Imaging of hepatic hypervascular tumors & clinical implications
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Matthanja Bieze was born on September 6th, 1983 in Zwolle, the Netherlands. She attended high school at the Agatina College location Carolus Clusius College, with a mix of interests: biology, science, history and gymnastics. At the age of 17 she enrolled in medical school at the Rijks University Groningen (RUG). During her college years Matthanja worked as a medical research assistant at Pharma Bio Research, as a student assistant for the department of Internal Medicine and the department of Ophthalmology of the University Medical Center Groningen (UMCG), and worked as an assistant for a family practitioner in Groningen.

The first encounter with research was the IMPROVE trial at the department of Internal Medicine at the UMCG. A side project resulted in a joint publication of Internal Medicine and Ophthalmology. Matthanja did her internship at the Isala Klinieken Zwolle, with a senior internship in traumatology (a collaboration between general surgery and orthopedics). After graduating medical school she continued working at the department of surgery at the Isala Klinieken. Ten months later she took leave to work with Doctors con Mision in Bolivia where she worked as a general physician on mobile missions to the countryside and on small outpost clinics. After her return to the Netherlands she resumed her work at the Isala Klinieken and took the opportunity for a PhD program at the Academic Medical Center Amsterdam under supervision of Professor Thomas M. van Gulik, HPB surgeon. During this period Matthanja had the opportunity to present her research at international congresses and was also given the opportunity to publish her photos in a book celebrating the 30 year anniversary of the Academic Medical Center. In July 2013 she started working at the Intensive Care Unit of the Rode Kruis Ziekenhuis, Beverwijk.
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CHAPTER 1

Imaging of Hepatic Hypervascular Tumors & Clinical Implications
Different tumors can arise in the liver. Some of these tumors are found by accident on imaging performed for an unrelated cause and some tumors manifest with symptoms. To determine the nature of the tumor imaging is performed to narrow down the differential diagnosis. If diagnosis remains inconclusive a biopsy of the tumor can be performed to evaluate the tumor with immunohistochemical analysis. The first step in diagnosis is to determine if the lesion is benign or malignant. And patients with a malignancy will be taken through the diagnostic work-up urgently to determine the stage of disease and initiate appropriate treatment. When patients with a benign tumor do not present with life-threatening complications, time is not essential for survival and the differentiation between benign hepatic tumors can be performed at a slower pace.

Benign Liver Tumors

The most common benign hepatic tumor is the hemangioma, occurring in the general population with incidences ranging from 0.4 to 20% [1]. Hemangiomas are composed of multiple, large vessels. Most hemangiomas are discovered at the mean age of 50 years and are seen more often in females [2]. The etiology is not understood, although a congenital anomaly has been suspected [1, 3]. Most hemangiomas are small, asymptomatic and are usually incidental findings. Since the lesion is benign, these hemangiomas usually require no treatment or follow-up. Hemangiomas >5cm are designated giant hemangiomas and because of size, may give rise to symptoms. Differential diagnosis includes other hypervascular tumors, such as hepatocellular adenoma and hepatocellular carcinoma. The second most common benign liver tumor is focal nodular hyperplasia (FNH). Most people will not know they have an FNH as the lesion rarely causes complications, symptoms or discomfort. FNH is predominantly found in women in their child bearing years. The etiology of this tumor is unknown, but is thought to be a hyperplastic response to (vascular) damage in the liver [4-6]. FNH is not associated with risks [4] and invasive treatment is not advised. Hepatocellular adenoma (HCA) on the other hand does hold risks of complications and is closely associated with hormone levels. HCA is predominantly seen in young women and prolonged use of oral contraceptives has been documented to influence growth of HCA [7]. This benign hepatic lesion might undergo malignant transformation in a small percentage of lesions [8]. Clinically more relevant is spontaneous rupture and bleeding of the tumor, causing pain and in some cases life-threatening hemorrhage [9]. Therefore, patients at risk for these two complications are advised to undergo preventive resection of the tumor(s). Diagnosis and treatment of benign hepatic tumors is not always straightforward and can cause confusion for both patient and treating
physician. In this thesis we mainly focussed on differentiating HCA from FNH using different imaging modalities along with treatment advises.

HEPATOCELULAR CARCINOMA

In the past decade the incidence of hepatocellular carcinoma (HCC) in the Western world has increased. In the Netherlands we have seen an increase from 340 new patients with primary liver cancer in 2001 to 544 in 2011 [10, 11]. Since 2008 a multidisciplinary team has been assigned in our institution to deal with diagnosis and treatment of this patient group. HCC usually develops in the background of cirrosis and parenchymal disease including hepatitis. Patients with known risk factors for HCC are screened every year with ultrasonography of the liver. When a suspicious tumor is found additional imaging is performed to confirm diagnosis of HCC. Various treatment algorithms have been proposed and the latest update of the guideline used at the AMC was by the European Association for the Study of the Liver (EASL) in 2012 [12]. The best outcome for survival is early stage of the disease with minimal tumor load, thereby increasing chances of curative treatment. However, most patients (approximately 70%) have intermediate to late stage of the disease and are treated with palliative or symptomatic care. In this thesis, detection and diagnosis of patients with HCC are dealt with to improve staging of HCC lesions ultimately resulting in more accurate treatment choices.

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The aim of this thesis was to evaluate diagnostic strategies and their clinical implications in patients with hypervascular hepatic tumors. The images of these tumors are shown with MR, CT and 18F-FCH PET/CT imaging.

**Chapter 1** is the introduction of the thesis. **Chapter 2** describes hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH); two benign hepatic tumors primarily seen in women between 20 – 60 years of age. We asked ourselves if MR imaging with Primovist® is of additional value for differentiation between both lesions. Another modality that we evaluated to differentiate HCA and FNH was the PET/CT with 18fluorocholine (18F-FCH) tracer **Chapter 3**. No complications are known of FNH and therefore there is no indication for invasive treatment. HCA on the other hand is known to give complications; a rare chance of malignant transformation and clinically more relevant, the chance of spontaneous bleeding or rupture of the lesion. Surgical intervention for HCA is therefore indicated in patients who are at risk of these complications. In **Chapter 4** we assessed the outcomes of surgical intervention in a cohort of patients with HCA or FNH. If the risk factors for bleeding in HCA were more clearly defined, the selection of patients to undergo (preventive) intervention would be more accurate. Therefore we first of all proposed a grading system with increasing severity for bleeding in **Chapter 5**. In **Chapter 6** we set out to determine patient characteristics and lesion characteristics associated with the risks of bleeding in HCA.

In **Chapter 7** the 6th most common malignancy worldwide is discussed: hepatocellular carcinoma (HCC). To improve detection of intrahepatic disease and extrahepatic extent of disease we hypothesized that the 18F-FCH PET/CT could be of additional value. While imaging modalities have become more and more of importance **Chapter 8** evaluated if staging laparoscopy (SL) for patients with HCC is still useful. In **Chapter 9** an overview is given of the HCC patient population and of management of the disease at the Academic Medical Center Amsterdam, The Netherlands.

**Chapter 10** shows the images of four interesting cases pertaining to different hepatic tumors: hepatoblastoma, HCA with hepatic granulomas, giant hemangioma, and FNH with bile duct hamartomas. This thesis finishes with a discussion including future perspectives, a summary, and conclusions in **Chapter 11**.
Our minds are constantly flooded by images from the world around us. We enjoy art, we love the movies, and take pictures of occasions we want to hold on to forever. In that respect, images are a way to communicate and can make us reflect on our view on the world, see another side of things, and show us what we cannot see with our own eyes. When it comes to medicine, we need images to help us in the diagnostic process, evaluate treatment options, and guide and follow-up the chosen path.

X-ray

In 1895 Wilhelm Röntgen discovered ‘A new kind of light’ to write an image [2]. The mechanism depends on the capture of electromagnetic radiation (X-rays) on photographic plates. X-rays are absorbed in various degrees by tissues where the air in lungs hardly absorbs X-ray, and bone absorbs most of the radiation. The result is that lungs appear in black, tissues in various shades of gray, and bones in white on an X-ray image. Röntgen discovered the medical potential of X-ray when he portrayed the hand of his wife. Not just the healthy human body was displayed but also the broken and diseased. Shortly after its discovery the X-ray machines were introduced in the medical practice and were soon used throughout the medical world [3, 4]. That X-rays have a downside became clear by the burns and ulcers occurring on X-ray machine operator who were exposed for a longer period of time. The best documented case might be that of Thomas Edison’s chief assistant Dally, dying an agonising slow death by the malignant consequences of the X-ray. Only 3-4 years after starting his work Dally had chronic ulcers on both hands, eventually leading to malignancies and he required amputation of his fingers, hands, and eventually arms until his death in 1904. Edison took a different path in his research and refused to undergo X-ray in the remainder of his life [1].

Computed tomography

The history of whole body imaging has a more positive note with a combination of Röntgen’s technology, mathematics, and music. Electric and Musical Industries Ltd. 1931 (EMI) signed the young rock group ‘the Beatles’ in 1962 [6] 7, and due to their world-wide success the company had a great deal of money to invest. In the early days of EMI the Company was closely involved in research project and with the extra cash flow of the record industry they could invest even more. Godfrey Hounsfield [7] 8 was one of the researchers who profited. He proposed to combine Röntgen’s X-rays with Allan Cormack’s [5, 8, 9] mathematical hypothesis and their collaboration enabled the build of the first computed tomography (CT) scanner.
or EMI scanner [9, 10, 101]. In October of 1971 the scanner enabled imaging of a patient’s brain with a cerebral cyst at Atkinson Morley Hospital in London [11]. By 1975 the whole body instead of solely the brain could be observed in thin slices. The summary of the Nobel Prize awarded to Hounsfield and Cormack in 1979 says quite poetic that the CT scan ‘has ushered medicine into the space age’ [5].

**Nobel Prize Winner in Literature Harry Martinson tells how, one day, the mimarobé, the computer guardian,... by means of Mima’s formula cycles, phase by phase,... saw into the transmutations,... and was able to see through everything as though it were glass...**

**Nobel Prize 1979 [5]**

**NUCLEAR MAGNETIC RESONANCE**

The downside of CT imaging is radiation exposure of X-rays. Therefore other possibilities were evaluated to image the human body without side effects. One of the proposed techniques was based on the resonant absorption of water (protons) in the human body. When a sample is placed in a high magnetic field these protons align with the direction of the magnetic field. A radio frequency current creates an electromagnetic field. As soon as the electromagnetic field is turned on the protons return to their original equilibrium. During this process of relaxation electromagnetic radiation is generated and detected by receiver coils. Professor Raymond Damadian [13] worked on the basic principles of MR imaging for medical purposes and published his ideas in Science 1971 [14] and images of the first ‘live human body’ in 1977 [15]. Sir Peter Mansfield (physicist at the University of Illinois) were the other major scientists in the field. It turned out difficult to make the scanning fast enough to be practical and to translate the scan to visual images. In 1977 Sir Peter Mansfield succeeded to perform an MRI in seconds rather than hours and to translate the scan to actual images. In the 80’s MR imaging developed into a more sensitive modality as a higher field-strength became available: the 1.5 Tesla. Most imaging is still performed with this Tesla.

**POSITRON EMISSION TOMOGRAPHY**

First work was performed in very different sciences and was dosed with a good deal of luck. After Rontgen’s discovery of X-rays the entire scientific world was experimenting with new rays and there potential. Henri Becquerel [18] took uranium salts with the aim to evaluate if there were ‘new rays’ and there potential. Henri Becquerel [18] continued in their academic footsteps and discovered artificial radioactivity in 1934 [20], the year Madame Curie died of leukemia due to the years of unprotected work with radiation. The world was overwhelmed by images of the inner body and new radiation. Science that wasn’t this mind-blowing was just not interesting. So with less uproar biologists discovered the ‘luminescence phenomena’ in the early 1900 [21]. Dr. Herly [22] described that ‘by means of ultraviolet light selective differentiation of tissues’ can be made, and Dr. Moore build on that idea to differentiate normal from malignant tissues by injected the dye sodium fluorescein [23]. In his later studies Moore would substitute the dye with radioactive isotopes including radioactive iodine and the first steps to nuclear medicine were made [24-26]. The development of radioisotopes that could be used in radioactive tracers to detect malignancies [27] was done by Merrill Bender (M.D), and his research partner Monte Blau (PhD in chemistry) [28]. They developed an imaging agent to localize a brain tumor and soon studies with localizing agents like sodium iodine [29], pancreas [30], and liver [31] and many other organs and organic systems followed. The first scanner was called the ‘head-shrinker’ and was built in 1961 by Dr. Robertson and colleagues at the Brookhaven National Laboratory. Dr. Fowler developed the fluorodexoxyglucose tracer which is still used today in positron emission tomography (PET) [32]. When PET was combined with CT imaging it was declared ‘the medical invention of the year’ by TIME magazine in 2000 [33]. MR imaging can also be used for topographic mapping of the PET image. Before undergoing the PET a short-lived radiopharmacon (tracer) is intravenously injected and decayed. The most commonly used tracer is an analogue of glucose: 18F-fluorodexoxyglucose (18F-FDG). The tracer will undergo decay: it emits a positron, which loses kinetic energy and interacts with an electron. This interaction results in a pair of gamma photons moving in opposite direction. These photon pairs are detected by the PET scanner and converted to a digital image. The scan shows a functional image of the human body and is combined with CT or MR imaging as topographic reference when combining both imaging techniques a reconstruction of the body can be made and a specific localization of high metabolism of the used tracer can be detected.

In medicine we have gotten used to seeing beyond the exterior. An image tells a story and if we can relate to the picture we can’t help but get involved. Quite literally, images of the human body get under our skin.

---

**April 1978:**

I climbed into the machine and signaled to Peter and Ian to push the button for a single pulse. There was an audible crack but I felt nothing.

I then signaled to start the scan. The magnet was enclosed in aluminum sheeting forming an RF screen. Due to lack of time there was no light inside. I was therefore clamped in the magnet vertically and in pitch darkness for 90 minutes until the procedure was completed. Our wives and fiancées were present to haul me out of the magnet in an emergency, but the whole experiment went well and images were recorded.

---

In cloudy days Becquerel discovered that even without direct sunlight the rocks had given of some radiation that left a dark imprint on the photographic plate (1896) [18]. His discovery intrigued Marie Curie who was in search of a subject for her doctoral thesis. She pursued the study of the uranium rays (or radiation) and was soon joined by her husband Pierre [19]. Daughter Irène Joliot-Curie and husband Frédéric Joliot-Curie continued in their academic footsteps and discovered artificial radioactivity in 1934 [20], the year Madame Curie died of leukemia due to the years of unprotected work with radiation. The world was overwhelmed by images of the inner body and new radiation. Science that wasn’t this mind-blowing was just not interesting. So with less uproar biologists discovered the ‘luminescence phenomena’ in the early 1900 [21]. Dr. Herly [22] described that ‘by means of ultraviolet light selective differentiation of tissues’ can be made, and Dr. Moore build on that idea to differentiate normal from malignant tissues by injected the dye sodium fluorescein [23]. In his later studies Moore would substitute the dye with radioactive isotopes including radioactive iodine and the first steps to nuclear medicine were made [24-26]. The development of radioisotopes that could be used in radioactive tracers to detect malignancies [27] was done by Merrill Bender (M.D), and his research partner Monte Blau (PhD in chemistry) [28]. They developed an imaging agent to localize a brain tumor and soon studies with localizing agents like sodium iodine [29], pancreas [30], and liver [31] and many other organs and organic systems followed. The first scanner was called the ‘head-shrinker’ and was built in 1961 by Dr. Robertson and colleagues at the Brookhaven National Laboratory. Dr. Fowler developed the fluorodexoxyglucose tracer which is still used today in positron emission tomography (PET) [32]. When PET was combined with CT imaging it was declared ‘the medical invention of the year’ by TIME magazine in 2000 [33]. MR imaging can also be used for topographic mapping of the PET image. Before undergoing the PET a short-lived radiopharmacon (tracer) is intravenously injected and decayed. The most commonly used tracer is an analogue of glucose: 18F-fluorodexoxyglucose (18F-FDG). The tracer will undergo decay: it emits a positron, which loses kinetic energy and interacts with an electron. This interaction results in a pair of gamma photons moving in opposite direction. These photon pairs are detected by the PET scanner and converted to a digital image. The scan shows a functional image of the human body and is combined with CT or MR imaging as topographic reference when combining both imaging techniques a reconstruction of the body can be made and a specific localization of high metabolism of the used tracer can be detected.

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Diagnostic accuracy of MRI in differentiating hepatocellular adenoma from focal nodular hyperplasia:

Prospective study of the additional value of gadoxetate disodium

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OBJECTIVE

The purpose of this article is to prospectively determine the sensitivity of hepatobiliary phase gadoxetate disodium enhanced MRI combined with standard MRI in differentiating focal nodular hyperplasia (FNH) from hepatocellular adenoma (HCA).

SUBJECTS AND METHODS

Patients suspected of having FNH or HCA larger than 2 cm underwent gadoxetate disodium–enhanced MRI. Standard MRI was evaluated separately from the additional hepatobiliary phase by two blinded radiologists. For the largest lesion in each patient, findings were compared with histologic diagnosis. Sensitivity, positive predictive value (PPV), and distinctive features were analyzed using McNemar and analysis of variance tests.

RESULTS

Fifty-two patients completed the study. Histologic diagnosis revealed 24 HCAs and 28 FNHs. Characterization on standard MRI was inconclusive in 40% (21/52) and conclusive in 60% (31/52) of lesions. The sensitivity for FNH was 50% (12/24) with a PPV of 100% (12/12). The sensitivity for FNH was 68% (19/28) with a PPV of 95% (18/19). After review of hepatobiliary phase, the sensitivity for HCA improved to 96% (23/24) with a PPV of 96% (23/24). The sensitivity for FNH improved to 96% (27/28) with a PPV of 96% (27/28). Features with significant predictive value for diagnosis in HCA included bleeding (p < 0.001), fat (p = 0.010), and glycogen (p = 0.024). The presence of a central scar was predictive for FNH (p < 0.001).

CONCLUSION

This study shows high sensitivity of gadoxetate disodium–enhanced MRI when standard series are combined with the hepatobiliary phase for differentiation of FNH and HCA in lesions larger than 2 cm.
sisted only of imaging or follow-up in a substantial number of included cases [18]. Therefore, the purpose of this study was to prospectively determine the diagnostic accuracy of the hepatobiliary phase of gadoxetate disodium–enhanced MRI combined with standard MRI in differentiating FNH from HCA, with histopathology as the standard of reference.

METHODS

This study was a prospective single-center diagnostic accuracy study with paired design for differentiating FNH from HCA conducted between January 2008 and June 2010. Standard MRI was compared with the hepatobiliary phase of gadoxetate disodium–enhanced MRI at a blinded reading. The institutional medical ethics committee approved the study, and written informed consent was obtained from all patients. A total of 67 consecutive patients were included (mean age, 39 years; range, 18–60 years). Patients either primarily presented to our surgical outpatient clinic or were secondarily referred from other centers with suspicion of FNH or HCA. Criteria for exclusion were primary malignancy, previous malignancy, and other risk factors, including chronic hepatitis, cirrhosis, hemochromatosis, and elevated alpha-fetoprotein or carcinoembryonic antigen levels in blood serum. Further exclusion criteria were pregnancy and contraindications for MRI (i.e., severe claustrophobia, metal objects or particles within the eyes or the abdomen, and impaired renal function, which was defined as serum creatinine level > 200 μmol/L). One patient discontinued the study because of claustrophobia. Six patients were excluded because our MRI revealed typical hemangioma or hamartoma. Eight patients were excluded because histologic confirmation was not obtained, either because of sampling errors or because consent was withdrawn. Three patients presented with major bleeding from the lesion for which arterial embolization was indicated. These patients were included in the overall analyses of differentiating HCA from FNH but were excluded from the subanalyses of enhancement. This was because of possible alteration in enhancement and signal intensity of the lesion after embolization of feeding vessels. Hence, data of 52 patients (2 men and 50 women; mean age, 39 years; range, 18–56 years) were available for evaluation.

MRI Protocol

The MRI was performed with a 1.5-T MRI scanner (Avanto, Siemens Healthcare) using a phased-array torso coil. MRI series consisted of 2D gradient-echo in- and opposed-phase imaging FLASH (TR/TE, 15/2.3 and 125/4.6; flip angle, 70°; matrix, 256 × 192); arterial, portal, and late phases. The lesions had to be 2 cm or larger except for small lesions in children. The lesions were categorized as homogeneous or inhomogeneous.

