced imaging, enhancement patterns in arterial, portal en delayed phase imaging were subjectively evaluated. The lesion-to-liver contrast-to-noise ratio (CNR) was calculated as the difference in signal intensity between the lesion and the liver scaled to the standard deviation of background noise. The percentage of contrast enhancement was calculated for Gadolinium chelates and the SPIO agent as follows:$[(SI_{enhanced} - SI_{unenhanced}) / SI_{unenhanced}] \times 100$, where SI is signal intensity.

Statistical analysis

Statistical parameters (mean, median, standard deviation, and range) are calculated using the Statistical Package for the Social Sciences (SPSS) program. Significance levels were determined by two-tailed Mann-Whitney test analysis. The unit of measure in our statistical analysis was number of lesions, rather than number of patients.

RESULTS

Signal intensity of the lesions

At T1-weighted imaging, signal intensity of the lesions compared to the surrounding liver parenchyma was slightly lower to isointense at both in-phase T1-weighted GRE (30 of 31 lesions (96.8%)) and opposed-phase T1-weighted GRE (21 of 31 lesions (67.8%)) images. The lesions appeared relatively brighter to much brighter to the liver at opposed-phase T1-weighted GRE in 24.5% (8 of 31 lesions). This was caused fatty infiltration of the liver parenchyma in those cases.

At T2-weighted imaging, the lesions showed an isointense to slightly higher signal intensity of the lesions at SSFSE T2-weighted images with short and long TE respectively (18 of 31 lesions (90.4%) and 26 of 29 lesions (89.6%). This implied that the lesion and the liver behaved very similar on both sequences, most likely because of the solid nature as well as comparable tissue composition.

At fat-suppressed T2-weighted FSE and diffusion T2-weighted BBEPI, the lesions showed a slightly higher to much higher signal intensity in 28 of 30 patients (93.3%) and 30 of 30 lesions (100%), respectively. In FSE, fat-suppression and fewer numbers of refocusing pulses per TR than SSFSE, most likely improved the liver-to-lesion contrast. In BBEPI, several factors improved the liver-to-lesion contrast, including 1) fat-suppression; 2) less magnetization transfer contrast effect than in FSE and SSFSE images due to the lack of refocusing pulses; 3) black-blood imaging based on the low diffusion-weighted gradient that dephased the signal from intrahepatic vessels; and 4) the application of the diffusion gradients was applied in all three orthogonal directions, and the composite image was a sum of three individual images. This improved the signal-to-noise ratio (SNR) of BBEPI.

Enhancement after Gadolinium

In arterial phase imaging after the administration of Gadolinium, an intense enhancement was observed in 27 of 28 lesions (95%). The enhancement was either completely homogeneous in 15 of 28 lesions (53.6%) or intensely homogeneous with sparing of septa and the central scar in 12 of 28 lesions (42.8%).

In the portal phase, most lesions remained higher or slightly higher in signal intensity compared to the surrounding liver parenchyma (18 of 28 lesions (64.2%)). The remaining lesions became almost isointense in 9 of 28 lesions (32.1%).

In the delayed phase, 11 of 28 (39.3%) lesions remained higher in signal intensity, whilst 14 of 28 (50%) lesions now showed an almost isointense signal intensity compared to the surrounding liver parenchyma. Enhancement of central scar and septa was noted in delayed phase imaging.

A quantitative analysis of the enhancement in the different phases showed a percentage increase of enhancement in liver parenchyma in arterial, portal and venous phases respectively of 110, 115 and 95%, and in the lesion this was 151, 182 and 160% ($p<0.0001$) (Figure 2). This shows that the lesions are typically hypervascular in the arterial phase, but behave in a similar pattern as the surrounding liver parenchyma in the portal and delayed phase.

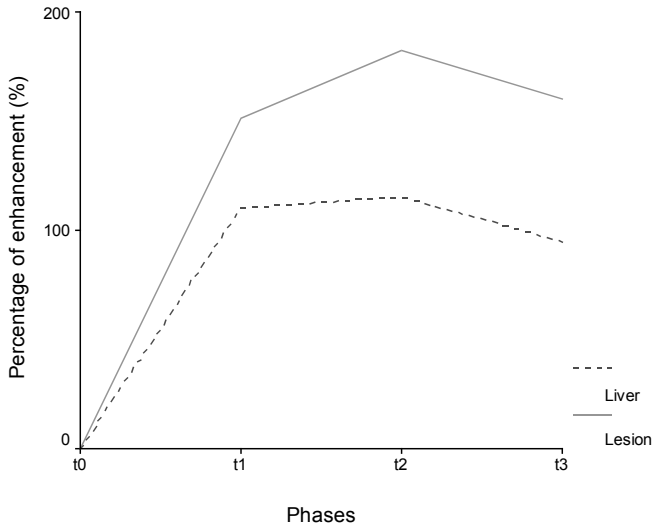

Figure 2. Percentage of enhancement of liver parenchyma and the lesion in arterial, portal and venous phases ($p<0.0001$). t0; pre-contrast phase, t1; arterial phase, t2; portal phase, t3; venous phase.

Signal intensity after SPIO-uptake

After administration of SPIO marked decrease in the signal intensity of the liver and spleen was observed at T2-weighted sequences, which indicated the accumulation of iron particles in the Kupffer cells. When compared to the same sequence before and after SPIO-uptake, all lesions showed loss of signal intensity. This finding, in fact, revealed the presence of Kupffer cells within the lesions, and hence their hepatocellular origin.

The lesions showed a marked uptake in 17 of 30 lesions (56.7%) and slight, but certainly present uptake in 13 of 30 lesions (43.3%). Conspicuity of specific lesion characteristics such as presence of a central scar and septa had improved in 90% (27 of 29) of the lesions.

A qualitative, subjective evaluation of signal intensity of the lesion compared to the surrounding liver parenchyma was repeated.

At T1-weighted imaging, signal intensity was slightly higher to isointense at in-phase T1-weighted GRE (23 of 30 lesions (76.7%)) and now slightly higher to much higher at opposed-phase T1-weighted GRE (30 lesions, 100%). This can be explained by intense lowering of signal intensity of the surrounding liver parenchyma both by shorter TE value at opposed

phase imaging combined with T2* effects caused by accumulation of SPIO in reticuloendothelial cells.

At T2-weighted imaging, signal intensity of the lesions was slightly to much higher at both fat-suppressed T2-weighted FSE and diffusion T2-weighted BBEPI (26 of 27 lesions (96.3%) and 22 of 23 lesions (95.7%)).

Contrast-to-noise ratio before and after SPIO-uptake

Based on the measurements of signal intensity of lesion and surrounding liver parenchyma, CNR values of the lesions before and after SPIO-uptake were calculated. These values were as follows: T1 in-phase -2.8 and 6.95 ($p<0.0005$), T1 opposed-phase -0.44 and 1.65 ($p<0.0005$), fat-suppressed T2-weighted FSE 6.45 and 16.4 ($p<0.9$) and BBEPI 5.64 and 9.25 ($p<0.05$) (Figure 3). The values for T1 in- and opposed-phase and BBEPI were significantly different. High CNR values in BBEPI demonstrated a more pronounced uptake in the liver parenchyma compared to the lesion, with sensitive detection through susceptibility (T2*) effects of iron particles in SPIO.