MRI Interpretation

The MRI series were evaluated in consensus by two radiologists with more than 10 years of experience in abdominal radiology. The readers were informed of the differential diagnosis of either FNH or HCA but were blinded to patient history and previous imaging findings. First, the standard images were evaluated, after which the hepatobiliary phase was evaluated in the same session. The following characteristics were used for evaluation of the liver: the number of lesions and the presence of steatosis (i.e., visual loss of signal intensity of the liver between in- and out of phase T1-weighted series). The following items were noted regarding the lesions: size, segmental localization, shape (round or lobulated), and demarcation (sharp or faint). High-signal foci on T1-weighted series were assessed; foci with loss of signal intensity on the T1-weighted out-of-phase series were regarded as fat, and small foci without loss of signal intensity were regarded as glycogen. Larger irregular high-signal areas on T1-weighted series were regarded as recent bleeding, whereas low-signal areas were regarded as older bleeding. Diffuse loss of signal intensity of T1-weighted out-of-phase series was regarded as diffuse fat content within the lesion. Furthermore, a central scar (a high-signal-intensity “spokes wheel” on true FISP T2-weighted series and low signal intensity on T1-weighted series, with or without enhancement during portal or late series). Lesion-to-liver intensity was noted on unenhanced T1-weighted and true FISP T2-weighted series, and contrast-enhanced arterial, portal, and late phases. The lesion enhancement pattern was expressed as a “peak pattern,” if arterial enhancement with clear loss of signal intensity during portal or late phases was seen, and as a “plateau pattern,” if signal intensity was sustained during portal and late phases of imaging. The two readers made a visual score of signal intensity and enhancement pattern. When in doubt, a region of interest was placed in the lesion to measure signal intensity of the lesion. The diagnosis of FNH was based on the presence of a central scar, arterial enhancement, and absence of signs of washout during portal phase. A diagnosis of HCA was based on arterial enhancement, with possible washout during portal phase; the presence of bleeding, fat, or glycogen; and the absence of a central scar. MRI of lesions without these characteristics was regarded as inconclusive. Finally, the lesions were evaluated for signal intensity compared with surrounding liver tissue on the T1-weighted hepatobiliary series at 20 minutes after injection. Isointense or hyperintense signal intensity of the lesion was regarded as diagnostic for FNH, and hypointensity was considered diagnostic for HCA. The pattern of contrast agent uptake was scored as either homogeneous or inhomogeneous.
The standard of reference was defined as histopathologic diagnosis. The histologic specimens were obtained by resection or liver biopsy from tumoral and normal liver tissue. The evaluating pathologist was blinded to patient history. In addition to standard liver stainings, including H and E, collagen, and CK7, glutamine synthetase staining was performed for confirmation of histomorphologic diagnosis [19]. The diagnosis of FNH as based on morphologic characteristics, including the presence of stellate fibrous scarring, dystrophic arteries, ductular reaction, variable infiltrate, and absence of cytologic abnormalities. Morphologic characteristics of HCA included a proliferation of nonatypical hepatocytes, with a well-developed reticulin framework, without a central scar.

In cases of multiple lesions, the largest lesion or the lesion most suitable for biopsy was selected on imaging. The location of this lesion was recorded by the investigator, who also instructed the interventional radiologist as to which lesion to biopsy. The investigator also monitored the preoperative selection of the lesions and the postoperative examination by the pathologist to guarantee proper matching between imaging and histopathology. Histologic diagnoses were 24 HCAs and 28 FNHs, diagnosed in 25 patients on resection and in 27 patients on biopsy specimens. Biopsy material (six HCAs and 21 FNHs) and resection specimens (18 HCAs and seven FNHs) were used. All FNHs but one showed a typical maitlike pattern staining of glutamine synthetase, which was absent in HCAs. This one lesion was composed of nonatypical hepatocytes together with scarring, ductular reaction, thick-walled vessels, and inflammatory infiltrates but lacked the typical maitlike glutamine synthetase staining. On the basis of morphologic features, lack of serum amyloid A, and C-reactive protein overexpression, the lesion was diagnosed as FNH.

Statistical analysis was per patient for the largest suitable lesion using SPSS (version 18, IBM). Descriptive statistics were used for the study population. Continuous data were tested for normal distribution and equal variances using the Levene test. Features on imaging were tested for significance between FNH and HCA using the analysis of variance and multivariate tests. The sensitivity, specificity, and positive predictive value (PPV) of the standard and hepatobiliary phases of gadoxetate disodium–enhanced MRI were calculated with the McNemar test and the 95% CI of the proportions on the Wilson procedure without correction for continuity [20]. Statistical tests were evaluated at the 5% level of significance.

Figure 1

28-Year-old woman with atypical HCA, dull pain in upper abdomen, and history of long-term oral contraceptive use. A: Transverse T2-weighted MRI (fat saturated; TR/TE, 5400/76; flip angle, 70°; matrix, 384 × 230) shows hyperintense lesion (arrow) in right liver. B: In sub-sequent arterial transverse T1-weighted image (TR/TE, 577/2.54; flip angle, 10°; matrix, 256 × 156), lesion (arrow) shows strong signal intensity to surrounding liver parenchyma, without typical features of FNH or HCA. C: Portal phase image shows slight hyperintense lesion (arrow) without typical features to differentiate between FNH and HCA. D: Differentiation could, however, be made on transverse hepatobiliary phase T1-weighted fat-saturated image 20 minutes after contrast agent injection. Lesion (arrow) was interpreted to have less signal intensity compared with surrounding liver tissue, which is consistent with HCA.
A total of 52 patients completed the study. The two men both presented with FNH. Forty-seven of the 50 women reported long-term use of oral contraceptives.Thirty-one patients presented with abdominal pain or discomfort, three of whom presented with acute bleeding requiring arterial embolization (16 with HCA and 15 with FNH). Eighteen of the 24 patients with HCA (75%) underwent resection of the lesion (mean [± SD] diameter, 8.5 ± 4.9 cm; range, 4.4–25 cm). Seven of 28 patients with FNH (25%) underwent resection of the lesion because of discomfort (mean diameter, 6.8 ± 3.0 cm; range, 3.7–12.0 cm). Patients who presented with discomfort often had bleeding (nine with HCA) or a large lesion with mass impact on the surrounding liver parenchyma and organs. However, one patient with extreme discomfort only had a 2.5-cm FNH. Thirty-five lesions were 5 cm or larger (20 HCAs and 15 FNHs), and resection was advised if the diagnosis was HCA. The group of patients with a lesion smaller than 5 cm (n = 17) consisted of four with HCA (24%) and 13 with FNH (76%). In the overall group, 15 patients had a solitary lesion at imaging (four with HCA and 11 with FNH), eight had two or three lesions (five with HCA and six with FNH), six had four to 10 lesions (five with HCA and one with FNH), and 12 patients had more than 10 lesions characterized on MRI (nine with HCA and three with FNH). Of the 19 patients with HCA and multiple lesions, three also presented with a lesion compatible with FNH on imaging, with high or isointense signal on the hepatobiliary phase. One lesion was also confirmed to be FNH at histopathologic analysis.

Imaging results are summarized in Table 1. For 31 of 52 patients, MRI was conclusive and diagnosed 12 lesions as HCA and 19 as FNH. Compared with histologic diagnosis, this resulted in a sensitivity for HCA of 50% (12/24; 95% CI, 31–69%), and a PPV of 100% (95% CI, 76–100%). The sensitivity for FNH was 64% (18/28; 95% CI 46–79%) with a PPV of 95% (18/19; 95% CI 75–99%). With standard MRI, characterization was inconclusive in 21 of 52 patients, including 11 with HCA (Fig. 1) and 10 with FNH (Fig. 2). Two of 10 FNHs showed a small central scar. In comparison, 16 of 18 FNHs contained a scar when diagnosis was conclusive on standard MRI. In 11 HCAs, the MRI was regarded inconclusive, although in five lesions, high-signal foci were dubiously present. The mean diameter of lesions was 7.1 cm on conclusive standard MRI and 6.4 cm on inconclusive MRI (p = 0.420).

On the hepatobiliary series, no cases were regarded as inconclusive (Table 1). Twenty-four lesions were hypointense compared with surrounding liver tissue and were characterized as HCA (Fig. 3). Twenty-eight lesions were isointense or hyperintense and therefore characterized as FNH (p < 0.01) (Fig. 4). Compared with the histologic diagnosis, this resulted in a sensitivity of 96% for HCA (43/45; 95% CI, 80–99%), with a PPV of 96% (95% CI, 80–99%). The sensitivity for FNH was 96% (27/28; 95% CI, 82–99%), with a PPV of 96% (95% CI, 82–99%). High signal intensity of FNH (n = 27) during the hepatobiliary phase was homogeneous in 14 cases (52%) and inhomogeneous in 13 cases (48%). One case
of FNH showed low homogeneous signal intensity compared with surrounding parenchyma during the hepatobiliary phase and was incorrectly characterized as HCA. One case of HCA was isointense and therefore falsely characterized as FNH.

**TABLE 1: Diagnosis of Hepatocellular Adenoma (HCA) and Focal Nodular Hyperplasia (FNH) on Standard and Hepatobiliary MRI Series**

<table>
<thead>
<tr>
<th>Type of MRI, Diagnosis</th>
<th>Histologic Diagnosis</th>
<th>FNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>HCA</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>FNH</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Hepatobiliary phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconclusive</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>HCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FNH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note—Data are no. of lesions.

**FIGURE 3**

35-year-old woman with hepatocellular adenoma (HCA) and acute pain in upper abdomen that started during pregnancy. **A**: Transverse T1-weighted in phase MRI shows isointense lesion in segment 3 with high-signal area centrally, consistent with recent bleeding. There is low-signal rim surrounding bleeding, consistent with older blood (blooming artifact). **B**: Transverse T1-weighted image obtained after injection of gadobenate dimeglumine in arterial phase shows homogeneous enhancement of lesion (signal intensity of 469, compared with 200 on unenhanced image) and no enhancement of area of bleeding.

**FIGURE 4**

22-year-old woman with focal nodular hyperplasia (FNH) and chronic dull pain in upper abdomen. **A**: Transverse arterial phase T1-weighted image (fat saturated TR/TE, 5.77/2.54; flip angle, 10°; matrix, 256 × 156) shows arterial enhancement of lesion in segment IV of liver (arrow), with hypointense area in center of lesion; central scar (arrowhead) is also seen. **B**: Corresponding hepatobiliary phase T1-weighted image obtained 20 minutes after contrast agent injection shows isointense-to-hyperintense signal of lesion (arrow) compared with surrounding liver, consistent with FNH.
**Features and Characteristics**

The lesion characteristics are summarized in Table 2. Diffuse parenchymal steatosis of the liver was found in nine of 24 patients with HCA (38%) and in three of 28 patients (10%) with FNH (p = 0.022). Features with significant predictive value for HCA included fat content in five cases (p = 0.010). High-signal foci on T1-weighted series consistent with bleeding were found in 11 HCAs and zero FNHs (p < 0.001). This was histomorphologically confirmed in five of six surgical specimens. Finally, glycogen was detected in four HCAs and zero FNHs as hyperintense small areas on T1-weighted imaging (p = 0.024). Features with significant predictive value for FNH include a central scar in 18 of 28 FNHs (p < 0.001). Among 14 FNHs smaller than 5 cm, six showed no central scar. FNH was often lobulated (21/28) compared with HCA (12/24; p = 0.064). Peripheral vessels were found in two FNHs and three HCAs (p = 0.523), and none of the lesions had central feeding vessels. Lesion-to-liver intensity is summarized in Table 3. Three HCAs were not included in the analyses because of prior arterial embolization of a feeding vessel after bleeding. During unenhanced T1-weighted series, FNHs overall showed significantly lower signal intensity than did HCAs, even if bleeding was excluded from analyses (p < 0.001). During the T1-weighted arterial phase, all 28 FNHs and 23 HCAs showed arterial enhancement. During the T1-weighted portal phase, hyperintense signal compared with surrounding liver parenchyma was seen in 22 of 28 FNHs and 24 of 21 HCAs (p = 0.008). On the portal phase, hypointensity (washout) was seen in three HCAs and in none of the FNHs. During the late phase, hyperintense signal was seen in 18 FNHs and 13 HCAs, isointense signal was seen in eight FNHs and six HCAs, and hypointense signal was seen in two FNHs and two HCAs, with no significant difference between the two groups (p = 0.802). The enhancement pattern showed a plateau pattern in FNHs and a peak pattern in HCAs (p = 0.009) (Table 4). In the hepatobiliary phase in 24 of 52 patients, the lesions were hypointense compared with surrounding liver tissue characterized as HCA and in 28 of 52 patients, the lesion was isointense or hyperintense and was characterized as FNH (p < 0.01) (Fig. 4).

**Discussion**

In previous studies, enhancement with gadoxetate disodium has shown promising results in differentiating FNH from HCA [7]. The limitation of those studies was the use of only CT or follow-up as the standard of reference in most of the included cases. Therefore, we evaluated our imaging results with histologic analysis as the standard of reference in all cases. The present study shows the high accuracy of gadoxetate disodium–enhanced MRI when the standard series are combined with the hepatobiliary phase for differentiation of FNH and HCA in lesions larger than 2 cm. In 40% of cases, standard MRI was inconclusive because of the lack of typical features. In the literature, this occurs in 30–42% of cases, especially when lesions are smaller than 3 cm [8, 10]. Difficulties may arise in detecting a small scar in FNH. For example, in one FNH, we detected the small scar on the hepatobiliary phase only. Bleeding was mostly detected as hyperintense signal foci on T1-weighted series consistent with bleeding were found in 11 HCAs and zero FNHs (p = 0.024). Features with significant predictive value for HCA include a central scar in 18 of 28 FNHs (p < 0.001). Among 14 FNHs smaller than 5 cm, six showed no central scar. FNH was often lobulated (21/28) compared with HCA (12/24; p = 0.064). Peripheral vessels were found in two FNHs and three HCAs (p = 0.523), and none of the lesions had central feeding vessels. Lesion-to-liver intensity is summarized in Table 3. Three HCAs were not included in the analyses because of prior arterial embolization of a feeding vessel after bleeding. During unenhanced T1-weighted series, FNHs overall showed significantly lower signal intensity than did HCAs, even if bleeding was excluded from analyses (p < 0.001). During the T1-weighted arterial phase, all 28 FNHs and 23 HCAs showed arterial enhancement. During the T1-weighted portal phase, hyperintense signal compared with surrounding liver parenchyma was seen in 22 of 28 FNHs and 24 of 21 HCAs (p = 0.008). On the portal phase, hypointensity (washout) was seen in three HCAs and in none of the FNHs. During the late phase, hyperintense signal was seen in 18 FNHs and 13 HCAs, isointense signal was seen in eight FNHs and six HCAs, and hypointense signal was seen in two FNHs and two HCAs, with no significant difference between the two groups (p = 0.802). The enhancement pattern showed a plateau pattern in FNHs and a peak pattern in HCAs (p = 0.009) (Table 4). In the hepatobiliary phase in 24 of 52 patients, the lesions were hypointense compared with surrounding liver tissue characterized as HCA and in 28 of 52 patients, the lesion was isointense or hyperintense and was characterized as FNH (p < 0.01) (Fig. 4).

**Table 3:** Lesion-to-Liver Intensity of Focal Nodular Hyperplasia (FNH) and Hepatocellular Adenoma (HCA)

<table>
<thead>
<tr>
<th>Lesion Type, Signal Intensity</th>
<th>Unenhanced Phase</th>
<th>Contrast-Enhanced Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 Weighted</td>
<td>T1 Weighted</td>
<td>Arterial</td>
</tr>
<tr>
<td>FNH (n = 28)</td>
<td>Hyperintense</td>
<td>18 (57)</td>
</tr>
<tr>
<td>Isointense</td>
<td>12 (43)</td>
<td>8 (29)</td>
</tr>
<tr>
<td>HCA (n = 21)</td>
<td>Hypointense</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Isointense</td>
<td>7 (33)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Hypointense</td>
<td>0 (0)</td>
<td>2 (10)</td>
</tr>
</tbody>
</table>

**Table 4:** Enhancement Pattern of Focal Nodular Hyperplasia (FNH) and Hepatocellular Adenoma (HCA)

<table>
<thead>
<tr>
<th>Pattern</th>
<th>HCA</th>
<th>FNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Plateau</td>
<td>12</td>
<td>25</td>
</tr>
</tbody>
</table>

**Note:** Data are no. (%) of lesions.

---

**Table 3**

**Table 4**

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Data are no. of lesions. Enhancement of the lesion can be expressed as a peak pattern with enhancement in the arterial phase of scanning, followed by loss of contrast during later phases. A plateau pattern is defined as arterial enhancement with lingering of contrast during later phases. This pattern was significantly different between both groups as FNH showed most likely a plateau pattern (p = 0.009).
However, not all features listed as typical for FNH or HCA were significant in our series. We mostly found lobulated FNH; however, no significant difference was found compared with HCA, in which 50% of the lesions also showed a lobulated shape. Peripheral vessels were found both in HCA and FNH. This feature is considered diagnostic for HCA on CT [12]. Hence, shape and peripheral vessels may not be used as sole criteria on which differentiation between HCA and FNH is based. Lesion-to-liver intensity during dynamic phases of MRI could further help in differentiating FNH from HCA. Three patients were excluded from these analyses after they were treated for bleeding from the lesion with embolization of one or multiple vessels before MRI. After this procedure, the normal anatomy of the lesion is structurally altered. Therefore, these cases cannot be compared with the lesions in the overall patient group.

Our series showed significant hyperintensity of HCA during unenhanced T1-weighted series compared with FNH. High-signal foci on T1-weighted images may be due to bleeding or glycogen content in lesions [24], but we did not include these foci in the evaluation of lesion signal intensity. Steatosis of the liver may also explain a relatively high signal intensity of the lesions on the T1-weighted fat-suppressed series. Steatosis was more often present in HCA compared with FNH, but this did not explain all the differences in signal intensity. Furthermore, histomorphology showed no significant difference for HCA because none of the FNHs showed hypointense signal on this phase. This might be the result of the disappearance of portal tracts and the increase of arterial feeding vessels, causing rapid loss of contrast agent after the arterial phase. However, this washout sign is highly suggestive for hepatocellular carcinoma (HCC) [25] and, therefore, cannot be used as a diagnostic criterion if any suspicion for malignancy exists. Overall, when intensity of the lesion to liver is evaluated, the unenhanced T1-weighted phase and signs of washout might help differentiate FNH from HCA. Regarding lesion enhancement patterns, we found FNH to have a plateau pattern. This is in contrast to the enhancement pattern seen in HCA, which loses contrast agent significantly faster, creating a peak pattern. These different lesion enhancement patterns may help differentiate FNH from HCA.

We found isointense-to-hyperintense signal intensity of the lesion in the hepatobiliary phase in all but one FNH and in one HCA, compared with surrounding liver parenchyma. In FNH, isointense-to-hyperintense signal intensity of the lesion on the hepatobiliary phase is seen in 83–90% of cases [17]. Other studies suggested this to be rare in HCA [18, 26]. In our single case of HCA, the signal intensity of the lesion was regarded as slightly hyperintense along the border of the HCA lesion. The lesion was difficult to compare with normal liver on axial scans because of motion artifacts. Histomorphology of the lesion was consistent with HCA and showed telangiectatic changes, ductular dilation, and inflammation. Immunohistochemically, this case was an inflammatory HCA with positive staining for C-reactive protein and serum amyloid A. The high signal intensity on the hepatobiliary series may be explained by sufficient functioning hepatocytes and ductular proliferation, which is seen in telangiectatic HCA, formerly described as telangiectatic FNH [27]. The lesion shranked from more than 7 cm to 3 cm in less than a year after discontinuation of oral contraceptive use. The ringlike high signal intensity possibly could be explained by regeneration. On standard MRI, this lesion showed signs of bleeding and was scored as HCA. Furthermore, one FNH showed hypointense signal on the hepatobiliary series compared with the surrounding liver. No typical characteristics of FNH or HCA were present at MRI. Histomorphology was consistent with FNH with the presence of a ductular reaction, inflammatory infiltrates, thick-walled vessels, and fibrotic bands. Immunohistochemistry showed no overexpression of serum amyloid A and C-reactive protein. However, the glutamine synthetase staining was negative. Glutamine synthetase staining has been reported to be negative in FNH-like nodules in a cirrhotic liver [28]. This does not apply to the patient discussed in here but should be considered when morphology and immunohistochemical staining results do not concur.

Uptake of hepatobiliary contrast agent has also been described in HCC [26, 29]. In welldifferentiated HCCs, the function of hepatocytes is preserved, and, thus, uptake of contrast agent is possible [29]. This implies that no diagnosis can be made solely on the basis of the hepatobiliary phase of the MRI in patients with a liver tumor in general. If a patient presents with a positive history of malignancy or with a lesion with washout on the portal phase, the diagnosis should be malignancy until proven otherwise [25].

The histologic standard of reference was obtained in all patients. Thus, patients presenting with a possible central scar also underwent a liver biopsy. This was done to standardize the design and to avoid misdiagnosing cases mimicking a central scar. This study has a selection bias, even though patients were included consecutively. Of all the lesions of included patients, 54% were diagnosed as FNH and 46% as HCA, whereas in the general population, the estimated prevalence of FNH is 5–10 times higher than that of HCA [30, 31]. Referral of patients with HCA may have been more likely because patients presented with symptoms (e.g., after bleeding when intervention was needed) or because patients presented with larger lesions for which resection was indicated. The latter is reflected in our patient group, because 64% of all lesions in this study and 83% of HCAs were larger than 5 cm. Patients with typical FNH may have been less likely to be referred, because there are no surgical consequences to this diagnosis. The current bias is therefore toward cases with a more problematic diagnosis. In conclusion, this study shows high accuracy of gadoxetate disodium–enhanced MRI when the standard series are combined with the hepatobiliary phase for differentiation of FNH and HCA in lesions larger than 2 cm.

The results of this study advocate the use of the gadoxetate disodium–enhanced MRI for accurate differentiation of FNH and HCA.

**Conclusions**
THE USE OF $^{18}$F-fluoromethylcholine PET/CT IN DIFFERENTIATING FOCAL NODULAR HYPERPLASIA FROM HEPATOCELLULAR ADENOMA:

A PROSPECTIVE STUDY OF DIAGNOSTIC ACCURACY

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(2011) 38:436-440
OBJECTIVE

Diagnosis of focal nodular hyperplasia (FNH) and hepatocellular adenoma (HCA) using conventional imaging techniques can be difficult; however, it is important to differentiate between them as these benign liver tumors require different therapeutic strategies. The aim of our study was to prospectively evaluate the use of PET/computed tomography (CT) with $^{18}$F-fluoromethylcholine ($^{18}$F-FCH) as a novel diagnostic approach in the differentiation between HCA and FNH.

SUBJECTS AND METHODS

Fifty-six consecutive patients with a suspicion of one or multiple HCAs or FNHs larger than 2 cm were prospectively included after written informed consent was obtained from them. All the patients underwent a PET/CT with $^{18}$F-FCH. Histopathology of the lesions was the standard of reference. The ratio of the standardized uptake value (SUV) of the lesions compared with normal liver uptake within the same patient was calculated. Statistical tests were evaluated at the 95% confidence interval.

RESULTS

Forty-nine patients with 60 lesions and histopathological diagnosis of FNH or HCA completed the study and were analyzed. The mean SUV ratio for FNH was 1.67±0.31 (mean±SD, n=28), resulting in a positive likelihood ratio of 32.3 for PET-positive FNH. The mean SUV ratio for HCA was 0.82±0.17 (n=32), with a likelihood ratio of 0 for PET-negative HCA. Receiver operating characteristic curve analysis revealed an optimal SUV ratio cutoff value of 1.13, which reached 100% sensitivity and 97% specificity in differentiating FNH from HCA.

CONCLUSION

This prospective study shows that PET/CT with $^{18}$F-FCH can accurately differentiate FNH from HCA and may become a valuable diagnostic tool when conventional imaging techniques fail to do so.

INTRODUCTION

Hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH) are benign focal hepatic lesions. It is generally accepted that FNH can be treated conservatively because of its benign nature and minimal risk of complications [1–3]. HCAs larger than 5 cm, unlike FNH, carries the risk for malignant transformation in up to 4% of lesions [4,5]. In addition, spontaneous rupture and bleeding have been reported in about 30% of patients during long-term follow-up [4,6–10]. For these reasons, resection of HCAs larger than 5 cm is advised, emphasizing the importance of reliable differentiation between HCA and FNH. When using radiologic imaging modalities, MRI with hepatobiliary contrast is regarded to be the most sensitive in differentiating FNH from HCA [11]. When radiological evaluation remains inconclusive, an ultrasound-guided or computed tomography (CT)-guided liver biopsy may be required.

Therefore, there is a place for additional noninvasive diagnostic imaging techniques. With the use of PET, the uptake and metabolism of a specific compound labeled with a radioactive tracer can be assessed within an organ or tumor. $^{18}$F-Fluoromethylcholine ($^{18}$F-FCH) is one of those tracers. Through choline transporter(s) [12] or by facilitated diffusion, choline is transported into the cell. Three major metabolic pathways for choline are known (Fig. 1). The first is the cytidine diphosphocholine (CDP) or Kennedy pathway, in which choline is phosphorylated to phosphocholine, which is catalyzed by choline kinase. Phosphocholine is in part converted to CDPcholine and further altered to phosphatidylcholine, a major constituent of the cell membrane. A second pathway for choline is the oxidation to betaine, an organic osmolyte. Betaine can maintain intracellular volume homeostasis and can donate its methyl group for the formation of S-adenosylmethionine. Betaine also has a significant role in clearing homocysteine from the body [13]. Homocysteine can be incorporated into phosphatidylcholine through the methylation pathway. Third, choline can be converted to the neurotransmitter acetylcholine in neural cells. A study on pharmacokinetics and radiation dosimetry of fluoro-labeled choline by DeGrado et al. [14] resulted in the following conclusions and recommendations: 10 min after injection with $^{18}$F-FCH, a steady distribution of the tracer is found in the liver. Further, no substantial clearance of the tracer from the liver is seen besides the physical decay of $^{18}$F-FCH, which has a half-life of 110 min. Finally, the kidney is a dose-critical organ and a maximum $^{18}$F-FCH dose of 4.07 MBq/kg is advised for human research. Preliminary reports from France [15] and from our group suggested that $^{18}$F-FCH PET/CT might become a promising diagnostic tool in differentiating FNH from HCA with high sensitivity and specificity [16]. Herein, we present the final results of our completed prospective study.
including those from the pilot study conducted previously on 21 patients. The aim of the study was to assess the diagnostic accuracy of \(^{18}\text{F-FCH PET/CT}\) for the differentiation of HCA from FNH in a large prospective patient series.

This study is a prospective, single-center study for the evaluation of the diagnostic accuracy of \(^{18}\text{F-FCH PET/CT}\) in the differentiation of HCA from FNH. No financial support was granted for this study. The local medical ethics committee approved the study and written informed consent was obtained from all patients before inclusion in the study. Patients were referred to our center with suspicion of FNH or HCA larger than 2 cm based on ultrasound, CT, and/or MRI after they had presented elsewhere with symptoms, or they were incidentally identified. Patients aged 18 years or older, with no history of malignancy or chronic liver disease, and with normal serum a-fetoprotein levels were included. Patients with known allergy to fluoro-labeled tracers or with impaired renal function (serum creatinine > 140 mmol/l), as 50% of the \(^{18}\text{F-FCH}\) tracer is cleared by the kidneys, were excluded. A total of 56 patients were included in the study and they underwent \(^{18}\text{F-FCH PET/CT}\) between May 2008 and April 2011 (Fig. 2). Twenty-one patients who had been studied previously and whose results have been published as a
preliminary report, were included in the present study [16]. The sample size was calculated on the basis of the initial published results of Bumsel and colleagues and first experience with the SUV ratio. Assuming an HCA SUV ratio of 1.0 (SD 0.3) and an FNH SUV ratio of 1.3 (SD 0.3), including 25 patients per group would yield sufficient power (90%, α = 5%) to validate the hypothesis. Taken together, the results of 49 patients (mean age 41 years; range 20–69 years) with 60 lesions were included in the analysis.

18F-FCH PET/CT

18F-FCH synthesis 18F-FCH was synthesized as previously described by DeGrado et al. [17]. This resulted in 18F-FCH with a radiochemical purity of 98% or more. Decay-corrected radiochemical yield was 20–30%. 18F-FCH PET/CT was performed using a Philips Gemini TF-16 PET/CT scanner (Philips Medical Systems, Eindhoven, the Netherlands) with a spatial resolution of 4.8 mm near the center of the field of view in transverse and axial directions. A CT scan in the supine position was acquired from the midtorax to the midabdomen, encompassing the entire liver. The 16-channel helical CT scanning parameters were as follows: 120 kVp, 50 mA/slice, rotation time 0.75 s, and slice thickness/interval 5 mm. No intravenous contrast was used. Fifteen minutes after intravenous injection of 150 MBq of 18F-FCH, emission scans were acquired from the midtorax to the midabdomen, encompassing the entire liver over three to four bed positions at 3 min per position. Image reconstruction used a list-mode version of a maximum likelihood expectation maximization algorithm with a time-of-flight kernel applied in both the forward and back-projection operations. CT data were used for attenuation correction.

18F-FCH PET/CT EVALUATION

PET images were analyzed by a nuclear radiologist and low-dose CT images by a radiologist experienced in abdominal radiology. Both readers were blinded to patient history and previous imaging results. 18F-FCH PET was performed and evaluated before histological analysis was carried out. Images were evaluated on a workstation (Hermes Medical Solutions, Stockholm, Sweden). As 18F-FCH uptake seems dependent on perfusion, variation in physiologic liver uptake was expected. Despite that, patients were asked to fast for 6 h before scanning. Compliance is a known bias, and therefore normalization of lesion uptake to normal liver uptake was performed. The maximum standardized uptake value (SUVmax) of the lesion(s) and the mean SUV of the surrounding nonaffected liver were determined. The SUV ratio was calculated by dividing the maximum SUV of the lesion (SUVmax lesion) by the mean SUV of the surrounding liver tissue (SUVmean liver): SUVratio = SUVmax lesion / SUVmean liver.

STANDARD OF REFERENCE

The final diagnosis of HCA or FNH was based on histopathological examination, and no treatment decisions were made on the basis of the results of 18F-FCH PET. The histological specimen was obtained by liver biopsy or by surgery and the evaluating pathologist was blinded to previous pathology reports, imaging reports, and patient history. Some patients were scheduled for surgery regardless of their histological diagnosis because of severe discomfort or because of the explicit wish of the patient. If this was not the case, patients underwent a biopsy on which diagnosis was based. Lesions larger than 5 cm for which biopsy revealed an HCA were subsequently resected. Therefore, some patients underwent both a biopsy and resection of the lesion. Standard liver stains for histomorphological diagnosis included hematoxylin and eosin, collagen, and cytokeratin-7. Morphological characteristics of HCA included proliferation of hepatocytes without cytonuclear atypia, with a well developed reticulin framework, and without the presence of stellate fibrous scarring. HCA was subclassified on the basis of morphological characteristics and additional immunohistochemical staining of C-reactive protein (CRP), serum amyloid A (SAA), glutamine synthetase (GS), and liver–fatty acid-binding protein (LFABP) [18]. Positive CRP and/or SAA immunostaining was regarded as diagnostic for inflammatory HCA. Negative LFABP staining compared with normal surrounding liver parenchyma was regarded as diagnostic for steatotic HCA due to an HNF-1α mutation. Diffuse GS staining was regarded as diagnostic for HCA due to a β-catenin mutation. Diagnosis of FNH was based on morphological characteristics, including the presence of stellate fibrous scarring, dystrophic arteries, a ductular reaction, and variable infiltrates, as well as the absence of cytological abnormalities. An immunohistochemical GS staining was performed for confirmation of histomorphological diagnosis [19]—FNH having a typical map-like staining pattern. The final diagnosis of HCA or FNH was based on histopathology, and no treatment decisions were made on the basis of 18F-FCH PET results (Figs 3–5).

RESULTS

Statistical analysis was carried out using SPSS (version 18; SPSS Inc., Chicago, Illinois, USA). Continuous data were tested for normal distribution, and equal variances obtained using the Levene test were compared by analysis of variance and expressed as mean±SD. Calculations of sensitivity and specificity were based on the McNemar test. Positive and negative predictive values for 18F-FCH PET/CT were calculated and the confidence interval (CI) of the proportions was based on the Wilson procedure without correction for continuity [20]. The probability of diagnosis of FNH and HCA in our study group was 52% (54/104) and 48% (50/104), respectively. The likelihood ratio (LR) of a positive or negative 18F-FCH PET/CT for FNH and HCA was calculated [21,22], and a receiver operating characteristic curve analysis was carried out. All statistical tests were evaluated at 95% CI.

On the basis of MR and/or CT imaging, a total of 56 patients presented with benign hepatic lesions, most likely HCA or FNH (Fig. 2). MRI and CT were performed and showed two hemangiomas and four benign but inconclusive lesions, besides HCA and FNH lesions. One of the lesions was proven by histopathology to be a cluster of hamartomas. Patients with hamartomas and hemangiomas were excluded from the study. The remaining 53 patients underwent the 18F-FCH PET/CT. No histopathological confirmation of diagnosis was obtained for three patients, and one patient had a hemangioma. These patients were excluded from further analysis. Forty-nine patients (two men and 47 women; mean age 42 years, range 20–69 years) were included in the study between May 2008 and April 2011. Suspicion of one or multiple FNHs and/or HCAs based on CT and/or MRI was raised in the case of 20 (41%) patients who presented with...
The top three figures show transverse MR images of focal nodular hyperplasia from left to right: A: arterial enhancing lesion in segments 2–3 of the left liver (Gd-EOB-DTPA; T1w 5.77/2.54, flip angle 101, matrix 256_156). B: the lesion on the 18F-fluoromethylcholine (18F-FCH) PET image 15 min after injection of 18F-FCH shows clear hyperintensity compared with the surrounding tissues. C: the fusion of both images, which makes both assessment of 18F-FCH metabolism and anatomical localization possible. The lower three figures show transverse MR images of hepatocellular adenoma (from left to right) D: MR image in the arterial phase (Gd-EOB-DTPA; T1w 5.77/2.54, flip angle 101, matrix 256_156), in which a central hepatic lesion shows slight arterial enhancement with corresponding photopenia on (E) the 18F-FCH PET image and (F) the fusion 18F-FCH PET computed tomography image.

Abdominal discomfort or pain and in four (8%) patients who presented with elevated levels of liver enzymes in the serum. In 24 (49%) patients the lesions were incidentally found on imaging performed for other unrelated indications. In one patient the presenting symptoms were not recorded. Patients were followed up for a mean period of 21 months (range 6–36 months). Eighteen patients showed hepatic steatosis on imaging or histopathologic analysis (37%). Histological diagnosis of FNH or HCA was obtained from 60 lesions larger than 2 cm (28 FNHs and 32 HCAs). Results are summarized in Table 1. Diagnosis was made for resection specimens from 37 lesions and for biopsy specimens from 23 lesions. All cases of FNH showed a typical map-like staining pattern for GS, which was absent in HCA. Of
the two male patients, one presented with FNH and one with steatotic HCA. HCA was classified as inflammatory with overexpression of CRP and/or SAA in 56% (18/32); as steatotic with negative staining for LFABP in 16% (5/32); and as the b-cateninmutated subtype with diffuse GS staining in 0%; 28% (9/32) remained unclassified. In two of the unclassified cases the biopsy material was either of insufficient quality or of insufficient quantity to perform additional immunohistochemical assessment.

In two resection specimens, extensive bleeding was found with a gradient of lower LFABP expression within the lesion when compared with the surrounding liver tissue, however, without pronounced steatosis. As the morphology and staining pattern were not typical for steatotic HCA and as additional molecular analysis could not be carried out, these HCAs were scored as unclassified. Four unclassified HCAs were found in the liver of one patient with extensive granulomatous hepatitis. Finally, in one resection specimen, CRP, SAA, and GS were not overexpressed and the LFABP was normally expressed. One patient presented with a lesion suspected to be HCA, but histopathologic evaluation after liver biopsy revealed hemangioma. Four patients with HCA and/or FNH also presented with typical hemangiomas on imaging, and one patient presented with concomitant bile duct hamartomas.

$^{18}$F-FCH PET/CT

Histological diagnosis showed a mean SUV ratio of 1.67±0.31 (n=28) for FNH and 0.83±0.19 (n=32, P<0.001) for HCA. The SUVmax of HCA had a mean of 7.75±2.15 (4.51–11.04) compared with 15.99±4.09 (10.19–27.43) for FNH. The SUVmean of the liver was 9.54±2.09 (5.84–16.49). Results are summarized in Table 1 and Supplementary Table 2. As predicted, the SUV ratio was more sensitive than the SUVmax of the lesion, and receiver operating characteristic curve analysis suggested that an SUV ratio cutoff value of 1.13 predicted patients with FNH as against those with HCA with 100% sensitivity (95% CI 88–100%) and 97% specificity (95% CI 84–99%). The LR of FNH was 32.3 when $^{18}$F-FCH PET/CT was evaluated as positive, with a 98% post-test probability for FNH. The LR of HCA was greater than 100 when $^{18}$F-FCH PET/CT was evaluated as negative, with a 99.9% post-test probability for HCA.

Patients with liver steatosis based on MRI or histopathological diagnosis (n=18) revealed an SUVmax of the liver of 10.16±1.69 (7.65–13.95) and those without liver steatosis (n=31) revealed an SUVmax of the liver of 9.18±2.24 (5.84–16.49). There was no significant difference in the SUVmax of the liver between patients with and those without liver steatosis (P=0.644). The inflammatory subtype showed a mean SUV ratio of 0.83±0.11 (n=18), the steatotic subtype showed a mean SUV ratio of 0.95±0.11 (n=5), and the unclassified group of HCA showed a mean SUV ratio of 0.77±0.16 (n=9). In one patient with a histological diagnosis of unclassified HCA, the lesion showed uptake of $^{18}$F-FCH with an SUV ratio of 1.30. Finally, evaluation of additional lesions showed the following results. Five patients presented with hemangiomas; 5/5 hemangiomas were larger than 1 cm and were evaluated [mean SUVmax 5.57 (2.9–5.6–8.2); mean SUV ratio 0.49 (0.33–0.50–0.69)]. One patient presented with an FNH and multiple small hamartomas, which were histopathologically confirmed. The largest lesion showed an SUVmax of 5.8, SUVmean of the liver of 9.9, and an SUV ratio of 0.59. None of the patients experienced acute adverse events from $^{18}$F-FCH PET/CT due to the administrated $^{18}$F-FCH tracer.
Our study shows that 18F-FCH PET/CT accurately differentiates FNH from HCA. On using an SUV ratio cutoff value greater than 1.13, high sensitivity and specificity were observed. Therefore, 18F-FCH PET/CT could be used as a valuable diagnostic imaging tool. This could very well be preferred over an invasive liver biopsy, which is associated with complications (bleeding) and is subject to sampling errors. The outcome of our study confirms our preliminary results reported previously [16], as well as preliminary results reported by others [15]. The study by Talbot et al. [23] focuses on the comparison between the PET tracers 18F-FCH and 18F-FDG in detecting liver lesions, particularly hepatocellular carcinomas (HCCs). The authors report 11 hepatic lesions, including eight FNHs (7/8 positive on 18F-FCH PET/CT) and eight HCAs (1/8 positive on 18F-FCH PET/CT), and, although this is a small sample size, it shows a trend similar to that seen in our study.

When using imaging modalities, MRI with hepatobiliary contrast has proven to be the most sensitive in differentiating FNH from HCA [24]. The sensitivity of MRI in differentiating HCA from FNH is 94%. In the remaining cases, in which diagnosis is inconclusive but clinically relevant for treatment decisions, 18F-FCH PET/CT provides a noninvasive alternative modality with high sensitivity. Subclassification of HCA is important because the β-catenin subgroup is thought to have a higher potential for malignant transformation compared with the other subtypes [25]. Diagnosis in this subgroup by means of noninvasive 18F-FCH PET/CT could provide a clear clinical benefit for these patients. This issue becomes even more relevant when 18F-FCH PET/CT is able to depict malignant transformation of HCA during follow-up. Well-differentiated HCCs show uptake of 18F-FCH and might therefore be differentiated from HCA [26]. However, no β-catenin-mutated HCAs were found in our patient series. It is noteworthy that in our study the HCA subtypes showed a trend in the uptake of 18F-FCH, although it was not significant. The steatotic subtype showed the highest mean SUV ratio of 0.95 compared with 0.81 in inflammatory HCA and 0.77 in unclassified HCA. Therefore, we call for a prospective study including all HCA subtypes to determine the usefulness of 18F-FCH PET/CT in subtyping HCA and its possible usefulness in the follow-up of high-risk HCAs.

In the HCA series presented in this study, a relatively high percentage of unclassified HCAs was found (55%), which is in line with the results of a previous Dutch study, which had 51% unclassified HCAs [27]. In two cases this was because of insufficient biopsy material hindering complete classification. In two resection specimens, extensive bleeding was found, interfering with immunohistochemical analyses. In the other unclassified HCA lesions, CRP, SAA, GS, and LFABP staining results were inconclusive.

The mechanism of enhanced 18F-FCH uptake in FNH is unclear. Hypothetically, this could be caused by an increased expression of choline transporters [12]. Further, the gradient of choline over the cell membrane could be altered, facilitating choline transport through the organic cation transporter OCT1. As mentioned above, three major pathways are known for choline metabolism (Fig. 1). First, the CDP pathway, in which phosphorylation of choline can be upregulated. Malignant tumor cells are known to have enhanced mitotic activity and cell duplication rates and therefore have an increased need for choline as a substrate for cell membranes [28]. This has been described in well-differentiated HCCs, and these lesions are known to show enhanced uptake of 18F-FCH [26, 29]. FNH is a benign liver lesion potentially caused by a vasculopathy and proliferates slowly, if at all. Thus, enhanced uptake of 18F-FCH in FNH can barely be explained by mechanisms involved in tracer accumulation in HCCs. Within this CDP pathway, a possible explanation is the metabolism of very-low-density-lipoproteins (VLDLs). Phosphatidylcholine is an important component of VLDL particles. Within the liver, fat and cholesterol are wrapped in these VLDL particles to make their transport through blood possible. These hypotheses will need further research to determine their possible role in the enhancement of 18F-FCH uptake in hepatic tumors.

In one patient with HCA we saw uptake of 18F-FCH. Histological diagnosis was made on the basis of a biopsy specimen in which no signs of malignancy were found. This HCA remained unclassified, as all immunohistochemical stainings were without abnormal staining patterns. A possible explanation for the uptake of 18F-FCH could be possible focal malignant transformation within the HCA lesion. As mentioned above, well-differentiated HCCs are 18F-FCH PET/CT positive. Focal sites of malignant transformation could easily be missed by liver biopsy because of sampling of a different area of the lesion but might still cause the 18F-FCH PET/CT-positive results. However, the patient was in good clinical condition after 12 months of follow-up without any signs of malignancy.

The results of this study can be interpreted only in the light of its strict inclusion and exclusion criteria. Only if a malignancy is unlikely and the differential diagnosis is mainly FNH or HCA are the results of this study applicable to the patient. As discussed above, HCC could also show uptake of 18F-FCH. Therefore, the results of this study cannot be extrapolated to a general patient with a focal liver lesion. Further, although all consecutive patients were included, some degree of selection bias did occur. Of the patients included, 52% had FNH and 48% had HCA, whereas in the general population the estimated prevalence of FNH is 10 times higher than that of HCA [26]. Referral of patients with HCA may have been more likely for the following reasons: because patients presented with symptoms, for example, after bleeding when intervention was needed, or because patients presented with larger lesions for which resection was indicated. Patients with typical FNH may have been less likely referred, because there are no surgical consequences to this diagnosis. The current bias is therefore toward cases with a more problematic diagnosis.
This prospective study shows that 18F-FCH PET/CT can accurately differentiate FNH from HCA. It is an additional diagnostic tool to confirm uncertain diagnosis based on conventional imaging studies.

REFERENCES

25. Bioulac-Sage P, Laumonier H, Couchy G, Le BB, Sa CA, Rullier A, et al. Hepatocellular adenoma imaging studies. This prospective study shows that 18F-FCH PET/CT can accurately differentiate FNH from HCA. It is an additional diagnostic tool to confirm uncertain diagnosis based on conventional imaging studies.