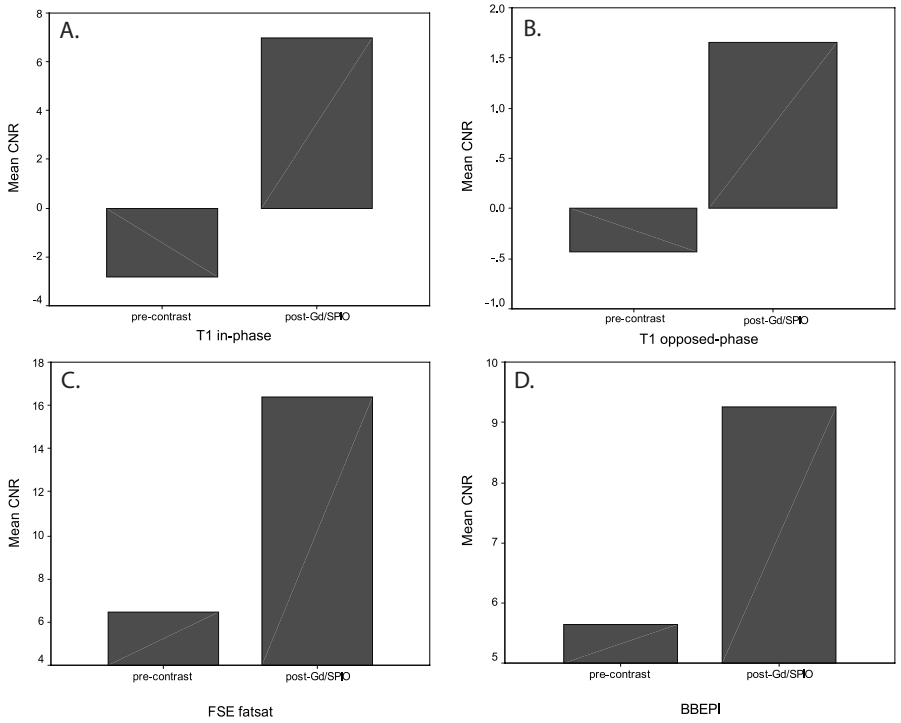

Figure 3. Contrast-to-noise ratio (CNR) before and after Gadolinium (Gd) and superparamagnetic iron-oxide (SPIO)-uptake. **A.** in in-phase T1-weighted GRE, showing a significant increase after contrast enhancement ($p<0.0005$). **B.** in opposed-phase T1-weighted GRE, showing a significant increase after contrast enhancement ($p<0.0005$). **C.** in fat-suppressed T2-weighted FSE (FSE fatsat), showing a non-significant increase after contrast enhancement ($p=0.9$). **D.** in diffusion-weighted black-blood echo planar imaging (BBEPI), showing a significant increase after contrast enhancement ($p<0.05$).

Miscellaneous findings

The liver parenchyma surrounding the lesions was normal in magnitude, shape and contour in 12 out of 14 cases (85.7%). Diffuse fatty infiltration of the liver was present in 3 out of 14 cases (21.4%), and focal fatty infiltration in 4 out of 14 cases (28.6%). Focal non-steatosis was seen in 2 of 14 cases (14.3%). No iron deposition was reported. Fatty infiltration within the lesion was noted in 2 of 33 lesions (6.1%). Visibility of a central scar and pseudocapsule varied between 3 and 15% of the lesions for different sequences, but was best in post-Gd sequences. Low detection rate of these characteristics can be explained by the relatively large amount of small lesions in this study.

DISCUSSION

In this study, a cohort of patients with pathology-proven FNH were examined to assess which of the characteristics derived from the state-of-the-art MR imaging of the liver are most useful for improved detection and characterization of FNH. The results of our study indicated that 1) the signal intensity of FNH was only slightly different from the surrounding liver on pre-contrast T1- and T2-weighted images; 2) chemical shift imaging showed fatty infiltration in a minority of FNH (6%) whereas the surrounding liver shows focal or diffuse fatty infiltration in up to 50% of the cases; 3) Almost all lesions showed intense homogeneous enhancement (with or without intra-tumoral septal sparing) in the arterial phase after the administration of Gadolinium; 4) the lesions faded almost to isointensity on the delayed phase; 5) the central scar and septa were visible only in a minority of patients; 6) all lesions showed uptake of SPIO with improved conspicuity of the central scar and septa; 7) most sensitive sequences to detect the SPIO-uptake were in- and opposed-phase T1-weighted GRE and diffusion T2-weighted BBEPI. The results of our study indicate that the following characteristics are significant for the diagnosis of FNH.

Firstly, the similarity of the signal intensity with the surrounding (non-cirrhotic) liver should be considered as a strong indicator that the lesion is most likely of hepatocellular origin.

Secondly, the presence of fatty infiltration in a relatively small number of lesions as well as in the surrounding liver is important. In our study, the lesions demonstrated fatty contents in only 6% of all lesions, confirming the fact that accumulation of fat inside FNH does occur but is an uncommon finding. Other primary liver lesions that contain fat include HCA, and HCC. HCA may have fatty contents in up to 35-77% and HCC in 35%[22].

Thirdly, the enhancement pattern at dynamic Gd-enhanced imaging is essential in the work-up of focal liver lesions. As shown in this study, in the case of FNH, lesions show intense enhancement in the early arterial phase, but show almost similar enhancement in the later phases; the lesions remain slightly more enhanced than the surrounding liver. This enhancement pattern is typical for primary solid liver lesions, such as FNH, HCA, and HCC. Particularly,

in HCA early arterial enhancement is often observed[23], but is often less intense compared to enhancement patterns observed in FNH[24]. As in FNH, HCA fades to near isointensity with the surrounding liver parenchyma in delayed phase imaging[23,24]. HCA, however, do not show any enhancing central scar and septa. In FNH, central scar and septa show high signal intensity at T2-weighted imaging, with enhancement in delayed phase imaging. Enhancement patterns in small HCC may show almost homogeneous enhancement in the arterial phase, but will often become heterogeneous (partial washout) or even homogeneously lower than the liver (complete washout). In addition, HCC often show enhanced tumor capsule in the delayed phase, and occur in livers with parenchymal disease such as fibrosis and cirrhotic livers. HCC in non-cirrhotic liver are often single lesions with a large size and strong heterogeneous enhancement in the arterial phase. Other lesions such as hemangiomas and metastases have quite different signal intensities and enhancement patterns[24]. Hemangiomas typically enhance in a peripheral nodular fashion, with slow centripetal enhancement over time, to become and remain isointense with the liver in delayed phase imaging. Enhancement patterns in metastases may vary according to the origin of the malignancy. Colorectal metastases typically demonstrate ring-like arterial enhancement, with filling of the central areas of the lesion over time and washout of contrast material in the active peripheral border of the lesion[24].

Fourthly, after administration of SPIO, all lesions showed uptake of contrast which caused signal loss in the lesion, the liver, and spleen on sequences with T2*-weighting, such as T2-weighted FSE, SSFSE, and BBEPI, and T1-weighted GRE sequences. The signal loss in the liver was most pronounced, followed by the spleen and the lesions. It should be noticed that relatively more signal loss in the normal liver rendered FNH lesions brighter to the liver, which may improve the detection rate of FNH. The intratumoral signal loss was mainly present in areas with hepatocytes that were mostly arranged in small nodules. The septa and the central scar surrounding the intralesional nodules therefore appeared brighter with improved conspicuity (Figure 4). This finding may improve the characterization of FNH, and may facilitate distinction from HCA. In our study, the most sensitive sequences in SPIO-enhanced imaging were BBEPI and T1-weighted GRE sequences. As demonstrated in the calculated CNR, T1-weighted sequences may be useful in analysis of lesions after Gd/SPIO. In particular, the opposed-phase T1-weighted sequence is useful, because of its shorter TE in combination with T2* effects of the administered SPIO. Although T1-weighted sequences are not commonly used in evaluation after Gd/SPIO, the ability of detection of intrinsic details and less artifacts in combination with high resolution compared to T2-weighted sequences make it a useful additional sequence, as has been demonstrated before[18,25]. In addition, high SNR and CNR in these sequences may allow a smaller amount of SPIO, which may facilitate further reduction of side effects.