CONCLUSIONS
Outcomes of liver resection in hepatocellular adenoma and focal nodular hyperplasia

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OBJECTIVE

The clinical management of hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH) is still subject to controversy, especially with respect to patient selection for surgery. The aim of this prospective cohort study was to assess the outcomes of surgical intervention.

SUBJECTS AND METHODS

Between January 2008 and September 2012, patients diagnosed with FNH or HCA based on magnetic resonance imaging or computed tomography were enrolled in this prospective study. Resection was undertaken in patients with HCA of >5 cm or symptomatic lesions. Lesion characteristics, extent of liver resection (minor: fewer than three segments; major: three or more segments), morbidity (by Dindo–Clavien class), mortality, postoperative length of stay and symptoms [McGill Pain Questionnaire, including a visual analogue scale (VAS)] were evaluated.

RESULTS

A total of 110 patients (106 female; median age: 39 years) were included; 51 patients had HCA and 59 had FNH. Of the 110 patients, 49 underwent resection (33 HCA patients; 16 FNH patients). Laparoscopic minor resection was performed in five HCA and five FNH patients; open minor resection was performed in 19 HCA and seven FNH patients, and open major resection was performed in nine HCA and four FNH patients. Severe postoperative complications were observed in four patients (Grade III, n = 3; Grade IV, n = 1). Median baseline scores on the VAS were 6 in FNH patients and 7 in HCA patients; the median VAS score after resection was 0 (P = 0.008).

CONCLUSION

If patients with HCA and FNH require surgery, limited resection can be carried out with low morbidity and without mortality. Patients with preoperative symptoms show a high rate of postoperative symptom relief.

INTRODUCTION

Whether liver surgery is indicated for benign liver lesions remains controversial [1] particularly in hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH). Both tumours are typically seen in middle-aged women and are often incidental findings on abdominal imaging studies [2]. Because of the risk for bleeding and malignant transformation, it is generally accepted that HCAs measuring >5 cm in size should be resected [3–6]. These risks do not apply in FNH and surgery is therefore not indicated for FNH [7, 8]. However, patients may present with severe abdominal complaints in the presence of a relatively small lesion or a lesion typical of FNH on imaging, without other underlying causes for discomfort. The issue of whether these complaints are correlated with the lesion and outweigh the possible risks of intervention in such patients creates a dilemma.

The diagnostic workup of HCA and FNH is based mainly on cross-sectional imaging studies, of which magnetic resonance imaging (MRI) and computed tomography (CT) are commonly used to characterize lesions. The most sensitive method of differentiating HCA and FNH is MRI with hepatobiliary contrast (Primovist® or MultiHance®) [9–11]. If imaging modalities are inconclusive, a liver biopsy may be necessary to achieve a final diagnosis [12]. When a patient is considered for surgery, he or she should be well informed and should ideally be included in a shared decision-making process. Subjective symptoms and impact on daily life are just as important as the statistics of surgical risks. Given these dilemmas in clinical decision making, the present study was conducted to assess the outcomes of surgical intervention in terms of complications and the relief of symptoms in patients presenting with lesions compatible with HCA or FNH.

METHODS

Between January 2008 and September 2011, all consecutive patients with suspected FNH or HCA of >2 cm based on imaging studies were enrolled in this prospective study (follow-up ended in September 2012). The local medical ethics committee approved the study protocol and written informed consent was obtained from all included patients. Exclusion criteria were suspected (metastatic) malignant disease and the presence of risk factors for malignant liver lesions, including chronic hepatitis, cirrhosis, elevated a-fetoprotein (a-FP) or carcinoembryonic antigen (CEA) in blood serum, and pregnancy.
Patients underwent MRI of the liver with Gd-EOB-DTPA (gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid; Primovist®) using a 1.5-T MRI scanner (Avanto; Siemens Healthcare AG, Munich, Germany). The dynamic contrast-enhanced T1-weighted volumetric interpolated breath-hold examination (VIBE) sequences were made at 30 s (arterial), 60 s (venous), 90 s and 180 s (late) after i.v. bolus injection of 0.025 mmol/kg gadoxetate disodium. Axial and coronal hepatobiliary phase images were made at 20 min after injection using single breath-hold sequences. The diagnosis of HCA was based on arterial enhancement, with possible washout during the portal phase, the presence of bleeding, fat or glycogen, and the absence of a central scar. The diagnosis of FNH was based on the presence of a central scar, arterial enhancement and the absence of signs of washout during the portal phase of imaging. Finally, the lesions were evaluated for signal intensity compared with surrounding liver tissue on the T1-weighted hepatobiliary series at 20 min after injection. An isointense or hyperintense signal status of the lesion was regarded as diagnostic for FNH, and hypointensity was considered diagnostic for HCA. Any MRI scans of lesions without these characteristics were regarded as inconclusive. The largest lesion in each patient was evaluated. Until the MRI with Primovist® was proven sensitive for differentiating HCA from FNH [11] a core biopsy of the lesion and normal surrounding liver parenchyma was standard in this study (using a 16-gauge needle, two lesional biopsies and one or two normal liver tissue samples). The morphological characteristics of HCA include hepatocellular proliferation without cytonuclear atypia, with solitary arteries and the absence of portal tracts. A well-developed reticulin framework is seen, without pseudoglandular growth patterns. In addition to standard liver stainings, including haematoxylin and eosin, collagen and CK7, additional immunohistochemical staining was performed to classify molecular subtypes of HCA [13]. Morphological characteristics of FNH include fibrotic strands, no nuclear atypia, and typical map-like glutamine synthetase (GS) expression on immunohistochemical staining. Halfway through 2011, the policy of standard biopsy was changed to one of biopsy only in the event of inconclusive MRI findings in lesions of >5 cm with or without symptoms.

ASSessment of Symptoms
Symptoms at the time of presentation (baseline) were assessed using a questionnaire; this was re-administered at 6 months from baseline or the intervention (second evaluation). The questionnaire was based on the validated McGill Pain Questionnaire [14] and its Dutch translation [15] and included a visual analogue scale (VAS) with which to assess pain and discomfort, the number of words count (NWC; S, sensory; A, affective; E, evaluation; NWC total), and a pain rating index (PRI; S, sensory; A, affective; E, evaluation; PRI total).

TREATMENT
Selective transarterial embolization (TAE) represented the treatment of choice in patients presenting with haemodynamic instability caused by tumoral bleeding. Surgical treatment of HCA was undertaken if the lesion was >5 cm. Smaller lesions were only resected if the patient presented with persisting complaints which could not be explained by other underlying causes including gallbladder, gastric, bowel, kidney or gynaecological conditions. Depending on the patient’s history and the physical examination and imaging findings already available, patients underwent additional endoscopy and/or colonoscopy, and abdominal imaging if the standard workup for the liver did not cover other plausible causes of discomfort. Focal nodular hyperplasia was only resected if symptoms were severe (VAS scores of ≥7 for >6 months, with the patient describing the complaint as ‘unbearable’ and ‘restrictive’ in daily life) and other possible causes of discomfort had been investigated and excluded. Liver resections were classified as major, defined as the resection of three or more Couinaud’s segments, or minor; defined as the resection of fewer than three liver segments, including enucleation and (sub) segmental resections. Surgery was performed using standard techniques. All major resections were performed in an open procedure, whereas minor resections were performed in open surgery or laparoscopically depending on the tumor’s location. Tumour characteristics, type of liver resection, postoperative morbidity (Dindo–Clavien class [16]) and mortality were recorded.

Figure 1
Flowchart of the study. HCC, hepatocellular carcinoma; TAE, transarterial embolization; HCA, hepatocellular adenoma; FNH, focal nodular hyperplasia.
A total of 120 patients with suspected HCA or FNH were initially enrolled. Nine patients (8%) were given other diagnoses after an initial diagnostic workup with MRI (hemangioma, n = 4, 3%; hepatocellular carcinoma, n = 2, 2%; hamartoma, n = 2, 2%; angiomylipoma, n = 1, 1%). One patient with HCA (1%) withdrew during the diagnostic workup (Fig. 1). The remaining 110 patients were included in the study (Table 1). Diagnosis was based on histopathological examination in 44 (66%) of the 66 patients with HCA (34/44 resection specimens; 10/44 biopsies) and 39 (66%) of the 59 patients with FNH (16/39 resection specimens; 24/39 biopsies). Because of sampling errors, biopsy materials of four (8%) HCA and four (7%) FNH lesions were not sufficient for diagnosis and diagnosis was therefore based on MRI findings. The subclassification of HCA was undertaken in 10 biopsy and 34 resection specimens. Six samples appeared insufficient for additional immunohistochemical staining. Results in the remaining 38 lesion samples showed inflammatory HCA in 20 lesions, steatotic HCA in eight lesions, and unclassified HCA in 10 lesions. No lesions were identified as being of the β-catenin subtype. In three (6%) patients with HCA and 14 (24%) with FNH, no histopathology was obtained and diagnosis was based on MRI findings alone.

### Imaging Characteristics

A total of 105 patients underwent MRI of the liver; this showed HCA in 45 (43%) patients (one of these 45 patients was misdiagnosed; histopathology revealed FNH) and FNH in 60 (57%) patients. Two lesions showed discrepancies between the hepatobiliary phase and dynamic series; the diagnosis of HCA was inconclusive and corroborated by histopathology in these patients. In one patient, MRI was inconclusive as a result of motion artefacts and the diagnosis of HCA was based on histopathology. No MRI was performed in four patients; two of these patients were claustrophobic and were diagnosed according to histopathology, and two underwent CT imaging. Hepatic steatosis was seen in 29 (57%) of the 51 patients with HCA and in 12 (20%) of the 59 patients with FNH (P = 0.024).

### Treatment

Results of treatment are summarized in Table 2. Conservative treatment was delivered in 61 (55%) patients, including 18 (35%) patients with HCA and 43 (73%) with FNH (P < 0.001). Eight (16%) patients with HCA presented at the emergency room with acute pain caused by bleeding of the lesion; these eight patients were admitted, stabilized and subjected to selective TAE. One of these eight patients underwent laparotomy within days of TAE because of abdominal compartment syndrome and four underwent elective resection of the lesion(s). Resection was performed in 33 (65%) patients with HCA and in 16 (27%) patients with FNH. Significantly more resections were performed for HCA than for FNH (P < 0.001). Figure 2 shows preoperative MRI, an intraoperative image and postoperative MRI in a patient with HCA. Figure 3 shows preoperative MRI and intraoperative images in a patient with FNH. Minor laparoscopic resection was performed in five (15%) of the 33 HCA patients and in five (31%) of the 16 FNH patients submitted to resection. Minor open resection was performed in 19 (58%) of the 33 HCA patients and in seven (44%) of the 16 FNH patients. Major resection was performed in nine (27%) of the 33 HCA patients and in four (25%) of the 16 FNH patients. Postoperative length of stay (LoS) differed according to the type of treatment. Lower LoSs were observed in patients with FNH, whereas HCA more often showed multiple lesions. Locations of the lesions throughout the liver were similar across both patient groups.

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### Table 1: Characteristics of patients in the study population (n = 110)

<table>
<thead>
<tr>
<th>Age, years, median (range)</th>
<th>39 (19–72)</th>
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<tbody>
<tr>
<td>Diagnosis</td>
<td>HCA 51 (46%)</td>
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<tr>
<td>Patients, n (%)</td>
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<tr>
<td>Liver function test, n (%)</td>
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<tr>
<td>Normal</td>
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<tr>
<td>Abnormal</td>
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<tr>
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<tr>
<td>a-FP, U/I (normal = &lt;60 U/I)</td>
<td>n = 11, 226 (129–486)</td>
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<tr>
<td>y-GT, U/I (normal = &lt;60 U/I)</td>
<td>n = 15, 101 (62–369)</td>
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<td>Median g-gt was significantly higher in patients with HCA than in those with FNH.</td>
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<td>Median g-gt was significantly higher in patients with HCA than in those with FNH.</td>
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<td>Median g-gt was significantly higher in patients with HCA than in those with FNH.</td>
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**Note:** The table includes only the key characteristics and statistical analysis. For a full understanding, please refer to the full text of the document.
surgery performed. Significant differences in LoS were found between patients undergoing laparoscopic and open surgery for HCA (P = 0.013), laparoscopic and minor open resection for HCA (P = 0.034), laparoscopic and open resection for FNH (P = 0.005), and laparoscopic and minor open resection for FNH (P = 0.005). However, no differences in postoperative LoS were seen between patients undergoing minor open and major open resection for either HCA or FNH (P = 0.740 and P = 0.263, respectively) (Table 2). Laparoscopic procedures took less time than open surgeries (HCA: P = 0.005; FNH: P = 0.005). In HCA patients, open minor resections took less time than open major resections (P < 0.001). Complications after surgery occurred in both groups and affected 11 of the 33 patients with HCA and seven of the 16 patients with FNH (P = 0.344). Grade I and II complications were most common and were seen in 14 of the 18 patients with complications.

SYMPTOMS

In total, 34 of the 49 patients who underwent resection reported abdominal complaints prior to surgery. Symptoms were relieved in 30 of these 34 patients after surgery (Table 3). Symptoms are summarized in Tables 3 and 4. The pain questionnaire was completed by 48 (96%) of the 51 patients with HCA. Pain categories present in at least one third of the patients with HCA and FNH are shown in Table 4. Specific to HCA rather than to FNH was ‘drilling’ (P = 0.043). Specific pain categories reported by the eight patients who submitted to emergency TAE but not by HCA patients who did not undergo emergency TAE included ‘shooting’ (P = 0.044), ‘lacerating’ (P = 0.032), ‘crushing’ (P = 0.034), ‘splitting (P = 0.001) and ‘wrenching’ (P = 0.023) pain. The NWC was higher in the emergency TAE patient group than in the entire HCA patient group (Sensory: P = 0.009; Affective: P = 0.025; Evaluation: P = 0.005; Total: P = 0.011), as was the PRI (Sensory: P = 0.001; Affective: P = 0.016; Evaluation: P = 0.013; Total: P = 0.005). No differences in the NWC and PRI were found between patients with HCA or FNH when corrected for patients who underwent emergency TAE (P = 0.775).

| Table 2 |

<table>
<thead>
<tr>
<th>Hepatocellular adenoma (n = 51)</th>
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<tr>
<td>Conservative treatment, n (%)</td>
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<td>Size, cm, median (range)</td>
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<td>Transarteral embolization, n</td>
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<td>Emergency care (bedding), n (%)</td>
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<td>Preventive care, n (%)</td>
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<th>Resection</th>
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<th>Open major</th>
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<tr>
<td></td>
<td>33 (65%)</td>
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<td>19</td>
<td>9</td>
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<td>1</td>
<td>9</td>
<td>5</td>
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<tr>
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<td>2</td>
<td>9</td>
<td>4</td>
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<tr>
<td>ASA 3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td>Surgical time, min, median (range)</td>
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<td>100* (69–144)</td>
<td>170 (58–231)</td>
<td>226 (200–406)</td>
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<td>Postoperative LoS, days, median (range)</td>
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<td>7 (3–13)</td>
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<tbody>
<tr>
<td>None</td>
</tr>
<tr>
<td>Grade I or II</td>
</tr>
<tr>
<td>Grade III</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Focal nodular hyperplasia (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative treatment, n (%)</td>
</tr>
<tr>
<td>Size, cm, median (range)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resection</th>
<th>Overall</th>
<th>Laparoscopic</th>
<th>Open minor</th>
<th>Open major</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 (27%)</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Size, cm, median (range)</td>
<td>6.2 (3–126)</td>
<td>4 (3–7)</td>
<td>5.8 (4–12)</td>
<td>8.6 (7–13)</td>
<td></td>
</tr>
<tr>
<td>ASA classification, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA 1</td>
<td>9</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>ASA 2</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ASA 3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Surgical time, min, median (range)</td>
<td>144 (82–267)</td>
<td>94* (82–107)</td>
<td>161 (98–231)</td>
<td>202 (100–467)</td>
<td>0.000*</td>
</tr>
<tr>
<td>Postoperative LoS, days, median (range)</td>
<td>6 (2–22)</td>
<td>4* (2–5)</td>
<td>7 (5–9)</td>
<td>7 (6–22)</td>
<td>0.05*</td>
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<table>
<thead>
<tr>
<th>Complications, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
</tr>
<tr>
<td>Grade I or II</td>
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<tr>
<td>Grade III or IV</td>
</tr>
</tbody>
</table>

ASA, American Society of Anesthesiologists physical status classification system; LoS, length of stay.
This prospective study of outcomes of treatment of HCA and FNH shows that resection of the lesion(s) is safe and results in the relief of complaints in the majority of symptomatic patients with HCA or FNH.

No mortality occurred and most postoperative complications were minor according to the Clavien–Dindo classification (Grade I or II). These findings are in accordance with a previous publication from the present authors’ institution, showing that liver resection for benign hepatobiliary lesions was not associated with mortality and resulted in less morbidity than it did in patients undergoing resection for malignancies [18].

Because HCA and FNH are benign tumours, limited resections usually suffice to remove all tumour tissue. Most of these tumours are amenable to parenchyma-sparing techniques. For example, lesions located in segment I allow the isolated resection of segment I, as was performed in three patients in the present series [19].

Of note are the blood transfusions required for minor resections in this series (two patients). Both HCA and FNH are hypervascular tumours and thus, in dissection, many blood vessels that traverse the interface between tumour and surrounding liver parenchyma are encountered. Enucleation of the tumour, therefore, may result in considerable blood loss. In the authors’ experience, the use of the Cavitron® Ultrasonic Surgical Aspirator (CUSA®), in combination with a Pringle manoeuvre, enables the surgeon to follow the plane between the tumour and adjacent parenchyma and to manage the blood vessels selectively. In addition, non-anatomical resections may result in longer dissection times and larger wound surfaces, both of which contribute to greater blood loss during the procedure.

Although both HCA and FNH are benign hepatic lesions, associated findings are quite different, as this study shows. Patients with HCA more often had elevated serum liver function tests (72%), hepatic steatosis (57%) and multiple lesions. Eight of the patients with HCA presented at the emergency room with acute pain caused by the bleeding of the lesion, whereas none of the patients with FNH needed emergency care. Significantly more resections were performed in HCA than in FNH patients. Without intervention, patients with HCA showed symptom relief over time. The differences between the groups may in part be explained by the occurrence of bleeding in HCA: some bleeding in HCA will need emergency intervention, and part of the discomfort caused by bleeding HCA will subside over time as the haematoma is absorbed.

This study showed not only differences between the types of hepatic lesion, but also similarities. Resection of HCA and FNH resulted in the relief of symptoms in both groups. These results are in line with those reported by Perrakis et al., who noted relief in 99% of symptomatic patients with HCA [1]. Patients with lesions in the left lateral segments that give rise to abdominal complaints and additional gastric complaints benefit particularly from surgery, which can

**Table 3**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients, n (%)</th>
<th>VAS score, median (range)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidental finding</td>
<td>20 (39%)</td>
<td>27 (40%)</td>
<td>NA</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>31 (61%)</td>
<td>7 (2–10)</td>
<td>0.005</td>
</tr>
<tr>
<td>Gastric complaints</td>
<td>6 (12%)</td>
<td>12 (5–44)</td>
<td>6 (1–70)</td>
</tr>
<tr>
<td>Left liver</td>
<td>5/22</td>
<td>0.044</td>
<td>1/20/8</td>
</tr>
<tr>
<td>Right liver</td>
<td>1/29</td>
<td>0.004</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Incidental finding</td>
<td>1 (2%)</td>
<td>2/51</td>
<td>0 (0–0)</td>
</tr>
</tbody>
</table>

| Baseline | 0 (0–10) | 0.013 | 0 (0–0) | <0.001 |
| Follow-up | 0 (0–7) | 0 (0–0) | 0 (0–0) |
| Resection | 33 (65%) | 16 (27%) | 0.008 | 6 (0–10) | 0.008 |

**Figure 3**

**Imaging of focal nodular hyperplasia (FNH).** (A) Transverse magnetic resonance imaging (MRI) in the arterial phase with Primovist® shows a large, slightly hypointense lesion (arrow), with a hypodense centre, in the right liver, consistent with a central scar (arrowhead). (B) The central scar is more prominent in the hepatobiliary phase of scanning and the lesion is isointense in comparison with the surrounding liver parenchyma, which is consistent with FNH. (C) At laparotomy, the lesion protrudes from the liver and (D) can be removed with minimal damage to the liver parenchyma.
The first 12 categories are 'sensory' categories. 12 categories mean a maximum score of 12 NWC per patient and every count has three severity gradations: mild, intermediate and severe. The maximum PRI is therefore \(3 \times 12 = 36\) per patient. Categories 13–16 are 'affective' categories, with a maximum NWC of 4 per patient and maximum PRI of \(4 \times 3 = 12\) per patient. The final categories 17–20 are 'evaluation' categories, with a maximum NWC of 4 and maximum PRI of \(4 \times 4 = 16\) per patient. Total NWC and PRI are given for each group of categories, and for all categories combined (sensory, affective and evaluation; median and range per patient). Patients in need of emergency TAE have a different pain pattern compared with HCA patients who are not in need of emergency care, with a higher NWC and PRI in all categories.

Achieve complete symptom relief. Gastric complaints could not be explained by any causes other than the lesion in the left liver. However, in the present study, size was not correlated with symptoms. This probably reflects some degree of selection bias as patients with abdominal complaints will seek medical attention and those without will present only if the lesion is found incidentally. The high rate of resections for FNH is also explained by this selection bias as those with severe complaints will seek medical assistance and will be more persistent in their wish for (even invasive) treatment. Complications in FNH are rare and are cited only in case reports [20]. Assessing the severity of symptoms and whether these originate from the detected liver lesion remains difficult. Abdominal pain or discomfort can have a number of other causes, which should be ruled out before surgery is planned. When feasible, a laparoscopic resection is preferred over an open procedure, especially for lesions in the left or anterior liver segments. It is well documented that the postoperative LoS is shorter after laparoscopic surgery and, particularly in this young and mainly female group of patients, the cosmetic result plays an important role [21]. However, the feasibility of a laparoscopic approach should not influence perceptions of indications for resection.