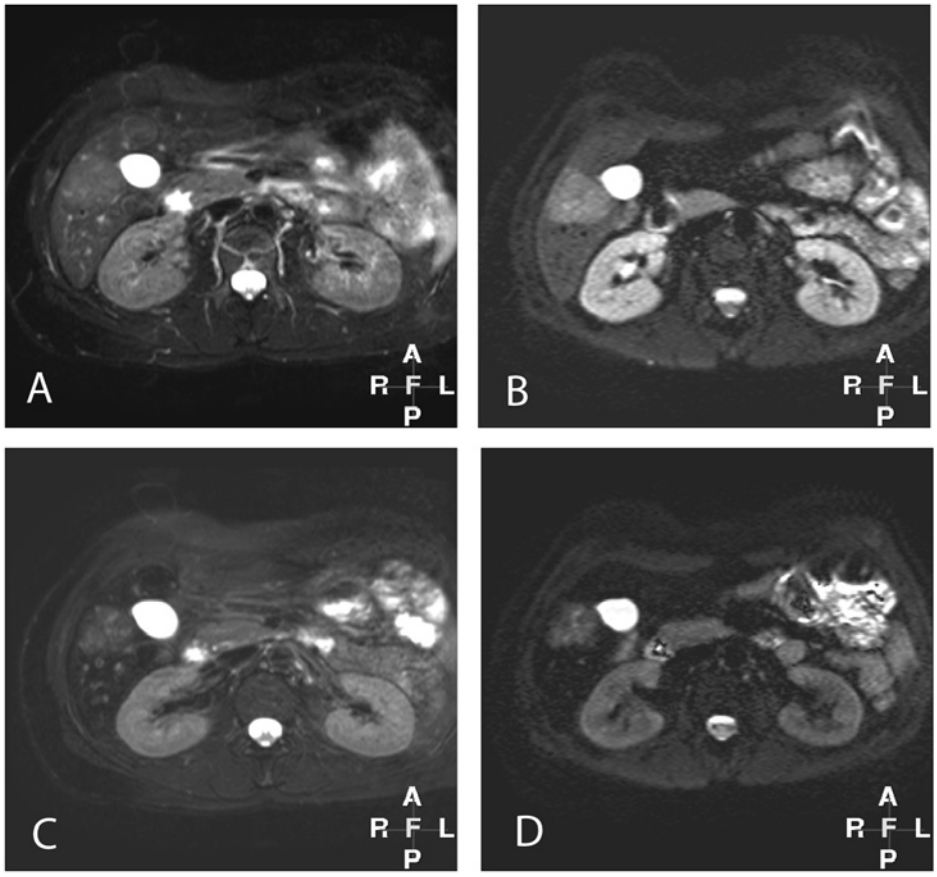

Figure 4. Improved conspicuity of central scar and septa after SPIO. **A.** Axial pre-contrast fat-suppressed T2-weighted FSE, in which a slightly hyperintense lesion is demonstrated. **B.** Axial pre-contrast diffusion T2-weighted black-blood echo planar imaging (BBEPI): higher signal intensity of the lesion. **C.** Axial post-SPIO fat-suppressed T2-weighted FSE, in which lower signal intensity of the liver is observed, due to absorption of contrast agent in the Kuppfer cells. Central scar and septa have a slightly higher signal intensity compared to pre-contrast sequences. **D.** Axial post-SPIO diffusion T2-weighted BBEPI: high signal intensity of central scar and septa with better conspicuity compared to pre-contrast sequences. Note that conspicuity is better in the BBEPI sequence compared to the T2-FSE sequence (C).

The results of our study indicate that FNH may show complete homogeneous enhancement (without any septal sparing), especially in smaller lesions. It may also be difficult to assess the intensity of enhancement for differentiation from HCA. In such cases, T2-weighted images and Gd-enhanced T1-weighted images in the delayed phase should be carefully assessed for the presence of central scar and septa. In addition, SPIO-uptake may reveal the presence of central scar and septa, making the distinction between FNH and HCA. Also, in a recent study it has been suggested that delayed imaging, 1-3 hours after administration of non-specific contrast material, may be helpful in differentiation between FNH and HCA[26].

Distinction between FNH and HCA is very important: 1. for follow up in pregnancy or use of oral anticonceptive medication; 2. because of the risk for hemorrhage and malignancy in

the case of a HCA; and 3. for assessment of the need for surgical or endovascular embolization treatment. At our institution, an asymptomatic single HCA of less than 5 cm in diameter or multiple HCA with variable diameters are subject to intensive follow-up with imaging and laboratory tests because of the risk of hemorrhage and malignancy. Whereas a single HCA larger than 5 cm or HCA with signs of malignancy at imaging (increasing size, changing density of signal intensity, changing enhancement, washout of contrast, enhancing fibrous tumor capsule) will often need surgical removal or at least biopsy. It is also important to know that HCA can present with intrahepatic or intraperitoneal hemorrhage that can be life threatening and may need intervention, including surgery or embolization.

Several studies have described imaging characteristics of focal liver lesions after administration of both specific and non-specific liver contrast agents. As has been described by Kim et al[18], Ba-Ssalamah[17] and Precetti et al[15], use of ferumoxide contrast agents may aid in better delineation of central scar and septa in FNH. Also, Paley et al[16] have shown a significant uptake of SPIO in pathology-proven FNH at T2-weighted imaging compared to other focal liver lesions. Recently, Scharitzer et al[14] have described the improved accuracy for differentiation between surgical and non-surgical liver lesions with mangafodipir-enhanced imaging. Few studies have evaluated the combined use of both Gd- and SPIO-enhanced imaging for focal liver lesions[17,19]. Ba-Ssalamah et al describe the imaging results of several focal liver lesions in separate imaging sessions for specific and non-specific contrast agents[17]. In addition to this study, we combine the use of dynamic Gd-enhanced imaging with T1- and T2-weighted imaging after administration of SPIO in one imaging session, to illustrate imaging findings of FNH using modern state-of-the-art MR sequences.

Our study has a limitation because of the relatively small cohort of patients. Only patients with a FNH lesion that was confirmed by percutaneous needle biopsy were included because histological proof is still considered to be the gold standard for diagnosis. However, since the introduction of state-of-the-art MR imaging at our department in 1999, FNH has been diagnosed non-invasively. Diagnosis of FNH is confirmed with at least one follow-up MR imaging examination at 6-12 months. Consequently, the small amount of patients that are included in this cohort were diagnosed with a needle biopsy before the availability of MR imaging or during analysis elsewhere before being admitted to our clinic.

In conclusion, our study indicates that combination of dynamic Gd-enhanced imaging with T1- and T2-weighted imaging after administration of SPIO facilitates detection and characterization of FNH. It is shown that: 1. signal intensity of FNH prior to contrast differs only slightly from the surrounding liver; 2. accumulation of fat is present in a minority of FNH; 3. enhancement of FNH is intense homogeneous in arterial phase imaging with fading to near isointensity in delayed phase imaging; 4. uptake of SPIO in FNH is pronounced with improved conspicuity of the central scar and septa. Most sensitive sequences to detect the SPIO-uptake are in- and opposed-phase T1-weighted GRE and diffusion T2-weighted BBEPI.

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5.3

Transcatheter arterial embolization as a safe and effective treatment for focal nodular hyperplasia of the liver.

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TRANSCATHETER ARTERIAL EMBOLIZATION AS A SAFE AND EFFECTIVE TREATMENT FOR FOCAL NODULAR HYPERPLASIA OF THE LIVER

ABSTRACT

When a surgical treatment is being considered for focal nodular hyperplasia, the risk of liver surgery must be carefully balanced against the benefit of resection, especially in the case of a large or centrally located lesion. However, when resection is contraindicated or even impossible, transcatheter arterial embolization should be considered as a safe and less invasive alternative treatment.

We describe two cases of young women who presented with abdominal pain and a hypervascular enhancing mass with the radiologic features of focal nodular hyperplasia. Arterial embolization was the therapy selected due to the risk of surgery. In both cases the procedure was successful, and the lesion showed shrinkage during follow-up.

INTRODUCTION

Focal nodular hyperplasia (FNH) is a benign liver tumour predominantly detected in young healthy women[1-3]. Although considered as a rare neoplasm, FNH is the second most common benign liver tumour after hemangioma[4,5]. Since most cases are incidental findings during abdominal imaging performed for other reasons, management of this solid liver lesion requires a systematic approach. A conservative approach for asymptomatic lesions is well established because there is no predisposition to haemorrhage or malignant transformation and symptoms may resolve during follow-up[1-3,6]. Nevertheless, large lesions (>4 cm) may be responsible for abdominal complaints due to pressure on surrounding tissues or the liver capsule, and surgery might be indicated[3,7]. In order to afford the best clinical approach, it is essential to evaluate whether symptoms are indeed related to the tumour or are caused by extrahepatic pathology.

On the basis of our experience with nonsurgical treatment of solid benign liver tumours, we treated two patients by arterial embolization. In this report, we describe this technique and the results of treatment in these female patients with abdominal complaints attributed to FNH in the liver.

CASE REPORTS

Case 1

A 29-year-old woman was admitted elsewhere for evaluation of a mild persistent right subcostal pain. Intermittently, she was nauseous and vomited. The patient had lost 3 kg in weight during the preceding 3 months when she had a decreased appetite. She denied fever, jaundice or a history of intravenous drugs or alcohol abuse. She had used an oral contraceptive in the past for 10 years but did not use steroids at presentation.

Physical examination revealed normal vital signs. There was slight tenderness in the right upper quadrant without clinical signs of hepatosplenomegaly or ascites.

Laboratory values of AST, ALT, alkaline phosphatase, total bilirubin, γ-glutamyl transferase, and α-fetopotein were within the normal limits. Serologic tests for HBsAg, anti-HBc, and anti-HCV were all negative.

Abdominal ultrasonographic examination showed a slightly hyperechoic lesion with a diameter of 4 cm, which was well circumscribed and lobulated. The remainder of the liver, intrahepatic and extrahepatic bile ducts, the gallbladder, and the urinary tract were normal without signs of stone disease. A spiral CT scan was performed and revealed a hypodense lesion with a strong homogeneous increase in density immediately after delivery of contrast. The lesion was centrally located and involved liver segments V, VI, VII, and VIII (Figure 1). Nonenhancing central areas suggested a central scar, characteristic for FNH. Other intra-abdominal organs appeared normal.

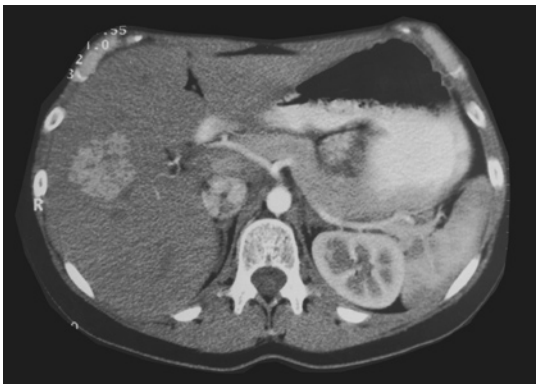
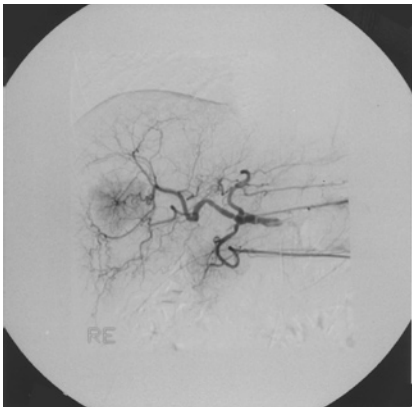


Figure 1. Case 1. Hyperdense lesion after delivery of contrast with nonenhancing central areas suggestive for a central scar, and a feeding branch from the right hepatic artery to the tumour.

An additional needle biopsy, which was performed elsewhere and reviewed in our hospital, was confirmatory for the histological diagnosis of FNH, and showed nodules of hyperplastic parenchyma completely surrounded by irregular fibrous septa and containing areas of dense ductular proliferation. The inflammatory infiltrate consisted mainly of mononuclear cells, and there was a lack of portal tracts and "native" bile ducts.

Given the location and relatively small size of the lesion, a gastroduodenoscopy was performed to exclude extrahepatic pathology that might have been causing the patient's complaints. There were no abnormalities in the gastroduodenal tract. Realising the risk of surgery for a centrally located liver lesion, a transcatheter arterial embolization was performed. During the angiographic procedure the right hepatic artery was catheterised selectively using a 4 Fr catheter. Then an angiographic series was performed to obtain an overview of the vascular anatomy and the feeding arteries of the FNH (Figure 2a). After all the feeding arteries had



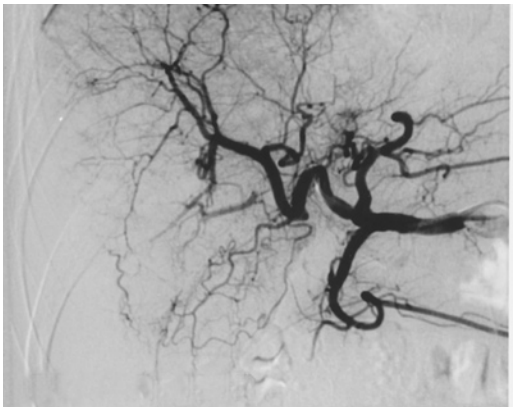


Figure 2. Case 1. **A.** Celiac angiography shows a hypervascular lesion with a central feeding artery radiating in a spoke-wheel manner into the lesion. **B.** Disappearance of the vascularity to the tumour after transcatheter arterial embolization.

been identified, an infusion microcatheter (Fastracker-18MX; diameter 0.533 mm; Boston Scientific) with its hydrophilic guidewire (FasDasher-14; diameter 0.3556 mm; Boston Scientific) were introduced superselectively through the 4 Fr catheter into the feeding arteries, which were embolised using embolisation particles (Contour; diameter 150-250 µm; Boston Scientific). At the end of the embolization procedure another angiographic series was performed using the 4 Fr catheter to evaluate the effect of the therapy (Figure 2b). During the procedure there was no need for a sedative or analgesic. Antibiotic prophylaxis was not used.

The results of treatment were followed up by CT scan, which showed an ischaemic area at the site of the previous lesion (Figure 3). No major treatment-related complications occurred during the hospital stay after embolization. The patient developed a temperature up to 38.3 °C with a minimal increase in serum transaminase levels (< 3x the upper limit of normal). These parameters returned to normal and the patient was discharged within 10 days post-embolization.

After 1 year of follow-up at the outpatient department, imaging methods showed shrinkage of the tumour and the lesion could no longer be visualised (Figure 4). At present, the patient is being treated for irritable bowel syndrome, and does not have complaints that might be related to the embolization procedure.

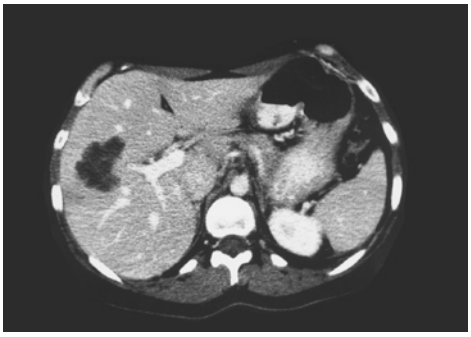


Figure 3. Case 1. CT scan performed 3 days after embolization shows an ischaemic area at the site of the previous lesion.