Few treatment options other than surgical intervention have been proposed. Percutaneous radiofrequency ablation (RFA) has been performed for HCA and FNH with good results and cost efficiency ratios [22, 23]. However, the procedure is limited by the location and size of the tumour. It is possible that residual tumour tissue is less problematic in a benign tumour. In the treatment of lesions of \(< 3\) cm, RFA is a good treatment option and, depending on the location of the lesion, may even be selected as the treatment of choice. Further research should determine the long-term outcomes and limitations of RFA in the ablation of HCA and FNH. At the present authors' institution, TAE is considered the first line treatment modality when a patient presents with massive bleeding and rupture of a hepatic tumour, including HCA [24, 25]. Through the close collaboration of a skilled interventional radiologist and surgeon, laparotomy can be avoided in these emergencies. The technique can also be used as a minimally invasive, preventive intervention that hypothetically decreases the risk for future bleeding; it was applied in this study in an HCA patient who was a Jehovah's Witness. As yet, no data are available on tumour behaviour after TAE, including the risk for malignant transformation of the remaining adenomatous tissue.

Based on the findings of the present study and the available literature, the present authors propose the following approach should be taken in patients with HCA and FNH. Diagnosic workup should include hepatobiliary contrast MRI [11]. In patients diagnosed with FNH, resection is advised only if abdominal complaints are severe and other causes of symptoms have been excluded. All patients with HCA should discontinue oral contraceptives. Until risk analyses during pregnancy have been properly studied, all patients should undergo close follow-

### Table 4

<table>
<thead>
<tr>
<th>Common categories (n = 20% of patients)</th>
<th>Hepatocellular adenoma (n = 48)</th>
<th>Focal nodular hyperplasia (n = 57)</th>
<th>NWC</th>
<th>PRI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Flickering, flashing, shooting</td>
<td>12 (25)</td>
<td>10 (21)</td>
<td>0.754</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAE (n = 8): shooting</td>
<td>4</td>
<td>9</td>
<td>0.044</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Pinching, boring, drilling</td>
<td>23 (51)</td>
<td>22 (42)</td>
<td>0.045</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Sharp, cutting, lacetting</td>
<td>20</td>
<td>34</td>
<td>0.886</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAE (n = 8): lacetting</td>
<td>6 (10)</td>
<td>10</td>
<td>0.032</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Pinching, pressing, crushing</td>
<td>24</td>
<td>38</td>
<td>0.650</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAE (n = 8): crushing</td>
<td>5 (9)</td>
<td>9</td>
<td>0.034</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Tapping, pulling, splitting</td>
<td>10</td>
<td>20</td>
<td>0.096</td>
<td></td>
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</tr>
<tr>
<td>TAE (n = 8): splitting</td>
<td>5</td>
<td>8</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Tight, squeezing, wrenching</td>
<td>19</td>
<td>48</td>
<td>0.791</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAE (n = 8): wrenching</td>
<td>5</td>
<td>11</td>
<td>0.023</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Dull, gnawing, persisting</td>
<td>22</td>
<td>39</td>
<td>0.476</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sensory 1–7, median (range)</td>
<td>3 (0–12)</td>
<td>5 (0–33)</td>
<td>NWC 0.781</td>
<td></td>
<td></td>
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<tr>
<td>TAE (n = 8) total sensory, median (range)</td>
<td>7 (10–9)</td>
<td>15 (8–22)</td>
<td>PRI 0.081</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Ting, arduous, exhausting</td>
<td>26</td>
<td>48</td>
<td>0.897</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Cranky, discontenting, depressing</td>
<td>13</td>
<td>29</td>
<td>0.668</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 Tense, suffocating, sickening</td>
<td>10</td>
<td>32</td>
<td>0.567</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 Fearful, frightening</td>
<td>19</td>
<td>34</td>
<td>0.066</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total affective 13–16, median (range)</td>
<td>1 (0–5)</td>
<td>2 (0–15)</td>
<td>NWC 0.486</td>
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<tr>
<td>TAE (n = 8) total affective, median (range)</td>
<td>4 (1–5)</td>
<td>5 (1–12)</td>
<td>PRI 0.113</td>
<td></td>
<td></td>
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<tr>
<td>18 Light, moderate, bad, severe</td>
<td>21</td>
<td>58</td>
<td>0.675</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 Bearable, troublesome, intense, unbearable</td>
<td>23</td>
<td>59</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 Bothersome, grueling, vicious, killing</td>
<td>22</td>
<td>44</td>
<td>0.796</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total evaluation 18–20, median (range)</td>
<td>1 (0–3)</td>
<td>1 (0–12)</td>
<td>NWC 0.237</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAE (n = 8) total evaluation, median (range)</td>
<td>3 (2–3)</td>
<td>6 (3–10)</td>
<td>PRI 0.260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall, median (range)</td>
<td>5 (2–20)</td>
<td>10 (0–59)</td>
<td>NWC 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAE overall, median (range)</td>
<td>3 (10–18)</td>
<td>22 (16–44)</td>
<td>PRI 0.011</td>
<td></td>
<td></td>
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</tbody>
</table>
up during pregnancy [26]. Hepatocellular adenoma in male patients and of 5 cm in female patients should be resected [5]. Liver adenomatosis is an arbitrary diagnosis when more than nine HCA lesions (whatever their size) are found, but in the present authors’ practice, it is not an indication for liver transplantation. Patients are treated according to the sizes of lesions and the presence of bleeding and symptoms, like any other patient with HCA. In addition, HCA lesions of 5 cm in size, and FNH lesions, if severely symptomatic, can be considered for resection after other possible causes of abdominal complaints have been evaluated. Future studies should determine whether different subtypes of HCA carry different profiles of risk for bleeding, recurrence (however small the risk) and malignant transformation. Subtype classification, however, requires the obtaining of biopsy material of the lesion, which is subject to sampling errors. Improvements in MRI techniques may play a role in the non-invasive assessment of these subtypes and facilitate the more accurate selection of patients who will benefit from surgery.

**Conclusions**

In conclusion, if patients with HCA and FNH require surgery, limited resection can be carried out with low morbidity and without mortality. Patients with preoperative symptoms show a high rate of postoperative symptom relief.


**References**

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ment of spontaneous haemorrhage and rupture of hepatocellular adenomas. A single-centre experience.
Pregnancy and liver adenoma management: PALM study. Gastroenterology 142:82.
Grading and management of bleeding in hepatocellular adenoma.

Analysis in a prospective series of 45 patients.

Chapter 5
OBJECTIVE

Hepatocellular adenoma (HCA) is a benign hepatic lesion with risk of spontaneous bleeding. In a prospective series of patients with HCA, bleeding was assessed in conjunction with a grading system. Outcomes of management were evaluated.

SUBJECTS AND METHODS

Consecutive patients from 2008-2012 diagnosed with HCA were included. Reference standard was histopathology, MR and/or CT imaging. Patient characteristics were noted. Bleeding was scored and graded on imaging: intratumoral (Grade I), intrahepatic (Grade II), and extrahepatic (Grade III). Treatment of bleeding consisted of observation in hemodynamically stable patients and selective transarterial embolization (TAE) in patients requiring blood transfusion. Elective resection was performed in HCA>5cm.

RESULTS

HCA was confirmed in 45 patients with a total of 195 adenomas. Bleeding was found in 29/45 (64%) patients and in 42/195 (22%) adenomas, graded as Grade I: 29/42, Grade II: 9/42, and Grade III: 4/42. Two patients with Grade I bleeding, 2 with Grade II, and 3 with Grade III required TAE. Size of bleeding-area was larger in patients undergoing TAE regardless of grading (P=0.011; cut-off 60mm. Relation to the liver capsule was significant for bleeding (P<0.001): intrahepatic adenomas 10/85, subcapsular 17/89, and exophytic 16/24).

CONCLUSION

We propose a grading system of bleeding HCA in which Grade I and II with bleeding-area larger than 6cm, and all Grade III bleeding are preferably treated with TAE. Additional care, with follow-up or preventive treatment is advised in patients with exophytic adenomas.

INTRODUCTION

Hepatocellular adenoma (HCA) is a benign lesion although not without risk of complications. Besides an estimated risk of 4.3% of malignant transformation in adenomas larger than 5cm [1], spontaneous bleeding and rupture have been reported in more than 30% of adenomas larger than 5cm and may have significant clinical consequences [2-7]. An undefined subset of patients present with symptoms of bleeding, ranging from minor upper abdominal pain to hypovolemic shock, requiring emergency care. Other patients have vague complaints of abdominal discomfort, fatigue, or elevated liver function tests in a routine blood test. Cross-sectional imaging of the liver is the first step in diagnosis of HCA with or without bleeding. Computer Tomography (CT) and Magnetic Resonance (MR) imaging with a liver specific hepatobiliary contrast agent play an important role [8]. Characteristics of contrast enhancement of the adenoma during arterial phase of dynamic imaging, no uptake of contrast on hepatobiliary phase of MR imaging [8], intra-tumoral fat and glycogen [9], and signs of bleeding [10]. Active arterial bleeding in HCA might be evident on contrast enhanced, cross-sectional imaging studies. When control of bleeding is required, selective transarterial embolization (TAE) of the feeding artery is the treatment of choice in medical centers with an interventional radiology department [11]. Oral contraceptive (OC) use has been associated with growth of HCA and possible increased risk of bleeding [12]. Therefore, treatment of HCA first of all consists of discontinuation of OC. This might result in shrinking or stabilization of growth of adenomas [13]. When the HCA does not reduce in size below 5cm, resection is advocated, because of the continued increased risks of bleeding and malignant transformation in this patient group [1]. To improve treatment strategies for patients suffering from bleeding HCA, bleeding needs to be better defined.

With this study we aimed to devise a grading system for bleeding in HCA according to the extent of bleeding relative to the adenoma and surrounding liver parenchyma. Secondly, we aimed to assess outcomes of observation and interventions in patients with bleeding in HCA.
(89)

Chapter 5

Assessment of bleeding on MR and CT imaging

Methods

This study is part of a prospective study including all patients referred with suspicion on HCA or focal nodular hyperplasia (FNH) from January 2008 until May 2012 [8]. All patients with an established diagnosis of HCA were selected (n = 45). All patient data were collected in a designated prospective database. Standard of reference was diagnosis based on either histopathology or imaging (MRI Primovist® [8] or CT imaging). The institutional Medical Ethics Committee approved the study and a written informed consent was obtained from all patients. Case characteristics were noted and symptoms at time of presentation were assessed with a questionnaire. Baseline and post-treatment visual analogue scale (VAS) were used to assess pain and discomfort [14].

Diagnosis of Hepatocellular Adenoma

Diagnosis of HCA was preferably made by MR imaging of the liver using hepatobiliary Gadolinium EOB-DTPA contrast (Primovist®, Bayer, Germany (Eovist® in the United States). Diagnosis of HCA was based on intra-tumoral hemorrhage, fat and/or glycogen, and arterial enhancement of the adenoma with subsequent loss of intensity compared to surrounding liver tissue in the hepatobiliary phase [8]. Multiphase CT imaging of the liver was only rendered diagnostic in the presence of an arterial enhancing adenoma with clear signs of hemorrhage and without suspicion on malignant disease [15]. Histopathological samples were obtained either by resection and/or liver biopsy from tumoral tissue. Systematic biopsy was performed until 2011, as of which time MR imaging with Primovist was proven sensitive for diagnosis of HCA [8]. Morphological characteristics of HCA include: hepatocellular proliferation without cytonuclear atypia in which solitary arteries are seen and portal tracts are lacking, with a well-developed reticulin framework without pseudoglandular or thickened trabecular growth patterns.

Characteristics on MR and CT Imaging

Liver adenomas were evaluated by one abdominal radiologist (SSKSP) with over 10 year experience with liver imaging, according to the following characteristics: number of adenomas (a max of 10–largest adenomas were assessed per patient), segmental location of adenomas, depth of adenomas in relation to the liver capsule: intrahepatic (adenomas more than 1 cm distance to the liver capsule); subcapsular (any part of the adenoma within icm distance of the liver capsule); exophytic (any part of the adenoma bulging beyond the contours of the liver).

Assessment of Bleeding

Signs of bleeding on CT imaging included intra- or peri-adenomal, irregular hypodense areas, without contrast enhancement. Or irregular, non-enhancing hyperdense areas, consistent with a recent bleeding or clot. These signs, in combination with free abdominal fluid were considered compatible with rupture of the bleed into the abdominal cavity. On MR inhomogeneous, non-enhancing areas of hypo- or hyperintensity on T1 w and T2 were regarded as consistent with bleeding. High intensity areas on T1 w sequence was regarded as acute bleeding. Signal loss on gradient sequences was regarded as sign of old bleeding (hemosiderin). If both CT and MR images were available, MR images were considered superior and used for evaluation (exception: when motion artefacts or technical difficulties intervened with the quality of the images). Bleeding was scored as Grade I (intratumoral), Grade II (intrahepatic) or Grade III (extrahepatic: rupture into the peritoneal cavity). If no remnant of tumor tissue was found on imaging bleeding was graded as confined within the liver (intrahepatic; Grade II) or extrahepatic (Grade III). Hemorrhage in histopathologic specimens was not evaluated as histopathology in this prospective patient cohort was designed to be used as HCA diagnostics and samples were taken from vital, non-bleeding, and non-necrotic areas for evaluation. Size of the adenoma and area(s) of bleeding were noted on baseline imaging and if follow-up took place, these factors were re-assessed over time.

In all patients diagnosed with HCA, oral contraceptives were discontinued as initial treatment. Patients with adenomas smaller than 5 cm underwent follow-up. Adenomas larger than 5 cm were considered for resection. If patients presented with signs of acute bleeding, a contrast enhanced CT scan was performed in an emergency setting. In the absence of signs of intra-abdominal rupture (free fluid) and hemodynamic stability, patients were admitted and observed. In case of hemodynamic instability, extensive intrahepatic bleed, rupture of the adenoma into the abdominal cavity, or extravasation on CT imaging, superselective catheterization of the hepatic arterial branches and embolization (TAE) were performed.

Statistical Analysis

Statistical analysis is per patient using SPSS 20 (IBM Corporation, Chica
go, IL). Descriptive statistics were used to assess study population. Mann Whitney test was used to assess continuous data. Pearson’s Chi square, Fisher’s exact, and Spearman correlation tests were used for categorical data analyses. Statistical tests were evaluated at the 5% level of significance.

Results

In all 45 patients (median age 39 years, 1 male) a total of 105 adenomas were evaluated. Final diagnosis of HCA was confirmed by histopathological examination in 42/45 patients (93% resection specimens; 12 histological biopsies) and in 3 adenomas (5 resection specimens; 16 biopsies). In the remaining 3 patients, MR and/or CT imaging were regarded diagnostic for HCA (with a total of 14 adenomas). If multiple adenomas occurred, all adenomas with similar radiological characteristics as the diagnostic adenoma were considered the same diagnosis. Patient characteristics are summarized in Table 1.
Chapter 5

Grading of bleeding

Table 1 — Patient characteristics

| Age | median (range) | 39 (22 - 60) |
| Male / Female | 1 : 44 |
| Oral contraceptive use (OC) | |
| Discontinuation before diagnosis | median months | 13 (69) |
| Discontinuation at time of diagnosis | 31 (29) |

Body Mass Index (BMI)

| Normal (< 25) | 11 (24) |
| Overweight (25 - 30) | 13 (29) |
| Obesity (30 - 40) | 16 (36) |
| Morbidly obese (40 <) | 5 (11) |

Hepatic steatosis

| Mild | 17 (38) |
| Intermediate | 3 |
| Severe | 7 |

Number of adenomas

| Solitary (%) | 14 |
| 2-5 (%) | 16 |
| 6-9 (%) | 6 |
| 10- (%) | 9 |

Table 2 — Bleeding & Imaging characteristics

| Diagnosis | Patients (n = 45) | Adenomas (n = 195) |
| Histopathology | 42 | 73 |
| Biopsy | 16 |
| Resection | 57 |
| Imaging | 3 | 122 |

Size median cm (range)

| 68* (0 - 250) | 24 (10 - 250) |

Location

| Left liver (%) | 58 (30) |
| Right liver (%) | 137 (70) |
| Intrahepatic (%) | 82 |
| Subcapsular (%) | 89 |
| Exophytic (%) | 24 |

Results are summarized in Table 2. All 45 patients underwent MR and/or multiphase CT imaging. Bleeding was seen in 42/195 adenomas (22%), in 29/45 patients (64%) and in 23 out of 31 (74%) patients with multiple lesions, more than 1 bleeding occurred (Table 3). Most bleeding sites were confined to the adenoma and graded accordingly as Grade I (29/42; 69%). In 9 adenomas the bleeding spread intrahepatically (Grade II, 21%), and in 4 adenomas the bleeding had ruptured into the peritoneal cavity (Grade III, 10%). Sixteen of 45 patients (36%) were asymptomatic at presentation and were analyzed for incidental adenomas after finding of elevated liver function tests, or imaging for unrelated causes.

Four patients presented with minor symptoms of abdominal discomfort showing signs of intra-tumoral bleeding in 3 cases (median VAS 1: 0-2); 12 patients had chronic abdominal complaints with 3 cases of intratumoral bleeding, 1 intrahepatic, and 1 extrhepatic bleeding (median VAS 7: 2-7); 14 patients had severe pain of acute onset showing signs of bleeding in 13/14 patients with additional intrahepatic expansion in 2 cases, and extrhepatic breach in 3 cases (median VAS 8: 7-10). Symptoms, bleeding and treatment are summarized in Table 2.

Location of HCA in relation to the liver capsula was ‘intrahepatic’ in 82/195, ‘subcapsular’ in 89/195, and ‘exophytic’ in 24/195 adenomas. Exophytic adenomas showed more bleeding (16/24; 67%) compared to intrahepatic (9/82; 11%) and subcapsular (17/89; 19%) adenomas (P < 0.001). None of the intrahepatic adenomas showed extrhepatic grade III bleeding (n = 82).
Grading of bleeding

Treatment and follow-up

Treatment and follow-up is summarized in Table 2. Emergency care with TAE was indicated in 7 patients: Grade I bleeding in 2 patients with bleeding area 40 and 62 mm, Grade II in 2 patients with bleeding area of 60 and 153, and Grade III bleeding in 3 patients with a median intrahepatic bleeding area of 75 mm (50-160 mm). The size of the bleeding area was significant for the need of TAE regardless of grading score (P = 0.017). Preventive TAE was performed in two patients: a Jehovah witness after an episode of intratumoral bleeding and another patient pre-operatively to reduce risk of bleeding during resection of a giant HCA of 25 cm. Emergency care with laparotomy was indicated for bleeding in two patients; one patient was unstable while no interventional radiologist was available at the hospital of presentation and the other patient required laparotomy for abdominal compartment syndrome after massive bleeding. Elective resection was performed in 29/45 (64%) patients, with 57 adenomas (median size 64 mm; 10-250 mm). Radiological signs of bleeding were seen in 18/29 (62%) patients and 21/57 (37%) adenomas: 16 Grade I, 3 Grade II, and 2 Grade III. One subclinical, new Grade I bleeding was seen in an adenoma during follow-up (after 22 months the adenoma had decreased 42% in size to 26 mm and showed a small area of bleeding of 2 by 7 mm). 36 adenomas with signs of bleeding enrolled in follow-up had a mean decrease in area of bleeding of 38% (median follow-up 15 months). Patients who had discontinued OC use at time of presentation had no more signs of bleeding compared to the group who discontinued OC well before presentation (P = 0.665). Fifty percent of all included women had been pregnant at least once before diagnosis of HCA was made. One of these patients presented with bleeding of HCA during the 17th week of her first pregnancy, classified as extrahepatic (Grade III) on MRI (Figure 2). This patient was successfully treated with TAE. 22 months after first presentation she suffered a Grade I re-bleed for which elective resection was performed.

| Table 2 | Table 3

### Table 2: Treatment

<table>
<thead>
<tr>
<th>Transarterial embolization</th>
<th>VAS Baseline</th>
<th>VAS Post</th>
<th>Lesion size (%)</th>
<th>Bleeding area</th>
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<tr>
<td>Emergency care</td>
<td></td>
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<tr>
<td>Grade I bleeding</td>
<td>2</td>
<td>8 (8-10)</td>
<td>78 (70-85)</td>
<td>51 (40-62)</td>
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<tr>
<td>Grade II bleeding</td>
<td>2</td>
<td>9 (7-10)</td>
<td>35 (10-60)</td>
<td>107 (60-153)</td>
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<tr>
<td>Grade III bleeding</td>
<td>3</td>
<td>6 (5-7 )</td>
<td>55 (10-123)</td>
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<tr>
<td>Preventive care</td>
<td>2</td>
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<td>55 (43-250)</td>
<td>10-37</td>
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<table>
<thead>
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<th>Resection</th>
<th>VAS Baseline</th>
<th>VAS Post</th>
<th>Lesion size (%)</th>
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<tbody>
<tr>
<td>Bleeding</td>
<td>29</td>
<td>7 (0-10)</td>
<td>64 (10-250)</td>
<td>40 (15-153)</td>
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<tr>
<td>No bleeding</td>
<td>18</td>
<td>7 (0-10)</td>
<td>90 (10-160)</td>
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<tr>
<td>Follow-up (median 19 months)</td>
<td>16</td>
<td>1 (0-10)</td>
<td>20 (10-140)</td>
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<tr>
<td>Grade I</td>
<td>6</td>
<td>0 (0-10)</td>
<td>45 (10-140)</td>
<td>17 (7-160)</td>
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<tr>
<td>Follow-up (median 14 months)</td>
<td>11</td>
<td>5 (0-10)</td>
<td>29 (0-62)</td>
<td>13 (0-91)</td>
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<tr>
<td>Grade II</td>
<td>3</td>
<td>9 (5-10)</td>
<td>45 (10-140)</td>
<td>10 (7-37)</td>
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<tr>
<td>Follow-up (median 22 months)</td>
<td>16</td>
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<td>40 (14-62)</td>
<td>10 (2-48)</td>
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<tr>
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<td>8 (5-10)</td>
<td>53 (32-81)</td>
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<td>Follow-up (median 16 months)</td>
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<td>5 (0-5)</td>
<td>27 (0-53)</td>
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<td>5</td>
<td>0 (0-5)</td>
<td>33 (10-55)</td>
<td>105* (50; 160)</td>
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<tr>
<td>Follow-up (median 20 months)</td>
<td>11</td>
<td>0 (0-5)</td>
<td>25 (0; 50)</td>
<td>61 (30; 91)</td>
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</tbody>
</table>

### Table 3: Number of lesions and bleeding

<table>
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<th>Total patients</th>
<th>Radiology of lesions</th>
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<tbody>
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<tr>
<td>Solitary lesions</td>
<td>14</td>
</tr>
<tr>
<td>Multiple lesions</td>
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<td>No bleeding</td>
<td>9</td>
</tr>
<tr>
<td>One bleeding adenoma</td>
<td>12</td>
</tr>
<tr>
<td>Multiple bleedings adenomas</td>
<td>10</td>
</tr>
</tbody>
</table>
In this prospective study of patients with HCA, 64% of the patients showed radiological signs of bleeding. We propose a clinical grading system to classify the severity of bleeding according to imaging features that can be used to direct therapy. Grade I bleeding is confined to the tumor and can usually be observed, requiring no active treatment. Grade II bleeding extends into the liver parenchyma whereas Grade III bleeding represents rupture of the parenchyma and bleeding beyond the confines of the liver capsule into the abdominal cavity. We advise to treat all active bleeding sites, bleeding sites of over 6 cm, and Grade III bleeding, with selective TAE of the feeding branch of the hepatic artery.