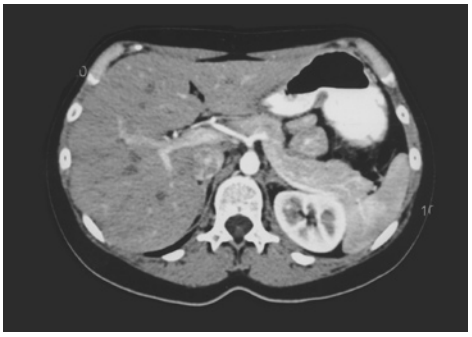


Figure 4. Case 1. CT scan after 1 year of follow-up, without signs of the tumour.

Case 2.

A 19-year-old woman was referred to our hospital for evaluation of a hepatic mass, which was detected elsewhere. The patient complained of persistent right upper abdominal pain radiating to the back, and fatigue. She had lost 10 kg in weight during a period of 6 months. She denied nausea, vomiting, diarrhoea, constipation, and changes in appetite. There was no previous history of jaundice, intravenous drugs or alcohol abuse. She had started to take an oral contraceptive during the month before admission.

On examination the patient was slim and appeared well. The abdomen was soft and non-tender. There was no palpable mass, or signs of liver insufficiency.

Routine liver tests and α-fetopotein were within the normal range, and serology tests for viral hepatitis were negative.

Abdominal ultrasound showed a solid liver lesion of 7 cm in the lobus caudatus with only a subtle change in echogenicity as compared with the surrounding normal liver parenchyma. Other intra-abdominal organs and structures appeared normal. An additional MRI examination, performed elsewhere, revealed typical features of FNH: homogeneous hyperdense enhancement on early phases with a rapid washout (Figure 5). The presence of a central scar, which showed enhancement only on delayed phases, made the diagnosis conclusive, and a needle biopsy was therefore unnecessary.

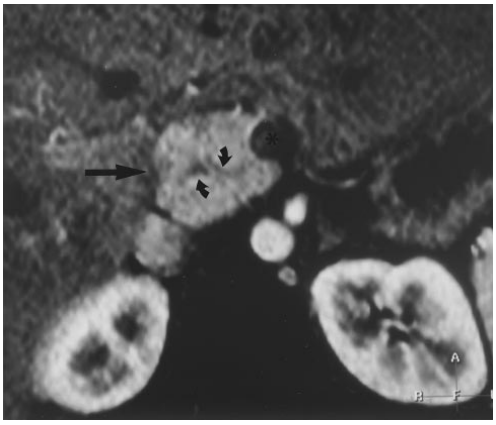


Figure 5. Case 2. A dynamic contrast-enhanced T1-weighted MR image during the arterial phase shows a tumour (large arrow) with intense homogeneous enhancement. The central scar (small arrows) shows less enhancement during this phase. Note that a pulsation artefact (asterisk), caused by the aorta, is obscuring part of the lesion.

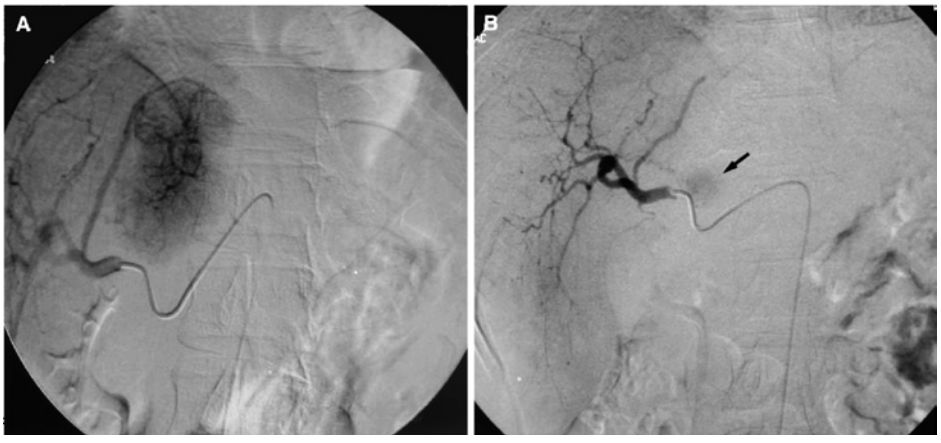


Figure 6. Case 2.

A. Celiac angiography shows a hypervascular lesion with a microcatheter placed in the left hepatic artery, which supplied the tumour.

B. Angiographic image after the embolization procedure. Note that only a small part of the lesion remains (arrow).

Considering the risk of surgery for this symptomatic lesion in segment I of the liver, an arterial embolization via the left hepatic artery was performed (Figure 6a). A small part of the lesion, which was supplied by the right hepatic artery, could not be embolised during the same session (Figure 6b). However, the embolization procedure was considered to be successful after a post-intervention angiography. And the procedure was ended. CT imaging showed an ischaemic area at the site of the lesion, and during a radiological follow-up of 6 months the tumour showed significant shrinkage (> 90%). The patient was free of symptoms.

DISCUSSION

Although the natural history of FNH is not precisely known, certain clinical and pathologic aspects of its behaviour are well known and form the basis for current clinical management. FNH is typically a benign, usually asymptomatic liver tumour (50-90%) with a strong predominance for young women[1,2,4]. While there is a clear association with the use of oral contraceptives and hepatic adenomas, the association of FNH with steroids has been denied[8].

During evaluation of a solid hepatic tumour, a benign lesion must be considered when clinical evidence of malignant disease is absent, serum α-fetoprotein levels are normal and hepatitis B and C serology tests are negative. Familiarity with dynamic contrast-enhanced CT and MRI allows an accurate diagnosis in most cases (sensitivity of 90-100%). Most FNHs are isodense or slightly hypodense to the liver on unenhanced CT. The typical contrast enhancement pattern of FNH is diffuse immediate homogeneous hyperdense enhancement on early phases (arterial and early portal venous) with rapid washout of contrast material, becoming isodense to the liver on late portal venous and delayed images. In particular the presence of a hypodense central scar on unenhanced images, showing a gradual filling-in on portal venous and delayed images, or a feeding artery radiating in a spoke-wheel pattern from the periphery to the centre of the tumour, is highly supportive of a diagnosis of FNH[4,9]. At MRI, FNH shows a similar enhancement pattern. However, MRI has a better specificity than CT because of its soft tissue signal characteristics on various T1- and T2-weighted images, better conspicuity of the central scar on T2-weighted and delayed contrast-enhanced images, and the availability of tissue-specific MR contrast media targeting either the Kupffer cells or hepatocytes[10]. The increasing use of these highly improved, fast scanning techniques will avoid the need for needle biopsies or aspirations in the near future.

A conservative approach to asymptomatic FNH lesions is justified due to the absence of risks for haemorrhage, necrosis and malignant degeneration[1-3,6,11]. In the case of a symptomatic lesion, surgical intervention can be considered although it is essential to determine whether the symptoms are caused by the tumour. The risk of significant and sometimes uncontrollable intraoperative bleeding during surgery for a hypervascular lesion, in addition to the common risks of any liver resection[12], should be carefully balanced against the benefit

that might be expected from resection. Mortality rates of surgery must be considered as serious and unacceptable in the management of a benign disease in young patients.

Transcatheter arterial embolization has been increasingly useful as a less invasive percutaneous tumour ablation technique in a variety of liver lesions and hemorrhage[13-16]. As it has been suggested that FNH is a hyperplastic response of hepatic parenchyma to a congenital arterial malformation, embolization appears to be a logical treatment option[1,17]. Besides, a central feeding artery is detected radiologically in 50-60% of cases, which makes this method more feasible[18]. Complications such as abscess formation and infections have been reported in the literature[19,20]. However, most of these, and some other complications, including major infarctions, tumour lysis syndromes and death, occurred in patients with serious underlying liver disease, or haemorrhagic shock from hepatic arterial or gastroduodenal bleeding[19,21]. In addition, the use of microcatheters will permit a more precise deposition of the embolization particles in the small feeding arteries, without occluding major arterial branches.