Clinical presentation of patients with bleeding may differ according to the severity of bleeding. Acute rupture of bleeding HCA requires emergency admission and resuscitation of the patient. Whereas a decade ago, the acute phase of intra- and extrahepatic bleeding (Grade II and III) with hemodynamic instability usually required laparotomy and control of the bleeding by packing of the liver, management has now shifted towards selective TAE. This technology is available in most large medical centers with state-of-the-art interventional radiology. In case of semi-acute bleeding, for example large intratumoral (Grade I) or intrahepatic (Grade II) bleeding without hemodynamic instability, TAE can be performed to prevent further bleeding. In our experience, an additional effect of TAE might be relief of pain, as presumably, the local pressure in the liver is reduced by proximal occlusion of the bleeding vessel(s). For these reasons, we treat patients presenting with (semi-)acute bleeding sites of >6cm and all Grade III bleeding with TAE. Most patients with small Grade I bleeding do not experience substantial discomfort and might not even seek medical attention. Another risk for bleeding was the relation of HCA to the liver capsule. Exophytic adenomas bled more often than intrahepatic or subcapsular adenomas, and intrahepatic adenomas did not cause Grade III bleeding. The pressure of surrounding liver parenchyma most likely prevents bleeding to spread. These findings have direct inferences for management as patients presenting with HCA with exophytic growth, or patients with large adenomas and concomitant obesity must be informed of the higher risks of severe bleeding. Preventive treatment options like TAE could be considered in these high risk patients, however this is an area of debate and will need further study. In our view, preventive TAE is of potential value in patients with increased risk of bleeding, patients unfit for surgery, or in patients who have previously undergone such surgery risks such as a Jehovah witness refusing blood transfusion.

Another issue is ‘what to do after bleeding of HCA’. First of all, we advise a wait-and-see policy whether or not the adenoma required TAE of an active bleeding site. After the acute phase, it is difficult to ascertain which parts of the adenoma constitute the original HCA and which parts are due to the bleeding, i.e. represent hematoma or clot. With time, the hematoma is cleared resulting in decrease of size of the adenoma as noted in 38% of adenomas in this series, leaving intact part(s) of the HCA and which parts are due to the bleeding, i.e. represent hematoma or clot. With time, the hematoma is cleared resulting in decrease of size of the adenoma as noted in 38% of adenomas in this series, leaving intact part(s) of the HCA at the site for assessment. In this series, one of the patients with severe Grade III bleeding underwent TAE, after which no residual HCA tumor could be found on follow-up imaging and hence, no resection of the tumor needed to be performed. Because of the intratumoral bleeding and rupture, part of the original tumor is destructed. This phenomenon we reported previously in 16 patients who underwent planned, delayed resection of the bleeding site after a bleeding episode of HCA [17]. Histopathologic examination of the resection specimen revealed necrosis and fibrosis at the site of the bleeding in 7 patients (43%) with detectable remnants of HCA [17]. We are now more conservative in resection of HCA after bleeding. As a result of the abovementioned policy, we undertook delayed resection in only two of the four patients that suffered Grade III bleeding in this study. Recurrent bleeding within the remnants of the same adenoma was encountered in one patient (Grade I), after which she underwent a segmental liver resection.

**Grading of bleeding**

- **Grade I bleeding**: Confined to the tumor and usually observable, requiring no active treatment.
- **Grade II bleeding**: Extends into the liver parenchyma.
- **Grade III bleeding**: Rupture of the parenchyma and bleeding beyond the liver capsule.

**Figure 2**

A: Transverse arterial MR image of a 34-year-old woman who during the 17th week of pregnancy experienced severe acute upper abdominal pain. A large arterial enhancing adenoma in segment 2/3 of the liver is seen (arrow) with a hypodense area consistent with bleeding (white arrowhead). With abdominal free fluid this bleed was categorized as an extrahepatic Grade III bleeding. Therefore the feeding hepatic arteries to the adenoma were selectively embolized. The fetus remained under extra care during the remaining pregnancy and the baby was healthy although prematurely delivered in the 34th week.

B: Transverse arterial CT image of the same woman 22 months after first presentation. After successful TAE the pain and discomfort subsided until similar less intense pain occurred again. Imaging was performed showing a smaller adenoma in the left liver (white arrow). However, a new Grade I bleeding was seen in the tumor.

C: Intra-operative image showing the exophytic adenoma in the left liver (white arrow). Spread through the liver, small greyish adenomas were present (arrowheads). Frozen section revealed granulomatous inflammation [16].
Adenomas in the other two patients did not require subsequent resection as the adenoma was undetectable. Likewise, 5 out of 9 adenomas with Grade II bleeding were resected. During follow-up none of the other adenomas presented with bleeding and all adenomas decreased in size or remained stable. On the basis of these experiences we advise a wait-and-see policy after TAE, even after severe Grade II and Grade III bleeding. The adenoma should be reassessed after 3-6 months, and secondary resection is only considered when there is evidence of residual HCA >5cm, or severe persisting abdominal complaints. Following this strategy, many adenomas do not require subsequent resection and can safely be observed.

Importantly, the differential diagnosis of HCA is hepatocellular carcinoma (HCC), and especially after bleeding it is difficult to distinguish HCA from HCC. In young women without cirrhosis, hepatitis, or other underlying (parenchymal) liver disease with a normal alpha fetoprotein, diagnosis of HCC is unlikely [18]. However, in male patients who present with bleeding adenoma in the liver and have not been taking androgenic hormones, suspicion on HCC should be high [19]. These patients are not elaborated herein, as the primary diagnosis of HCC excluded them from the present study.

The only one male patient included in this study, did present with typical signs of HCA, without underlying parenchymal disease or history of malignancy. Even though the adenoma was smaller than 5 cm (the current standard to advise resection), the adenoma was resected with generous margins. Final histopathological diagnosis in this patient was steatotic HCA without signs of malignancy.

This study has some limitations. First of all bleeding was only assessed on imaging and was not corroborated with histopathology. The study design of the prospective patient cohort included histopathology as reference for diagnosis of HCA and not as reference for bleeding. Therefore specimens were corroborated with histopathology. The study design of the prospective patient cohort included histopathology as reference for diagnosis of HCA and not as reference for bleeding. Therefore specimens were obtained from vital tumor tissue and bleeding was not prospectively noted and correlated to imaging. Using radiology as standard of reference for bleeding enabled us to assess every HCA in the liver and to accurately evaluate the proposed grading system in regard with clinical presentation. Finally, imaging was evaluated by one abdominal radiologist and no inter-observer analysis was performed.

CONCLUSIONS

We propose a grading system of bleeding for HCA in which intratumoral (Grade I) and intrahepatic (Grade II) bleeding larger than 6cm, and extrahepatic (Grade III) bleeding should be treated with TAE, while most small, grade I intratumoral bleeding do not need treatment. After the acute phase of bleeding with or without treatment with TAE, adenomas should be reassessed in time; in the absence of (remnants of) HCA >5cm after 3 months, further observation may be restricted to patients with large exophytic adenomas.
RISK FACTORS FOR BLEEDING IN HEPATOCELLULAR ADENOMA

MATTHANJA BIEZE
SAFFIRE S.K.S. PHOA
JOANNE VERHEIJ
KRJN P. VAN LIENDEN
THOMAS M. VAN GULIK
OBJECTIVE

Hepatocellular adenoma (HCA) is a benign hepatic lesion with sometimes severe bleeding complications, but the risk for bleeding is still ill defined. We aimed to assess risk factors for bleeding in patients diagnosed with HCA and during follow-up.

SUBJECTS AND METHODS

Patients with HCA were prospectively included from January 2008 until July 2012. Case characteristics including body-mass-index (BMI) were noted. Patients underwent dynamic MR and/or CT imaging at presentation and during follow-up. Lesion characteristics on (follow-up) imaging were noted, and bleeding was graded as intratumoral (Grade I), intrahepatic (Grade II), or extrahaepatic (Grade III). Standard of reference for diagnosis was histopathology, or dynamic MR and/or CT imaging.

RESULTS

In 45 patients included (median age 39 years; 22-60 years, female/male 44:1), a total of 195 lesions were evaluated (median size 24mm (10-250mm)). Bleeding was seen in 29 (64%) patients and in 42 (22%) lesions with a median size of 62mm (10-160mm). Patients with BMI>25 showed an increased risk for severe bleeding Grade II&III (12/31 versus 1/11; P=0.010). Lesions >35mm showed more bleeding compared to lesions <35mm. Exophytic lesions showed a higher incidence of bleeding (16/24; 67%: P=0.001) compared to intrahepatic (9/82;11%) and subcapsular lesions (17/89;19%). Lesions in segment 2-3 showed more bleeding compared to lesions in the right liver (11/32 versus 31/163; P=0.049). Lesions with peripheral or central arteries were more likely to show bleeding (10/13; P<0.001).

CONCLUSION

Risk factors for bleeding of HCA include size >35mm, BMI >25, presence of lesional arteries, location in the left liver, and exophytic growth.

INTRODUCTION

Hepatocellular adenoma (HCA) is a benign hepatic lesion with a risk of malignant transformation [1] and a risk of spontaneous bleeding [1-6]. In a recent systematic review by van Aalten et al [7] it is estimated that the overall frequency of bleeding is 27.2% with more severe bleeding in 17.5% of patients presenting with HCA. Bleeding complications in HCA have been associated with tumor size and use of oral contraceptives (OC) [8]. Women in today’s Western society have been using and are still using OC. Bleeding of HCA can range from subclinical, minor intratumoral bleeding (Grade I) to extrahepatic bleeding (Grade III) [8] with severe abdominal pain and hypovolemic shock, requiring emergency care. Arterial embolization has become the treatment of choice for these bleedings in the liver and to date, surgery is performed less frequently in an emergency setting [10].

Diagnosis of HCA is made based on cross sectional imaging of the liver. Magnetic resonance (MR) imaging with a liver-specific hepatobiliary contrast agent is most sensitive [11]. Characteristics of HCA are contrast enhancement during the arterial phase of dynamic imaging, no uptake of contrast on hepatobiliary phase [11], intra-tumoral fat and glycogen [12], and hemorrhage [13]. Diagnosis is primarily based on imaging and to date, biopsy of the lesion is hardly necessary to determine diagnosis. Histopathology is now mainly obtained in specimens after resection and in recent years a subclassification of HCA has become available [14]. This subclassification could be helpful in risk analysis of malignant transformation of HCA as a possible association of the beta-catenin subtype with malignant transformation has been identified. Until this day it remains unclear if these subtypes are associated with an increased bleeding tendency of the lesions.

Treatment of HCA depends on the clinical status of the patient at time of presentation. All patients with a diagnosis of HCA will start with discontinuation of oral contraceptive use. In some cases this will result in shrinking or stabilization of growth of the lesion. When the HCA does not shrink to less than 5cm, resection is advocated because of the remaining risks of bleeding and malignant transformation in this patient group [15]. In patients presenting with massive hemorrhage in HCA, an emergency protocol using transarterial embolization (TAE) is initiated. Thus, risk assessment for bleeding has only been based on size of a lesion, which remains marginal to fully estimate the risk in the individual patient. With this study we aimed to assess the risk factors for bleeding in HCA that can be derived from imaging or clinical parameters.
Lesion characteristics on MR & CT imaging

Diagnosis of HCA

Diagnosis of HCA was preferably made by MR imaging of the liver using hepatobiliary Gadolinium EOB-DTPA contrast (Primovist®, Bayer, Germany (Eovist®)). Diagnosis of HCA was based on intra-tumoral hemorrhage, fat and/or glycogen, and arterial enhancement of the lesion with subsequent loss of signal intensity compared to surrounding liver tissue in the hepatobiliary phase [11]. Multiphase CT imaging of the liver was only rendered diagnostic in the presence of an arterial enhancing lesion with clear signs of hemorrhage and without suspicion of malignant disease. Histopathological samples were obtained by resection and/or liver biopsy from tumoral tissue. Systematic biopsy was only performed until 2011, as of which time MR imaging with Primovist was proven sensitive for diagnosis of HCA [11]. Morphological characteristics of HCA include: hepatocellular proliferation without cytonuclear atypia in which solitary arteries are seen and portal tracts are lacking, with a well-developed reticulin framework. In addition to standard liver stainings, including HE, collagen and CK7: additional immunohistochemical staining was performed for subcellular features of HCA (42). Diffuse glutamate synthetase (GS) staining is associated with the beta-catenine mutated HCA subtype, loss of liver fatty acid binding protein (LFABP) with the ‘steatotic’ HNFa2 mutated subtype, and finally, diffuse positive C reactive protein (CRP) and/or positive serum amyloid A (SAA) staining with the inflammatory subtype. Remaining lesions which did not correspond to the mentioned subclassification were scored as unclassifiable when the staining could not be performed due to sampling errors or insufficient quality material.

Lesion characteristics on MR & CT imaging

Liver lesions were evaluated by one abdominal radiologist with over 10 years experience with liver imaging, according to the following characteristics: number of lesions (a max of 10 - largest - lesions were assessed per patient), segmental location of lesions, depth of the lesion in relation to the liver capsule: intrahepatic (lesion more than 1cm distance to the liver capsule); subcapsular (any area of the tumor within 1cm distance of the liver capsule); exophytic (any part of the lesion bulging beyond the contours of the liver). Enhancement of the lesion after contrast was scored (arterial enhancement is typical for HCA). Vascularization of the lesion was scored as follows: no obvious arterial or venous blood supply; presence of a central feeding artery; presence of a ‘peripheral artery’ surrounding the lesion or present in the periphery of the lesion without penetrating to the center. Hepatic steatosis of the liver was scored on MR imaging as none, minor, intermediate, or severe on Tiw and in out of phase series.

Methods

This study is part of a prospective study including all consecutive patients referred with suspicion on HCA or focal nodular hyperplasia (FNH), from January 2008 until July 2012 [11]. For the present study patients with FNH were ignored and patients with an established diagnosis of HCA were included. All patient data were collected in a designated database. Standard of reference for diagnosis of adenoma was based on either histopathology or imaging studies (MRI Primovist [11] or CT imaging).

Standard of reference for the presence of bleeding was radiological signs of bleeding on MR and/or CT imaging. The institutional Medical Ethics Committee approved the prospective study and a written informed consent was obtained from all patients. Of patients diagnosed with HCA, case characteristics were noted, with special detail for diabetes mellitus and body-mass-index (BMI): normal weight 18.5-25, overweight 25-30, obese 30-40, morbidly obese > 40 (or BMI >35 with additional cardiac, kidney, and/or lung disease). Symptoms at time of presentation were assessed with a questionnaire: the validated McGill Pain Questionnaire [16] and its Dutch translation [17] including the Visual Analogue Scale (VAS) were used to assess pain and discomfort.

Assessment of bleeding

Signs of bleeding on contrast enhanced, CT (cross-sectional imaging) included intra-or peri-lesional, irregular hypodense areas, or irregular areas of non-enhancing hyperdense areas on all phases, consistent with a recent bleeding or clot. Contrast extravasation was regarded as an active bleeding. Free abdominal fluid, especially when accompanied with a hypotensive episode and/or haemoglobin drop, was considered compatible with bleeding into the abdominal cavity. On MR inhomogeneous, none-enhancing areas of hyper signal intensity on T2 weighted sequences were regarded as bleeding sites. On Tiw series signal loss on gradient sequences were regarded as a sign of old bleeding (hemorrhoid). Bleeding was scored as Grade I (intratumoral), Grade II (intrahepatic) or Grade III (extrabepatic: rupture into the peritoneal cavity) [9]. Hemorrhagic features in histopathological specimens were not taken into account because histopathology in this prospective patient cohort was designed as HCA diagnostics and therefore only vital, non-bleeding, and non-necrotic areas were taken for evaluation to avoid potential sampling error. Sizes of the lesion and area(s) of bleeding were noted on baseline imaging and on follow-up imaging. If no adenomatous tissue was visible in the area of bleeding, the bleeding was graded as intrahepatic or extrabepatic. If the patient underwent follow-up imaging, the above mentioned factors were re-assessed over time.

In all patients diagnosed with HCA, oral contraceptives were discontinued as initial treatment. Patients with lesions smaller than 5cm underwent follow-up of the lesions. Lesions larger than 5cm were considered for resection. If patients presented with signs of acute bleeding, a contrast enhanced CT scan was performed in an emergency setting. In the absence of signs of intra-abdominal rupture (free fluid) and hemodynamic stability, patients were admitted and observed. In case of extensive intrahepatic bleed or rupture of the lesion into the abdominal cavity, superselective catheterization of the hepatic arterial branches and embolization was performed (TAE). After emergency TAE no surgery was performed in the acute phase. The patient was re-evaluated after 3-6 months and only if the lesion was larger than 5cm (bleeding area excluded) resection was indicated. Arterial embolization in this series was performed twice as preventive treatment (before resection of a giant adenoma to diminish intra-operative blood loss, and in a Jehovah witness in which surgery was contra-indicated).

Treatment

Risks for bleeding
Statistical analysis

All 45 patients underwent MR and/or multiphase CT imaging. Bleeding was seen in 29/45 patients (64%) and in 42/195 lesions (22%) with a median lesion diameter of 62mm (10-160mm). Patients with more than 10 lesions had more often bleeding compared to patients with <10 lesions (8/9 versus 21/36; P = 0.041). Most bleeding sites were confined to the lesion, i.e. Grade I (29/42; 69%). In 9 lesions the bleeding extended into the surrounding parenchyma (Grade II; 21%), and in 4 lesions the bleeding broke through the liver capsule into the peritoneal cavity (Grade III; 10%).

Hepatic steatosis in surrounding liver parenchyma was seen in 17/45 patients on imaging (38%; 3 minor, 7 intermediate, 7 severe). Of these 17 patients, 1 had normal weight, 5 were overweight, 7 were obese, and 4 were morbidly obese. Categorical analyses showed that the presence and degree of hepatic steatosis in the surrounding liver did not differ between patients with or without bleeding (P = 0.438), nor did it influence severity of bleeding (P = 0.547). The risk of severe bleeding was increased in patients with a BMI of 25 or higher compared to patients with normal weight (12/31 Grade II and III bleeding versus 1/11; P = 0.010; Fig. 1.). The highest percentage of severe bleeding, i.e. 63%, was seen in patients with morbid obesity.

Risk factors for bleeding of HCA are summarized in Table 3 and Table 4. Median diameter of 195 lesions was 24mm (10-250mm), of 42 lesions with signs of bleeding 62mm (10-160mm), and size of the lesion minus the area of bleeding was 37mm (0-140mm). With increasing diameter, bleeding was more frequent, especially from 35mm and up (Fig. 2A.: 7/129 (5%) lesions smaller than 35mm versus 34/64 (53%) larger than 35mm; P <0.001). When corrected for the area of bleeding, diameter of tumor tissue remained significant for occurrence of bleeding (Fig. 2B.). Lesions in segment 2-3 showed more bleeding compared to lesions located elsewhere (11/32 (34%) versus 31/163 (19%); P = 0.049).

Severity of bleeding was not different between both groups (P = 0.493). Location of the lesion in rela-
Risks for bleeding

Chapter 6

Figure 1

Histopathology & subclassification

Treatment

Table 2 — Bleeding and presentation of patients

<table>
<thead>
<tr>
<th>Patients (n = 45)</th>
<th>Lesions (n = 195)</th>
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<tr>
<td>VAS</td>
<td>Lesion size</td>
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<td>Incidental finding</td>
<td>9</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>20</td>
</tr>
</tbody>
</table>

Bleeding grading system

- Grade I: intratumoral
- Grade II: intrahepatic
- Grade III: extrahepatic

No bleeding

- Incidental finding: 7 | 0 | 67 | 18 (10-250) |
- Symptomatic: 9 | 7 (2-8) | 86 | 22 (10-153) |

Table 2

<table>
<thead>
<tr>
<th>Bleeding classification</th>
<th>Grade I: Intratumoral</th>
<th>Grade II: Intrahepatic</th>
<th>Grade III: Extraplateal</th>
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</tr>
<tr>
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<td>normal (&lt;20 BMI)</td>
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<td></td>
</tr>
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<td>1</td>
<td>Aspetic (20-30)</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>Unstable (30-40)</td>
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<tr>
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<td>Mortal obesity (&gt;40)</td>
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</table>

Bleeding classification versus BMI

Subclassification of HCA in biopsy and resection specimens showed inflammatory HCA in 31/76 lesions (41%; 19 patients), steatotic HCA in 7/76 (9%; 6 patients) and 35/76 (46%) lesions were unclassifiable either because of sampling error, insufficient material or absence of typical immunohistochemical staining. No lesions were identified with the beta-catenin subtype. None of the patients with multiple resected or biopsied HCA had more than 1 subtype present in the liver (Supplement Table I). Patients with inflammatory HCA had a higher BMI compared to the BMI of patients with steatotic HCA (P = .021). Bleeding occurred in all HCA subtypes. When evaluating severity of bleeding, there were no differences between the subtypes.

TREATMENT

Treatment is summarized in Supplement Table II. Nine patients presented at the emergency department with severe bleeding. Seven patients underwent emergency selective arterial embolization (TAE) because of active bleeding. Two patients were hemodynamically stable on admission and did not need emergency intervention. Preventive TAE was performed in a patient who is a Jehovah witness and in a patient prior to resection of a giant HCA (250mm). Elective surgery was performed in 29/45 (64%) patients, of whom 15 underwent resection of a single lesion or multiple lesions without further follow-up (Supplement Table I). Median follow-up of the remaining 30 patients was 14 months (1-48 months) with a total of 171 lesions. Either, patients did not want to undergo surgery of lesions larger than 5cm, or the follow-up was of the unrected lesions smaller than 5cm.
Risks for bleeding

Chapter 6

Corrected lesion size = median size (mm) of the lesion minus the area of bleeding.

Table 3 — Risk factors for bleeding of hepatocellular adenomas

<table>
<thead>
<tr>
<th>Patients (n = 45)</th>
<th>Lesions (n = 195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Bleeding (n = 42)</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>P = 0.617</td>
</tr>
<tr>
<td>Normal</td>
<td>28 (18)</td>
</tr>
<tr>
<td>Present</td>
<td>17 (11)</td>
</tr>
</tbody>
</table>

Body Mass Index (BMI)

| (< 25) | 11 (7)          | 47 (11) |
| (25 - 30) | 13 (8)          | 35 (10) |
| (30 - 40) | 16 (10)         | 89 (13) |
| (40 <)   | 5 (4)           | 24 (8) |

Number of lesions: P = 0.096

Lesions (n = 195)

<table>
<thead>
<tr>
<th>Total</th>
<th>Bleeding (n = 42)</th>
<th>Bleeding severity</th>
</tr>
</thead>
</table>
| Location
| Left liver (s2-3) | 32 (16)         | 11 (34) | P = 0.049 | P = 0.493 |
| Right liver      | 163 (84)        | 31 (19) |
| Relation to capsule
| Intrahepatic     | 82 (42)         | 9 (11)  | P < 0.001 | P = 0.355 |
| Subcapsular      | 89 (46)         | 17 (19) |
| Exophytic        | 24 (12)         | 16 (67) |
| Vascularization
| None             | 182 (93)        | 32      | P < 0.001 | P = 0.597 |
| Arteries (central or peripheral) | 13 | 10 |
| Size
| Overall          | 24 (10-250)     | 62 (10-160) | P < 0.001 | P = 0.223 |
| Corrected size**| 22 (5-250)      | 37 (5-140) |

Table 4 — Risk factors

<table>
<thead>
<tr>
<th>Size</th>
<th>Bleeding</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mm (range)</td>
<td>22 (5-250)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Size lesions with bleeding mm (range)</td>
<td>62 (10-160)</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Size lesions with bleeding corrected for bleeding-area mm (range)</td>
<td>37 (5-140)</td>
<td>P = 0.002</td>
</tr>
</tbody>
</table>

Risk factors corrected for size of the lesion

| Body Mass Index                  | P = 0.131 | P = 0.808 |
| Morbidly obese, severity II&III  | P = 0.010 | P = 0.032 |
| Segment 2-3                      | P = 0.049 | P = 0.05 |
| Relation to capsule              | P < 0.001 | P < 0.001 |
| Vascularization                  | P < 0.001 | P < 0.001 |

Figure 2

A: The horizontal axis shows the categorical size of the lesions; n = 195, median size of 24mm (range 5-250mm). On the vertical axis the count of lesions per size category are shown. The white bars are lesions without bleeding; the striped bars represent the lesions with bleeding. As is shown in the figure bleeding occurs even in small lesions. However, lesions with bleeding have a median size of 62mm (10-160) (P = 0.001). When lesions are larger than 50mm, bleeding occurs more often.

B: Shows the same values plotted as figure (A) with lesion size corrected for size of bleeding area. Median size of lesion without bleeding was 20mm (40-250mm) and the 45 lesions with bleeding (corrected for the area of bleeding) had a median size of 53mm (940mm) (P < 0.001).
Chapter 6

Fifty percent of all included women had been pregnant at least once before diagnosis of HCA was made (21/44). One patient presented with bleeding of HCA during the 17th week of her first pregnancy, classified as extrahepatic (Grade 3) on CT imaging. Successful TAE was performed and the patient gave birth to a healthy child in the 34th week. This premature birth was due to onset of severe diabetes during the pregnancy. All 45 patients were advised to discontinue OC. Thirteen patients had already discontinued OC for other reasons than diagnosis of HCA before presenting at the outpatient clinic, with a median discontinuation of 70 months. The group of patients that did not undergo second radiological evaluation before resection was excluded for analysis of size reduction after discontinuation of OC. The remaining 21 patients with 122 lesions had a median (radiological) follow-up of 15 months. Median decrease in size was 25% in 15 months (n = 122). In patients with multiple lesions, the lesions often exhibited the same changes during follow-up: in 18 patients size of more than 1 lesion decreased with remaining lesions stable, 6 patients showed stability in size of all lesions, 1 patient showed increase in size of 3 lesions with 1 lesion remaining stable in size, and in only 3 patients the lesions all behaved differently (increase, decrease and no change in size). There were no significant differences in size reduction (or size increase) during follow-up in patients who had discontinued OC before presentation compared to patients who discontinued OC at time of presentation (P = 0.438). Patients who used OC at time of presentation had no more signs of bleeding compared to the group who had discontinued OC at least 3 months before presentation at our clinic (P = 0.620).

Pregnancy & Oral Contraceptive Use

Fifty percent of all included women had been pregnant at least once before diagnosis of HCA was made (21/44). One patient presented with bleeding of HCA during the 17th week of her first pregnancy, classified as extrahepatic (Grade 3) on CT imaging. Successful TAE was performed and the patient gave birth to a healthy child in the 34th week. This premature birth was due to onset of severe diabetes during the pregnancy. All 45 patients were advised to discontinue OC. Thirteen patients had already discontinued OC for other reasons than diagnosis of HCA before presenting at the outpatient clinic, with a median discontinuation of 70 months. The group of patients that did not undergo second radiological evaluation before resection was excluded for analysis of size reduction after discontinuation of OC. The remaining 21 patients with 122 lesions had a median (radiological) follow-up of 15 months. Median decrease in size was 25% in 15 months (n = 122). In patients with multiple lesions, the lesions often exhibited the same changes during follow-up: in 18 patients size of more than 1 lesion decreased with remaining lesions stable, 6 patients showed stability in size of all lesions, 1 patient showed increase in size of 3 lesions with 1 lesion remaining stable in size, and in only 3 patients the lesions all behaved differently (increase, decrease and no change in size). There were no significant differences in size reduction (or size increase) during follow-up in patients who had discontinued OC before presentation compared to patients who discontinued OC at time of presentation (P = 0.438). Patients who used OC at time of presentation had no more signs of bleeding compared to the group who had discontinued OC at least 3 months before presentation at our clinic (P = 0.620).
The risk of severe bleeding remains a worrisome burden for the patient and a reason for the treating physician to advise resection for lesions larger than 5cm. A better risk stratification could result in improvement of patient care with more selective treatment. In this prospective study of a large cohort of patients with HCA, radiological signs of bleeding were found in 64% of patients and in 22% of lesions. Bleeding, even in emergency cases, can be treated successfully by non-surgical means.

This study shows that bleeding is frequent and the following risk factors were identified with regard to patient characteristics: Patients who are overweight or obese have a higher risk of severe Grade II and III bleeding compared to patients with normal weight. Evaluation of CT and MR imaging revealed the following lesion characteristics as risk factors: Size of the lesion, as bleeding was more common in lesions of 35mm or larger. Lesions located in segment 2-3, or exophytic lesions protruding from the contours of the liver, were more likely to bleed. Even though only 12 out of 195 lesions showed visible arterial vascularization, if this was the case, the chance of bleeding increased dramatically from 18 to 83%. This finding will have to be confirmed by other (larger) studies. All of these findings have direct implications for management as patients presenting with HCA larger than 35mm, with peripheral or central arteries, located in the left lateral liver segments, with an exophytic growth, or patients with concomitant obesity carry a higher risk of bleeding. These patients should be informed about the risk of bleeding and (preventive) treatment options. The five risk factors for bleeding identified in this study provide the basis to predict bleeding in patients diagnosed with HCA.

Some reassuring data were also revealed in this study. Most of bleeding was Grade I and thus confined within the lesion (69%) and only a small percentage of bleeding broke through the liver capsule into the peritoneal cavity (9%). This was less than reported in previous studies that estimated overall intraperitoneal rupture in 17.5% of patients [7]. Because all lesions were radiologically evaluated in the present study, even small intratumoral bleeding sites were found in incidental lesions, explaining the high number of Grade I bleeding and relatively small percentage of severe Grade III bleeding. The size of the bleeding area correlated with increasing VAS score. Based on clinical presentation of the patient and dynamic imaging, an adequate risk assessment for (life-threatening) bleeding can be made. Acute rupture of bleeding HCA might require emergency resuscitation of the patient. Selective transarterial embolization is first treatment in these patients and to date is available in most large medical centers with state-of-the-art interventional radiology. In case of semi-acute bleeding, an additional effect of TAE is the relief of pain, as presumably, the local pressure in the liver is reduced by occlusion of the bleeding vessel(s). Most patients with Grade I bleeds do not experience great discomfort, and do not need treatment. The role of TAE in the prevention of bleeding in HCA, especially in lesions with increased risk for bleeding, is up for debate. In our view, preventive TAE is of potential value in patients who present with 2 or more of the above mentioned risk factors, patients who are unfit for surgery, or in patients who have increased surgical risks such as a Jehovah witness refusing blood transfusion.

Another important point of debate is pregnancy. The hormonal changes during pregnancy allegedly increase the risk of the lesion to bleed; this could not be proven in our study albeit that only 3 women became pregnant during our study. We did find that half of the women had been pregnant at least once in the time before they presented with HCA, and one of these patients had severe bleeding complaints requiring emergency care. The main dilemma when dealing with this topic is not only the life of the patient, but also of her unborn child [18]. Even if risk of bleeding were not increased during pregnancy, the possible consequences for the child make it hard not to take preventive measures. Therefore, further study into the risk of bleeding during pregnancy is needed before those worries can rationally be acted upon or silenced [19].

Subclassification of HCA [14] revealed what has been shown in previous studies that patients with inflammatory HCA more often have a high BMI and hepatic steatosis consistent with the metabolic syndrome [20, 21]. In this study no beta-catenin mutated HCA were found and therefore, no comments can be made about the risk of bleeding in this subtype. The relative high number of unclassifiable HCA in our cohort is explainable by a number of specimens that only provided morphological diagnosis of HCA without immunohistochemical subclassification. This was mainly due to bleeding artefacts which compromised subclassification and insufficient material in the paraffin blocks for additional immunohistochemical stainings, especially in cases for which only biopsies were available. Between the cases in which subclassification could be made, there was no difference between the subtypes in frequency and severity of bleeding.

During a median radiological follow-up of 15 months, one re-bleed occurred and one new bleeding, both Grade I. Of all 122 lesions that were included in this follow-up a tendency to decrease in size was seen of 25% after correction for absorption of the area of bleeding. Furthermore, in patients with multiple lesions, follow-up showed similar behavior of the lesions within one patient. Only in 3 patients did the lesions show both increase and decrease in lesion size. The exact mechanism of both increase and decrease in size of HCA with time is uncertain. The use of oral contraceptives has been correlated with growth of HCA and possibly, the risk of bleeding [7, 8]. All patients discontinued oral contraceptives at first presentation, or had discontinued OC well before presentation. Interestingly, in some patients the lesion con-
continued to decrease in size even after discontinuation of OC years earlier, in some patients no change was seen after discontinuation, and in some patients the lesions increased in size even when OC was discontinued years ago. As described by Kapp et al [22], no hard evidence for the role of OC was found in literature for either growth or decrease in size of HCA lesions. Our data also not provide a convincing answer to whether OCs have a vital influence on HCA. We still advise patients to discontinue OC use and to consider alternative contraceptives among which a (local) hormonal intra uterine device. However, if results in increased gynecological discomfort we support restart of OC if one or none of the above mentioned risk factors are present and the patient participates in a strict follow-up regime for the next 2 years to see if the lesion(s) changes in size or aspect. Thusfar, we included 3 patients in such a regime and the lesions hardly changed in size, nor did bleeding occur.

This study has some limitations. The study was derived from a prospective database of consecutive patients with HCA and focal nodular hyperplasia (FNH). Therefore, bleeding was not prospectively scored on histopathology, as histopathology was designed to confirm the diagnosis of HCA and therefore only vital, non-bleeding, and non-necrotic areas were sampled in most instances. Therefore histopathology may have underestimated the frequency of especially small bleedings. Radiological signs of bleeding were used as endpoints for grading of bleeding and not the clinical severity of the bleeding. However, with this approach we found many (small) subclinical bleeding sites. These findings will show on imaging and by including these lesions a better estimation and prediction of risk factors could be assessed. Finally, only one radiologist evaluated imaging and no analysis between observers was performed.

**CONCLUSIONS**

Risk factors for bleeding of HCA include size $>$35mm, BMI of more than 25, radiological presence of central or peripheral arteries, location in the left lateral liver segments, and exophytic growth.

### Table III suppl — Patients with multiple lesions; size of lesions per patient during follow-up

<table>
<thead>
<tr>
<th>Patient</th>
<th>OC use</th>
<th>Nr of lesions</th>
<th>Reseption</th>
<th>Stable</th>
<th>Decrease (median, range)</th>
<th>Increase (%)</th>
<th>Follow-up (months)</th>
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<tr>
<td>Decreasing or stable size</td>
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<td></td>
<td></td>
<td></td>
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**Stable size**

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<th>Patient</th>
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<th>Reseption</th>
<th>Stable</th>
<th>Decrease (median, range)</th>
<th>Increase (%)</th>
<th>Follow-up (months)</th>
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**Increasing size**

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<td>2 (12; 20)</td>
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</tr>
</tbody>
</table>


PART III

HEPATOCELLULAR CARCINOMA
CHAPTER 7

Diagnostic accuracy of 18F-methyl-choline PET/CT for intra- & extrahepatic hepatocellular carcinoma

Matthanja Brize
Heinz-Josef Klömpen
Joanne Verheij
Ulrich H.W. Breuers
Saffire S.K.S. Phoa
Thomas M. van Gulik
Roelof J. Bennink
OBJECTIVE
Diagnosis of hepatocellular carcinoma (HCC) primarily involves imaging. The aim of this study was to assess the sensitivity and specificity of 18F-fluorocholine (18F-FCH) PET for detection of HCC and evaluation of extent of disease.

SUBJECTS AND METHODS
Patients with HCC >1cm were included between 2009 and July 2011, follow-up closed February 2013. Diagnosis was based on AASLD criteria and all patients underwent 18F-FCH PET/CT-baseline prior to treatment, 6 underwent a second PET/CT post-treatment, and 1 patient a third during follow-up. Whole-body PET and low dose CT imaging were performed 15 minutes after 18F-FCH injection. Evaluation of imaging was done with standardized uptake value (SUV) ratios: SUVmaximum of the lesion divided by the SUVmean of surrounding tissue. Statistical analyses included descriptive analyses, ROC curve, McNemar test, and Kaplan Meier at 5% level of significance.

RESULTS
Twenty-nine patients revealed 53 intrahepatic lesions. In 48/53 lesions 18F-FCH PET was positive (SUV-ratio 1.95 ± 0.66; sensitivity 88%, specificity 100%). PET/CT showed uptake in 18 extrahepatic lesions and no uptake in 3 lesions affirmed non-HCC lesions, all lesions were confirmed with additional investigation (accuracy 100%). In 17/29 patients additional lesions were found on PET/CT imaging, with implications for treatment in 15 patients. Post-treatment PET/CT showed identical results compared to standard treatment evaluation.

CONCLUSION
This study shows additional value of 18F-FCH PET/CT for patients with HCC. The 18F-FCH PET/CT has implications for staging, management and treatment evaluation because of accurate assessment of extrahepatic disease.

INTRODUCTION
Hepatocellular Carcinoma (HCC) is the sixth most common malignancy world wide [12] and varies greatly in geographic occurrence. The incidence of HCC in Eastern Asia and Middle Africa is at least 10 times higher as in Europe and the United States, although the incidence is increasing with the prospect of the rate seen in recent data from developed countries in Asia [1]. The strongest correlation between underlying disease and HCC development is the cirrhotic liver were 80% of HCC occurs [4], also viral hepatitis, storage diseases and NASH can lead to HCC [4]. The Barcelona-Clinic Liver Cancer (BCLC) classification is generally used as standard classification for HCC and was endorsed by the EASL and AASLD (figure 1) [5; 6].

This classification offers a correlation between the tumors’ stage, underlying disease, treatment strategy and prognosis. In a cirrhotic liver diagnosis of HCC is based on multiphasic CT imaging modalities used for diagnosing HCC, detection and characterization of small (≤2cm) lesions remains difficult in the cirrhotic liver [10]. To maximize patients’ treatment options, early and accurate detection of (metastatic) HCC is crucial in diagnostic work-up and in follow-up of patients [5; 11]. The 18F-Fluoro-deoxy-glucose (18F-FDG) PET/CT scan is used in oncological work-up and response adapted treatment of certain tumor types including esophagus [12] and ovarian carcinomas [13]. Also for high risk patients with breast cancer there is increasing evidence that the 18F-FDG PET/CT can be used to modify staging and management, and to evaluate treatment including neoadjuvant chemotherapy [14]. The diagnostic work-up for HCC does not include standard 18F-FDG PET/CT imaging, because diagnostic accuracy is limited especially in well-differentiated HCC [15]. 18F-FDG PET/CT has no additional value to conventional imaging in detection of HCC [16], and PET/CT imaging is therefore not implemented in guidelines for diagnostic work-up of HCC[5]. Different radioactive tracers have been evaluated for HCC. In a study by Talbot et al [17] 18F-methyl-choline (18F-FCH) showed a
sensitivity of 88% compared to FDG with 68% and was found to be useful for detection and follow-up of patients with HCC. In a recent study by Cheung et al. [18] the authors strongly suggest the use of dual-tracer PET/CT (FDG and 11C-Acetate) in staging liver transplant patients as this modality has a higher sensitivity and specificity than contrast enhanced CT alone. Bone scintigraphy is only advised as pre-operative staging prior to liver transplantation [6] and no routine bone scan is necessary to detect asymptomatic bone metastases in patients with resectable HCC [19]. Some data is available on cases in previously published studies and uptake of choline tracer in HCC bone metastases [15; 20]. Early detection of (extrahepatic) HCC is of clinical importance [21; 22]. The \(^{18}\)F-FCH PET/CT is a promising additional diagnostic tool which might be useful in the diagnostic work-up of HCC, including assessment of metastatic disease and follow-up to assess treatment effectiveness, recurrence and disease progression.

‘The aims of this study are [1] to assess the sensitivity and specificity of the \(^{18}\)F-FCH PET/CT for detection of intrahepatic and metastatic HCC; [2] to determine the role of \(^{18}\)F-FCH PET/CT in patient management and to determine if \(^{18}\)F-FCH PET/CT accurately evaluates tumor response to treatment.’

Barcelona Clinic Liver Cancer (BCLC) staging classification [39]: Strategies are altered according to treatment effectiveness and side effects.
This study is a prospective, single center, investigator driven study for diagnostic accuracy. The study was approved by the local medical ethics committee and written informed consent was obtained from all patients.

Patients with suspicion of HCC were presented at multidisciplinary meetings and screened for potential inclusion for the study. Patients were eligible if primary or recurrent intrahepatic HCC larger than 2 cm was present and the patients were 18 years of age or older. Patient inclusion depended on availability of the 18F-FCH tracer in regard with the fast-track treatment plan, on the mobility of the patient and his or her proximity to the hospital (over 30 minutes of travelling time were considered unethical for the severely ill patient). Only if PET imaging could be combined with other necessary investigations were these patients asked to participate in the study. After patient inclusion laboratory tests were assessed for alfa-fetoprotein and liver function tests (AST normal <40 U/L; ALT normal <40 U/L; AP normal <120 U/L; yGT normal <60 U/L). History of hepatitis, Gau- ther’s disease, haemochromatosis and other pre-existing hepatic conditions were noted.