In the two patients described in this report, the technique of superselective transcatheter arterial embolization was performed successfully, confirming the experience of others[1,22]. We conclude that arterial embolization should be considered as a safe and effective alternative to surgical treatment of symptomatic cases of FNH, especially those with a considerable risk of surgery because of the location of the tumour.

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CHAPTER 6

Summary and implications of the thesis

SUMMARY AND CONCLUSIONS

In **part 1.1** a historical overview lines out the beginning of understanding the aetiology and pathogenesis of hepatocellular adenoma as a milestone in diagnosis and treatment of benign liver tumours, followed by an outline of the thesis in **part 1.2.**

In **part 2.1** an extensive review of the literature is presented in order to describe epidemiology, aetiology, pathogenesis, histology, and radiologic features of the most common benign liver tumours. The role of improved imaging modalities versus the role of liver biopsy in diagnosis of benign liver tumours is discussed and treatment options are pointed out. This review shows that the state-of-the-art MR imaging has a high accuracy in diagnosing benign liver lesions and should be part of the diagnostic work-up of focal liver lesions. Knowledge of these imaging features will avoid the need for liver biopsy that has it own diagnostic difficulties and pitfalls. Treatment options that are described in the literature vary from observation to surgery or other invasive interventional techniques. Reviewing the indications for treatment of benign liver tumours, it seems to be rarely indicated to perform surgery for a benign liver lesion, as most of these are asymptomatic and have an uncomplicated natural course.

The authors' own experience with the diagnosis and treatment of benign liver tumours is reported in **part 2.2.** In a large series of 208 patients who presented with hepatocellular adenoma, focal nodular hyperplasia, and cavernous haemangioma in a 20-year period, indications and long-term outcome after either a conservative or surgical treatment are reported. In the surgically treated population the liver lesion was an incidental finding in 36 per cent of patients. Operative morbidity and mortality was 27 and 3 per cent, respectively. Twenty-two per cent of patients with an incidentaloma, developed complaints of abdominal pain after hepatic surgery. During observation of the tumour in the conservatively managed group, 87 per cent of patients who presented with complaints were asymptomatic during a mean follow-up of 45 months. These results clearly justify a conservative approach to benign liver lesions as focal nodular hyperplasia and haemangioma. Surgery for liver lesions should be advised when there is an inability to exclude malignancy, e.g. due to a high a priori chance for malignancy as in metabolic or viral liver disease, or in case of severe complaints related to the tumour. Data from literature indicate that resection is always advocated for a large hepatocellular adenoma to reduce the risk of rupture and malignant degeneration. This study emphasises that it is important to inform patients about complaints that may persist after surgery, and that hepatic resection for benign lesions is still related to serious morbidity and even mortality.

Part 3 presents the results of a retrospective study, which has been performed to investigate the safety of a conservative management of giant haemangiomas. The medical records of 49 patients with a haemangioma of at least 4 cm in diameter were reviewed to document clinical presentation, diagnostic strategies, treatment, complications, and follow-up. This study showed that symptoms often resolved spontaneously during a mean follow-up of 52

months, and operation was not completely successful in terms of symptomatic relief. Liver haemangiomas have been resected because of a perceived risk of spontaneous or traumatic rupture, abscess formation, and the possibility of the Kasabach-Merritt syndrome. However, the potential for complications of a liver haemangioma is minimal and does not justify resection of all haemangiomas. As supported by the present observation, it can be concluded that observation of giant haemangiomas can be performed safely. Surgery for liver haemangioma is advocated only in patients with incapacitating symptoms, and size of the lesion is not a criterion for resection.

In **part 4.1** special attention is paid to the management of hepatocellular adenoma detected during pregnancy. High levels of endogenous steroid hormones and increased liver bloodflow during pregnancy increases the chances of liver rupture. Rupture of a hepatocellular adenoma during pregnancy carries a much higher mortality rate, as there may be a serious delay in diagnosis because of confusion with other pregnancy-related diseases. Supported by data from literature a successful resection of a hepatocellular adenoma was performed in a 32-year-old pregnant woman, which is reported in this chapter. Because of the unpredictable behaviour of hepatocellular adenomas and high maternal and foetal mortality rates in case of a rupture during pregnancy and partus, resection is recommended once a large (more than 5 cm) or a growing hepatocellular adenoma is diagnosed.

In **part 4.2** a study is presented which has been performed to evaluate early management and treatment of ruptured hepatocellular adenoma. In this study 12 patients with a ruptured hepatocellular adenoma are reported. As the morbidity and mortality rates associated with emergency resection are high, the initial management of a ruptured hepatocellular adenoma should be non-surgical by haemodynamic stabilisation. Definitive resection is required for rebleeding or for tumours exceeding 5 cm in diameter, and a conservative approach may well be justified in the case of regression of an asymptomatic hepatocellular adenoma.

In **part 4.3** special emphasis is made on the diagnostic challenges that may be encountered during differential diagnosis of a focal liver lesion. A review of the literature is performed assisted by the authors' own experience of three female patients who underwent surgery because of a focal liver lesion with an uncertain diagnosis despite of an extensive work-up. Although histological examination by fine needle biopsy is still considered to be the gold standard in the diagnosis of benign and malignant liver tumours, the availability of highly advanced radiological techniques provides a non-invasive diagnostic tool that is being used frequently. The use of a state-of-the-art pattern recognition approach, the combination of various MR sequences and tissue specific MR contrast media makes it possible to diagnose most hepatic tumours with confidence. This imaging modality may have equalled or even exceeded the value of needle biopsy as the gold standard. The accuracy rate of these modalities seems to be similar, and it should be questioned if an additional pre-operative needle biopsy will have therapeutic implications after having performed state-of-the-art MR imaging of the liver.

In **part 5.1** the pathologic spectrum of focal nodular hyperplasia is described with an emphasis on the pathologic classification that divides focal nodular hyperplasia into classic and nonclassic forms. The most recent concepts about the pathologic features of focal nodular hyperplasia including its angioarchitecture are described. This report also demonstrates the full spectrum of findings in focal nodular hyperplasia at state-of-the-art MR imaging in comparison with ultrasonography and CT scanning.

In **part 5.2** a prospective study is presented in which a cohort of patients with focal nodular hyperplasia has been imaged in order to assess which of the characteristics on state-of-the-art MR imaging of the liver are most useful for improved detection and characterization of this lesion. Pathology-proven focal nodular hyperplasias were prospectively examined with the state-of-the-art MR imaging using Gadolinium and superparamagnetic iron-oxide (SPIO) contrast media. This study indicates that combination of dynamic Gadolinium-enhanced imaging with T1- and T2-weighted imaging after administration of SPIO facilitates detection and characterization of FNH. It is shown that signal intensity of focal nodular hyperplasia prior to contrast differs only slightly from the surrounding liver; accumulation of fat is present in a minority of focal nodular hyperplasia; enhancement of focal nodular hyperplasia is intense homogeneous in arterial phase imaging with fading to near isointensity in delayed phase imaging; and uptake of SPIO in focal nodular hyperplasia is pronounced with improved conspicuity of the central scar and septa. Most sensitive sequences to detect the SPIO-uptake are in- and opposed-phase T1-weighted GRE and diffusion T2-weighted BBEPI.

In **part 5.3** superselective transcatheter arterial embolisation is described as an alternative treatment for focal nodular hyperplasia. As it has been suggested that focal nodular hyperplasia is a hyperplastic response of hepatic parenchyma to a congenital arterial malformation, embolisation appears to be a logical treatment option. Besides, a central feeding artery is detected radiologically in 50-60% of cases, which makes this method more feasible. When a surgical treatment is being considered for focal nodular hyperplasia, the risk of liver surgery must be carefully balanced against the benefit of resection, especially in the case of a large or centrally located lesion. Transcatheter arterial embolisation should be considered as a safe and less invasive percutaneous tumour ablation technique, and as an effective alternative to surgical treatment of symptomatic cases of focal nodular hyperplasia, especially those with a considerable risk of surgery because of the location of the tumour.

CONCLUSION

From history till now, at least some things have changed in diagnosis and treatment of focal liver lesions. Different radiological and nuclear tools have been used to obtain an accurate diagnosis and most importantly to differentiate benign from malignant lesions, each of them with a less or more invasive nature, or radiation hazard. Nowadays, state-of-the-art MR imag-

ing and the use of tissue specific contrast media, will permit lesion characterisation based on its cellular composition, enhancement pattern and morphological features. The use of this highly advanced imaging modality during differential diagnosis of a focal liver lesion will prevent unnecessary liver biopsy or surgery. The accuracy rate of the state-of-the-art MR imaging and needle biopsy as the gold standard seems to be similar, and it should be questioned if an additional pre-operative needle biopsy will have therapeutic implications after having performed MR imaging of the liver.

Concerning therapeutic options for benign liver lesions, it should be realised these lesions, except for hepatocellular adenoma and cystadenoma, are often incidentalomas and possess a benign natural course with a minimal risk of complications that does not justify a primary surgical treatment. Even when the patient is symptomatic, it is essential to evaluate if complaints are related to the lesion as they may persist after surgery, and more importantly, asymptomatic patients may develop symptoms while being exposed to a treatment with a considerable risk of morbidity and mortality.

In the case of a bleeding hepatocellular adenoma, a primary non-surgical management might afford the best clinical approach with a minimal risk for complications. However, surgery might well be necessary for a large or growing hepatocellular adenoma, or a cystadenoma. Transcatheter arterial embolisation should be considered as a safe and effective alternative treatment of vascularised lesions when there is a considerable risk for surgery.

The treatment of benign liver lesions can thus be summarised with the statement "conservative, unless…"

Dutch summary

SAMENVATTING EN CONCLUSIES

In **hoofdstuk 1.1** wordt in een korte historische inleiding aandacht besteed aan de ontwikkeling van ideeën over de etiologie en pathogenese van het hepatocellulair adenoom als mijlpaal in de diagnose en behandeling van benigne levertumoren, gevolgd door de opzet van het proefschrift in **hoofdstuk 1.2.**

In **hoofdstuk 2.1** wordt een uitgebreid literatuuronderzoek gepresenteerd met als doel een overzicht te bieden van de epidemiologie, etiologie, pathogenese, histologische en radiologische aspecten van de meest voorkomende benigne lever tumoren. In dit hoofdstuk wordt de rol van nieuwe diagnostische modaliteiten versus de rol van het histologisch naaldbiopt tijdens de differentiaaal diagnose van benigne lever tumoren besproken en worden de behandelingsopties voor deze tumoren uiteen gezet. Dit literatuuroverzicht laat zien dat de huidige moderne MRI scan met geavanceerde en geoptimaliseerde sequenties een hoge accuratesse heeft in het diagnostiseren van benigne lever tumoren en dat deze onderdeel moet zijn van de work-up van focale lever afwijkingen. Een exacte kennis van alle radiologische kenmerken van deze tumoren zal in de praktijk vaak de behoefte aan een leverbiopt en de diagnostische dilemma's die inherent zijn hieraan, voorkomen. De verschillende behandelingsopties die in de literatuur beschreven worden, variëren van een conservatieve, niet chirurgische behandeling tot resectie van de tumor of andere invasieve interventie technieken. Naar aanleiding van dit literatuuronderzoek naar de behandeling van benigne lever tumoren, wordt geconcludeerd dat er steeds minder vaak plaats is voor een chirurgische behandeling van benigne lever tumoren aangezien deze lesies vaak asymptomatisch zijn en een ongecompliceerd naturlijk beloop hebben.

Hoofdstuk 2.2 beschrijft een retrospectief onderzoek dat verricht is met het doel een inventarisatie te verrichten naar eigen ervaringen met de diagnostiek en behandeling van benigne lever tumoren. In een grote serie van 208 patiënten die zich in een periode van 20 jaar presenteerden met een hepatocellulair adenoom, focale nodulaire hyperplasie of een caverneus hemangioom worden de indicaties en lange termijn resultaten van een conservatieve of chirurgische behandeling geanalyseerd. In de chirurgisch behandelde groep was de lesie een toevalsbevinding in 36% van de patiënten. De chirurgische morbiditeit en mortaliteit bedroegen respectievelijk, 27% en 3%. Van de patiënten waarbij de tumor een toevalsbevinding was ontwikkelde 22% klachten van buikpijn na de chirurgische behandeling. In de groep die conservatief benaderd werd, verdwenen daarentegen de klachten bij 87% van de patiënten gedurende een mediane follow-up van 45 maanden. Deze studieresultaten rechtvaardigen een conservatieve benadering van benigne lever tumoren zoals het hemangioom en focale nodulaire hyperplasie. Een resectie is aangewezen indien een maligniteit niet uit te sluiten is of indien er een hoge a priori kans bestaat op maligniteit, zoals het geval is bij metabole of virale leveraandoeningen. Een primair chirurgische behandeling is eveneens geïndiceerd in geval van een groot hepatocellulair adenoom in verband met het risico op bloedingen of ma-

ligne degeneratie. In alle gevallen dient men de voordelen van een chirurgische behandeling af te wegen tegen de eventuele complicaties en risico's van leverchirurgie.

In **hoofdstuk 3** wordt een retrospectieve studie gepresenteerd dat verricht is met het doel om de conservatieve benadering van giant hemangiomen en de veiligheid van een dergelijk beleid te evalueren. In deze studie worden data bestudeerd van 49 patiënten met een hemagioom van minstens 4 cm in diameter met speciale aandacht voor de klinische presentatie, het diagnostische traject, de behandeling, complicaties en periode van follow-up. Deze studie toont aan dat de meeste patiënten die niet geopereerd zijn, symptoomvrij waren na een mediane follow-up duur van 52 maanden en dat klachten kunnen persisteren na een chirurgische behandeling. Hemangiomen van de lever worden vaak chirurgisch behandeld in verband met het vermeende risico op een spontane of traumatische ruptuur, abcesvorming en de mogelijkheid op het Kasabach-Merritt syndroom. Echter, de kans op complicaties bij een hemangioom van de lever is minimaal en rechtvaardigt niet een resectie van alle hemangiomen. Geconcludeerd wordt dat observatie van giant hemangiomen veilig is en dat een chirurgische behandeling van hemangiomen overwogen kan worden in geval van invaliderende klachten.

In **hoofdstuk 4.1** wordt ingegaan op de behandeling van het hepatocellulair adenoom tijdens zwangerschap. Hoge hormoon spiegels en een toegenomen doorbloeding van de lever tijdens de zwangerschap verhoogt het risico op een ruptuur van het hepatocellulair adenoom. De mortaliteit van een geruptureerd hepatocellulair adenoom gedurende een zwangerschap is hoog in verband met de kans op verwarring met zwangerschap gerelateerde pathologie en de daarmee samenhangende delay in behandeling. Ondersteund door deze literatuurgegevens werd er een resectie verricht van een hepatocellulair adenoom bij een 32 jarige zwangere vrouw, hetgeen beschreven wordt in dit hoofdstuk. In verband met het onvoorspelbare beloop van een hepatocellulair adenoom en de hoge mortaliteit van zowel de moeder als het kind in geval van een ruptuur, is het aan te raden een groot adenoom (diameter groter dan 5 cm) dat ontdekt is tijdens de zwangerschap te reseceren.

In **hoofdstuk 4.2** wordt een studie beschreven, waarin het beleid bij een geruptureerd hepatocellulair adenoom wordt geëvalueerd. In verband met de hoge morbiditeit en mortaliteit die geassocieerd is met een acute leverresctie, wordt in deze studie geconcludeerd dat het beleid bij een geruptureerd hepatocellulair adenoom primair een niet-chirurgische benadering moet zijn waarbij hemodynamische stabilisatie op de voorgrond staat. Een electieve resectie dient verricht te worden in geval van een herbloeding of een tumor diameter groter dan 5 cm en een conservatieve benadering is gerechtvaardigd indien er sprake is van regressie van een asymptomatisch hepatocellulair adenoom.

In **hoofdstuk 4.3** wordt nader ingegaan op de diagnostische dilemmas die kunnen ontstaan tijdens de differentiaal diagnose van een focale lever tumor. Aan de hand van drie patiënten die een resectie ondergingen van een focale lever afwijking die ondanks een uitgebreide analyse niet nader gakarakteriseerd kon worden, wordt een overzicht gegeven van

de meest recente literatuur betreffende de diagnostiek van focale lever afwijkingen. Ondanks de beschikbaarheid en het gebruik van de meest ontwikkelde radiologische technieken die een niet-invasief middel vormen voor de diagnostiek van benigne en maligne lever tumoren, wordt het histologisch naaldbiopt heden ten dage nog steeds beschouwd als de "gouden standaard". Het gebruik van de meest geavanceerde MRI scan met de mogelijkheid om verschillende moderne sequenties te combineren en de beschikbaarheid van weefsel-specifiek contrast maakt het mogelijk de meeste lever tumoren met een hoge accuratesse te diagnostiseren. De waarde van de MRI scan lijkt derhalve de rol van het histologisch naaldbiopt als de "gouden standaard" te evenaren of soms zelfs te overstijgen. De accuratesse van deze twee modaliteiten zijn overlappend en de vraag reist of een pre-operatief naaldbiopt van de tumor therapeutische implicaties zal hebben nadat er een MRI scan van de lever is verricht.

Hoofdstuk 5.1 bevat een overzicht van het pathologische spectrum van focale nodulaire hyperplasie met een nadruk op de histologische classificatie die onderscheid aanbrengt in de klassieke en niet-klassieke vorm. Hierin worden de meest recente concepten wat betreft de histologische kenmerken van focale nodulaire hyperplasie, inclusief de vasculaire opbouw, beschreven. Ook wordt in dit artikel het volledige radiologische spectrum van focale nodulaire hyperplasie op een geavanceerde MRI scan met de meest optimale scan sequenties uiteengezet en vergeleken met de bevindingen op een echo en CT scan.

In **hoofdstuk 5.2** wordt een prospectief cohort onderzoek uiteengezet waarin patiënten met een focale nodulaire hyperplasie zijn geïncludeerd. Het doel van deze studie was het bestuderen van karakteristieken van deze benigne lesie op geavanceerde MRI scan sequenties, waarbij gebruik wordt gemaakt van geoptimaliseerde, moderne scan parameters. In deze studie werd gebruik gemaakt van Gadolinium en SPIO (superparamagnetic iron-oxide) contrast. Dit onderzoek illustreert dat de combinatie van een dynamisch MRI onderzoek met Gadolinium en een T1- en T2-gewogen opname na toediening van SPIO contrast de detectie en differentiatie van focale nodulaire hyperplasie bevordert. De signaal intensiteit van focale nodulaire hyperplasie op blanco T1- en T2-gewogen sequenties verschilt slechts marginaal van de signaal intensiteit van de lever. Een klein percentage van de lesies bevat vet deposities. Het aankleuringspatroon na contrasttoediening is intens homogeen in de arteriële fase en er is sprake van een versterkte opname van SPIO contrast in de lesie waarbij het centrale bindweefselschot en de verschillende septa goed te visualiseren zijn. Daarnaast zijn de meest sensitieve sequenties om SPIO-opname te detecteren de in- en uit-fase T1-gewogen gradient echo sequentie en diffusie T2-gewogen BBEPI sequentie.

In **hoofdstuk 5.3** wordt de superselectieve arteriële embolisatie beschreven als een alternatieve behandeling voor focale nodulaire hyperplasie. Aangezien een van de etiologische concepten suggereert dat focale nodulaire hyperplasie een hyperplastische respons is van het leverparenchym op een congenitale arteriële malformatie, lijkt embolisatie een vanzelfsprekende behandeling. Bovendien is een centraal voedend vat radiologisch aantoonbaar in 50-60% van de gevallen, hetgeen deze methode toepasbaar maakt. Wanneer een chirur-

gische behandeling overwogen wordt voor focale nodulaire hyperplasie, dienen de risico's van leverchirurgie, zoals in geval van een grote of centraal in de lever gelocaliseerde tumor, nauwkeurig afgewogen te worden tegen het voordeel van een resectie. Arteriële embolisatie is een veilige en minimaal invasieve percutane techniek voor een ablatieve behandeling van benigne levertumoren. Het lijkt dan ook een effectief alternatief te zijn voor een chirurgische behandeling van symptomatische patiënten met een focale nodulaire hyperplasie, in het bijzonder bij een verhoogd risico op complicaties ten gevolge van de localisatie van de tumor.

CONCLUSIE

In de diagnostiek van focale levertumoren zijn er gedurende de afgelopen jaren verschillende radiologische en nucleaire technieken toegepast om te kunnen differentiëren tussen benigne en maligne lesies en om een accurate diagnose te stellen. MRI onderzoek biedt hierin de meest optimale afbeeldingsmogelijkheden zonder enige stralingsbelasting. In het bijzonder is de beschikbaarheid van weefsel-specifieke contrastmiddelen een mogelijkheid bij uitstek om lesies te karakteriseren op basis van cellulaire compositie, contrast opname en morfologische eigenschappen. Het gebruik van deze geavanceerde modaliteit gedurende de differentiaal diagnose van een focale levertumor zal onnodige invasieve ingrepen zoals een leverbiopsie of chirurgie tot een minimum beperken. De waarde van de MRI scan lijkt derhalve de rol van het histologisch naaldbiopt als de "gouden standaard" op zijn minst te evenaren. De accuratesse van deze twee modaliteiten zijn overlappend en de vraag is of een pre-operatief naaldbiopt van de tumor therapeutische implicaties zal hebben nadat er een MRI scan van de lever is verricht.

Wat betreft de therapeutische mogelijkheden in geval van een benigne levertumor, is het van belang om te realiseren dat het vaak een toevalsbevinding betreft. Met uitzondering van het hepatocellulair adenoom en het cystadenoom, beschikken deze tumoren over een benigne aard en een naturlijk verloop met een zeer gering risico op complicaties, hetgeen een primair chirurgische behandeling niet rechtvaardigt. Zelfs indien er sprake is van symptomen, is het essentieel om te evalueren of de klachten gerelateerd zijn aan de tumor, aangezien deze kunnen persisteren na een chirurgische behandeling. Van groter belang is het feit dat asymptomatische patiënten klachten kunnen ontwikkelen na een resectie terwijl zij onderworpen zijn aan een behandeling met een aanzienlijk risico op morbiditiet en mortaliteit.

In geval van een geruptureerd hepatocellulair adenoom, verdient een primair niet-chirurgische behandeling als de meest aangewezen benadering met een minimaal risico op complicaties, de voorkeur. Een chirurgische behandeling dient in ieder geval toegepast te worden in geval van een groot of groeiend hepatocellulair adenoom of in geval van een cystadenoom. Daarnaast vormt arteriële embolisatie een veilige en effectieve behandeling van goed gevasculariseerde lesies als alternatief voor risicovolle leverchirurgie.

De behandeling van benigne levertumoren kan dan ook worden samengevat met de stelling "conservatief, tenzij…".

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