Thirty non-consecutive patients, median age 65 (range 28 - 84 years) were included between 2008 and July 2011, follow-up closed February 2011. Table 1 summarizes patient character-istics. In 3 patients the lesion(s) were incidentally found on imaging performed for general check-up or other unrelated indications. In 12 patients the lesion(s) were found during follow-up of high-risk underlying parenchymal disease, and in 15 patients the presenting symptoms were consistent with HCC on imaging.

18F-FCH PET/CT

18F-FCH has a half-life of 110 minutes, the kidney is the dose-critical organ, and 18F-FCH reaches a steady distribution in the liver within 10 minutes [23]. Via the choline transporter(s) [24] or facilitated 18F-FCH has a half-life of 110 minutes, the kidney is the dose-critical organ, and 18F-FCH reaches a steady distribution in the liver within 10 minutes [23]. Via the choline transporter(s) [24] or facilitated 18F-FCH PET imaging could be combined with other necessary investigations were these patients asked to participate in the study. After patient inclusion laboratory tests were assessed for alfa-fetoprotein and liver function tests (AST normal <40 U/L; ALT normal <40 U/L; AP normal <120 U/L; yGT normal <60 U/L). History of hepatitis, Gau- ther’s disease, haemochromatosis and other pre-existing hepatic conditions were noted.

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Methods

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18F-FCH PET/CT

18F-FCH has a half-life of 110 minutes, the kidney is the dose-critical organ, and 18F-FCH reaches a steady distribution in the liver within 10 minutes [23]. Via the choline transporter(s) [24] or facilitated diffusion choline is transported into the cell. Three major metabolic pathways of choline are known [25] (Figure 2), with radiolabelled phosphocholine (PC) as the major metabolite in cancers responsible for the choline uptake in PET imaging [26; 27]. 18F-FCH was synthesized as previously described by Degrado et al (28). This resulted in 18F-FCH with a 68% or more, radiochemical purity. The PET/CT was performed using a Philips Gemini TF-64 PET/CT scanner (Philips Medical Systems, Eindhoven, the Netherlands) with spatial resolution near the field of view center of 4.8 mm in transverse and axial directions. A whole body low dose CT scan in the supine position was acquired, encompassing the body from scull base to mid thigh. The 12-channel helical CT scanning parameters were: 120 kVp, 50 mA/slice, rotation time 0.75 s, slice thickness/interval 5.0 mm. No intravenous contrast was used. At 15 min after intravenous injection of 150 MBq (irrespective of body weight) of 18F-FCH, whole body emission scans were acquired from mid thigh to scull base. Image reconstruction employed a list-mode version of a maximum likelihood expectation maximiza-tion algorithm with a time-of-flight kernel applied in both the forward and back-projection operations. CT data were used for attenuation correction. PET images were analyzed by a nuclear radiologist (15 years experience in nuclear medicine and a 2 year abdominal radiology fellowship training), and the low-dose CT images by a radiologist experienced in abdominal year radiology (12 year experience in liver- and abdominal radiology). Both readers were blinded for patient history previous imaging and pathology reports, but were aware of the differential diagnosis of HCC. PET/CT images were evaluated on a workstation (Hermes Medical Solutions, Stockholm, Sweden). HCC often presents in the background of a cirhotic liver. This leads to inhomogenous uptake of the 18F-FCH tracer in the liver surrounding the HCC lesion. We therefore decided to use a ratio to evaluate uptake of the tracer: this made comparison between patients possible as every patient is his/her own control.

The maximum standardized uptake value (SUV) of the lesion(s) and the mean SUV of non-affected (liver) tissue were determined. The SUV ratio was calculated by dividing the maximum SUV of the lesion (SUVmax lesion) by the mean SUV of the non-affected liver (SUVmean liver). The SUVmean of the liver was determined in part of the liver without tumorload (detected on MR/CT imaging) with using a cirkel ROI of 50 pixels. In case of extraregional localization of 18F-FCH uptake in the surround-ing or contralateral mesenterial, bone or lung tissue was used as mean reference, depending on the location of the lesion (SUVmean tissue).

Diagnosis, staging and treatment selection was made according to the AASLD criteria [5; 6; 29]. The primary diagnosis was based on one or two imaging modalities consistent with HCC: MR imaging with Gadolinium contrast or with additional hepatobiliary contrast EOB-DTPA (Primovist®, Bayer, Germany) were used to confirm diagnosis. The MR was performed with a 1.5 Tesla MRI scanner (Avanto, Siemens Medical System, Erlangen). MR series consisted of conventional m- and opposed-phase imaging, coronal T2 fatsat, diffusion weighted echo planar imaging, T2w HASTE, pre- and post-contrast T1 fatsat. Hepatobiliary phase images, if used, were made at 20 minutes post-injection. The images were evaluated on characteristic morphology of the lesion. Hyperintensity on the arterial T1w series with subsequent loss of signal intensity (wash-out) on the portal T1w series was diagnostic for HCC. As secondary imaging modality multiphasic CT imaging was used. CT images consisted of pre-contrast, arterial, portal/venous, and late series. Characteristics of HCC included hyperintensity on the arterial phase and subsequent wash-out during portal or late phase of imaging. Whenever histo-pathology was obtained this was used as final standard of reference. The histological specimen was ob-tained by biopsy or resection. In 1 patient (18 years old) the 4 hepatic lesions were primarily diagnosed as HCC and after resection diagnosed as hepatic blastomas [31]. The 18F-FCH PET/CT imaging data from this patient were excluded from analyses.

Staging and extent of the disease was assessed with standard of care using CT thorax and abdomen [5]. Size, location, and additional hepatic lesions were noted. Abdominal lymph nodes and lung nodules larger than 1 cm in short axis were considered enlarged in patients without underlying inflamma-tory hepatic disease, and larger than 2 cm in patients with inflammatory hepatic disease. No radiologi-cal screening for bone lesions was performed as part of standard of care [5]. Results of 18F-FCH PET/CT imaging were always checked on primary imaging, additional investigation, or close follow-up, especially when treatment might be altered based on the results. See flowchart of the study (figure 3).
Statistical analysis was performed using SPSS 20 (IBM Corporation, Chicago, IL). Descriptive statistics were used to assess study population. A Kaplan Meier estimator plot of cumulative survival was made. An ROC curve was performed to assess the cut-off for the SUV-ratio. Mann Whitney test was used to assess continuous factors. Pearson’s Chi square and Fisher’s exact correlation tests were used for categorical data analyses. Sensitivity and specificity were based on the McNemar test. The positive and negative predictive value of the test was calculated and the confidence interval of the proportions was based on the Wilson procedure without correction for continuity [30]. All statistical tests were evaluated at the 5% level of significance.

Diagnosis in the 29 patients with HCC was confirmed with histopathology in 17 patients (14 resection specimen, 3 biopsy specimens). In 12 patients diagnosis was based on imaging. Curative treatment was performed in 13 patients with resection and 1 patient with RFA. Palliative care was performed in 15 patients: 6 with TACE and 9 with Sorafenib (with or without local treatment with RFA and/or TACE). One patient died of other causes and was excluded from survival analyses. Eleven patients died due to spread of the disease. Seventeen patients were alive in February 2013 when follow-up closed. The cumulative survival is shown in figure 4.

In all, 29 patients with 81 lesions on baseline 18F-FCH PET/CT were evaluated: 53 intrahepatic HCC and 28 extrahepatic lesions. Results are shown in the flowchart and online supplement Table I. The ROC of SUVratio on baseline PET/CT imaging was performed, with Figure 5), resulting in a SUV-ratio cut-off of 1.12 (sensitivity 0.912; specificity 1.0).

35/53 (66%) intrahepatic lesions were typical HCC on standard imaging and 18/53 (34%) lesions were missed, atypical, or non-HCC on standard imaging (online supplement Table I). The additional findings were found correct on imaging, additional investigation, or by means of follow-up (online supplement Table I). Extrahepatic lesions were found on standard imaging in 4/28 (14%) lesions. 18/28 (64%) lesions were missed, atypical, or non-HCC on standard imaging and found correct on standard imaging, additional investigation, or by means of follow-up (online supplement Table I). The remaining 6 lesions (4 patients) did not have reference on standard imaging or additional investigation; however, if lesions were found positive this would not have changed treatment in 3/4 patients, therefore no additional investigation needed to be performed. In 1/4 patient there was no thorax imaging to corroborate additional lung and lymph node lesions detected on 18F-FCH PET/CT. This might have changed treatment strategy from local therapy (TACE) to Sorafenib. Future follow-up will have
to determine the extent of disease. These 6 lesions were excluded from $^{18}$F-FCH PET/CT SUV ratio evaluation for extrahepatic disease. AFP was not significant for increased SUV ratio of SUV max of the lesion (0.941 and $P = 0.825$). AFP was significant for overall survival: patients with $\text{AFP}>30$ had worse survival compared to patients with normal AFP levels ($P = 0.003$).

With intra- and extrahepatic lesions combined, a total of 36 additional lesions on $^{18}$F-FCH PET/CT imaging were found in 17/29 (59%) patients. This led to change in 15/29 (52%) patients (flowchart). In 1/30 patient the intrahepatic lesion was photopenic on $^{18}$F-FCH PET/CT, but typical HCC on standard imaging. Final histopathology of the resection specimen showed moderately differentiated HCC. Baseline $^{18}$F-FCH PET/CT imaging for intrahepatic HCC showed a sensitivity of 88% (CI 76-94%; Table 2), with median SUV ratio of 1.95 ± 0.66 (range 1.14 - 4.24) for positive lesions. Baseline $^{18}$F-FCH PET/CT imaging for extrahepatic lesions showed a sensitivity of 100% (CI 82-100%); with median SUV ratio of 4.41 ± 3.62 (2.48-13.80) for positive lesions (Table 2).

In 6 patients treatment evaluation $^{18}$F-FCH PET/CT was performed. Results are shown in the flowchart and online supplement Table II. In 4/6 patients evaluation of treatment was possible with $^{18}$F-FCH PET/CT and showed identical results as standard imaging: No recurrence in one patient and progressive disease in 3 patients. Progressive disease presented as increase of SUV ratio (Supplement Table II, indicated under PET/CT with $\uparrow$) and/or presence of new (extrahepatic) lesions on $^{18}$F-FCH PET/CT (figure 3C). Additional findings were made with the $^{18}$F-FCH PET/CT: In 1/6 treatment evaluation $^{18}$F-FCH PET/CT showed extrahepatic disease (lung and adrenal gland), while standard imaging of the patient showed no new disease or recurrence as the findings were outside the imaging field. Finally, one patient showed progressive disease on $^{18}$F-FCH PET/CT imaging and standard imaging by increased size and number of lesions. However, treatment evaluation and additional follow-up $^{18}$F-FCH PET/CT showed decrease in SUV ratio.

**TABLE 2** — Sensitivity and specificity of baseline FCH PET/CT

<table>
<thead>
<tr>
<th></th>
<th>FCH PET/CT intrahepatic lesions *</th>
<th>FCH PET/CT extrahepatic lesions **</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCC</td>
<td>No HCC</td>
</tr>
<tr>
<td>FCH positive</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Sensitivity</td>
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<td>Specificity 1,0</td>
</tr>
<tr>
<td>FCH negative</td>
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<td>3</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>1,0</td>
<td>Specificity 1,0</td>
</tr>
</tbody>
</table>

* 6 INTRAHEPATIC LESIONS WERE EXCLUDED FROM ANALYSES BECAUSE NO REFERENCE FOR DIAGNOSIS WAS AVAILABLE.
** 7 EXTRAHEPATIC LESIONS WERE EXCLUDED FROM ANALYSES BECAUSE NO REFERENCE FOR DIAGNOSIS WAS AVAILABLE.
PPV = POSITIVE PREDICTIVE VALUE
NPV = NEGATIVE PREDICTIVE VALUE (NPV IS CALCULATED FOR HCC LESIONS, WITH ONLY ONE NON-HCC LESION. THIS NPV CAN THEREFORE NOT BE USED TO CONCLUDE ON NON-HCC LESIONS WHICH ARE ASSUMED NEGATIVE USING $^{18}$F-FCH PET/CT.)
Cumulative survival curve of patients in this study treated with curative and palliative care. Median 2-year survival for patients treated with curative intent was 75% compared to 40% for patients treated with palliative care.

ROC curve. The cut-off with highest sensitivity and specificity was an SUV ratio of 1.12.

A: Shows a hyperintense hepatic HCC lesion in segment 2/3 on coronal, sagittal and transverse 18F-FCH PET/CT images (center of the orange cross).

B: Shows a hyperintense peritoneal lesion compared to surrounding mesentery, suspect for HCC metastasis. Standard imaging missed this lesion, and additional biopsy proved HCC. (From left to right: coronal, sagittal and transverse 18F-FCH PET/CT images).

C: Shows a hyperintense area in the left femur head of a patient with HCC (center of the orange cross). The patient developed local pain in that area, which was successfully treated with radiotherapy.
### Suppl Table I

<table>
<thead>
<tr>
<th>Additional findings on FCH PET/CT imaging in primary imaging</th>
<th>Treatment</th>
<th>Standard imaging</th>
<th>PET/CT baseline</th>
<th>Standard imaging</th>
<th>PET/CT post-treatment</th>
<th>Treatment Implications</th>
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<tr>
<td>NA</td>
<td>Additional investigation not applicable;</td>
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<td></td>
<td></td>
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<tr>
<td>NF</td>
<td>No reference for findings on ¹⁸F-FCH PET/CT;</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>B</td>
<td>Additional investigation: biopsy HCC;</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>B -</td>
<td>Additional investigation: biopsy no HCC;</td>
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<tr>
<td>I</td>
<td>Additional investigation: imaging HCC;</td>
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<tr>
<td>I -</td>
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<td>H</td>
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<tr>
<td>F</td>
<td>Additional investigation: follow-up HCC (typical HCC, or increase in size and number);</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>F -</td>
<td>Additional investigation: follow-up no HCC (no typical HCC, or increase in size or number);</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>*</td>
<td>False negative HCC lesion on ¹⁸F-FCH PET/CT</td>
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### Suppl Table II

<table>
<thead>
<tr>
<th>Treatment &amp; Lesions</th>
<th>Standard imaging 1</th>
<th>PET/CT baseline</th>
<th>Standard imaging 2</th>
<th>PET/CT post-treatment</th>
<th>Conclusion</th>
</tr>
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<tr>
<td>ID_05 TACE</td>
<td>Hepatic lesion</td>
<td>Yes</td>
<td>Yes</td>
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<td></td>
<td>Lung node I</td>
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<td>Yes</td>
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<tr>
<td></td>
<td>Lung node II</td>
<td>No</td>
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<td>ID_06 Sorafenib I</td>
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<td></td>
<td>Skeletal lesions</td>
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<tr>
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<td>Lung node</td>
<td>Yes</td>
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<tr>
<td>ID_07 Resection</td>
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<td></td>
<td>Lung lesions</td>
<td>No</td>
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<tr>
<td></td>
<td>Adrenal glands</td>
<td>No</td>
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<td>Sorafenib</td>
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<td>ID_12 Resection</td>
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<td></td>
<td>Lung lesions</td>
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<td>Yes</td>
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<td>ID_28 TACE &amp; Sorafenib</td>
<td>Hepatic lesions</td>
<td>Yes</td>
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<td>Lung nodes</td>
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</table>

↑ Increase in size, number, or SUV ratio.
↓ Stable disease; stable SUV ratio.
↓ Decrease in size, number, or SUV ratio.
*I*R Standard imaging in retrospect HCC
* Clinical progressive disease with elevated AFP.
** Additional investigation proved HCC.
(histopathology, imaging)
This study showed that the 18F-FCH PET/CT can depict intrahepatic HCC with 88% accuracy. Second is the detection of extrahepatic disease on 18F-FCH PET/CT which is not visible on standard imaging. Finally, the results suggest the option for a potential novel way to evaluate the biological response to treatment.

In case HCC shows no extrahepatic spread of the disease, ablative local regional treatment is possible. However, extrahepatic metastases are not uncommon and treatment of these patients is restricted to palliative systemic treatment with poor prognosis. Therefore, accurate pre-treatment staging of HCC is crucial. Our study shows that in over half of the included patients additional lesions were found on 18F-FCH PET/CT imaging, with treatment implications in 50% of patients. The additional value of the 18F-FCH PET/CT lies in accurate whole body assessment in regards to extent of disease which has direct implications for staging and treatment decisions. Sensitivity for the 18F-FCH PET/CT for hepatic HCC was 95% and for extrahepatic HCC sensitivity was 100%.

In this study, 6 patients underwent post-treatment 18F-FCH PET/CT imaging and based on 18F-FCH PET/CT treatment evaluation was accurate compared to standard imaging.

Local effects after TACE, RFA, or Sorafenib including necrosis in the lesion were shown as decrease in SUVratio as an indication of altered tumor metabolism. Also, recurrence of HCC after RFA and TACE or detection of new (extrahepatic) lesions shows on 18F-FCH PET/CT and could be used for follow-up of HCC patients. Song M et al. used SUVratio (SUVmax / SUVmean liver) as a method to evaluate HCC lesions with 18F-FDGPET/CT. The authors concluded that with this method tumor progression can be predicted. The use of SUVratio is especially useful with underlying parenchymal disease like a cirrhotic liver, which affects the tracers’ uptake. The patient is his or her own control as the surrounding liver is used as reference and in this way the SUVratio better represents tumor metabolism in light of underlying disease. Hypothesis generating 18F-FCH PET/CT imaging could be used in the future for a modified RECIST for HCC. One patient, who underwent a total of three 18F-FCH PET/CT studies, showed results that differed from the expected results: The first two 18F-FCH PET/CT studies showed positive hepatic disease with extrahepatic spread with progression both in size and in SUVratio. The final 18F-FCH PET/CT study, after several months of Sorafenib use, showed decrease in SUVratio of the hepatic lesion (extrahepatic disease positive). The size of hepatic involvement did increase, as well as serum AFP, and the number of extrahepatic lesions. This decrease in SUVratio could be explained by dedifferentiation of the hepatic lesion during the course of the disease, resulting in no uptake of 18F-FCH. Studies show that 18F-FCH is most sensitive in well- and moderately differentiated HCC, and less in poorly differentiated hepatic HCC lesions.

When patients present with typical HCC and a history of another malignancy, lung lesions for example are difficult to characterize on imaging as one or the other. 18F-FCH PET/CT imaging in this study was sensitive in differentiating extrahepatic HCC lesions from renal cell carcinoma and urothelial carcinoma. A study by Talbot et al. suggests that 18F-FCH PET/CT imaging does not show uptake in colorectal liver metastases. However, further study will have to determine whether colorectal lung metastases do show up on 18F-FCH PET/CT imaging and could differentiate between both entities.

The SUVratio might also have prognostic value as was shown by Morris et al for breast cancer. MR imaging is the most sensitive imaging modality for (small) HCC lesions as it has the potential to combine dynamic evaluation of the lesion, in and out phase, and diffusion images. The latter is useful for detection of very small lesions (<2 cm) and this method increases detection of possible HCC lesions. The additional value of the 18F-FCH-PET/CT is therefore not intrahepatic, but extrahepatic: to evaluate metastatic disease.

This study has some limitations. The inclusion of patients was not consecutive due to logistical and evaluation of 18F-FCH PET/CT images was performed by one experienced nuclear medicine physician. Logistics of 18F-FCH PET/CT imaging might impair its use as synthesis of the 18F-FCH tracer and the possibility of PET/CT imaging are not available in every medical center. Finally, PET/CT imaging is costly when implemented in pre-treatment work-up for patients with HCC. However, accurate pre-treatment staging will prevent unnecessary interventions including expensive surgery, TACE and experimental local treatment. This study has a limited number of patients and therefore further investigation in a larger cohort is warranted to confirm our findings and to determine in more detail at what timepoint the FCH PET/CT is most valuable for the individual patient. A study with prospective design, including consecutive patients with HCC confirmed on imaging is preferable. Nuclear medicine physician(s) should be blinded for outcomes of standard imaging and abdominal radiologist(s) evaluating standard imaging should be blinded for outcome of PET/CT imaging. If possible results should be discussed in MDT to discuss outcomes of both imaging modalities to maximize treatment options and evaluation.

This study shows additional value of 18F-FCH PET/CT to conventional imaging in assessment of extent of intra- and extrahepatic disease in patients with HCC. 18F-FCH PET/CT has additional value in accurate assessment of hepatic involvement, and by Lee et al for HCC.

MR imaging is the most sensitive imaging modality for (small) HCC lesions as it has the potential to combine dynamic evaluation of the lesion, in and out phase, and diffusion images. The latter is useful for detection of very small lesions (<2cm) and this method increases detection of possible HCC lesions. The additional value of the 18F-FCH-PET/CT is therefore not intrahepatic, but extrahepatic: to evaluate metastatic disease.

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References

Staging laparoscopy in patients with hepatocellular carcinoma: is it useful?

Lisette T. Hoekstra
Matthanja Bieze
Olivier R. C. Busch
Dirk J. Gouma
Thomas M. van Gulik

Surgical Endoscopy (2013) 27:826–831
OBJECTIVE

Staging laparoscopy (SL) is not regularly performed for patients with hepatocellular carcinoma (HCC). It may change treatment strategy, preventing unnecessary open exploration. An additional advantage of SL is possible biopsy of the nontumorous liver to assess fibrosis/cirrhosis. This study aimed to determine whether SL for patients with HCC still is useful.

SUBJECTS AND METHODS

Patients with HCC who underwent SL between January 1999 and December 2011 were analyzed. Their demographics, preoperative imaging studies, surgical findings, and histology were assessed.

RESULTS

The 56 patients (34 men and 22 women; mean age, 60 ± 14 years) in this study underwent SL for assessment of extensive disease or metastases. For two patients, SL was unsuccessful because of intraperitoneal adhesions. For four patients (7.1%), SL showed unresectability because of metastases (n = 1), tumor progression (n = 1), or severe cirrhosis in the contralateral lobe (n = 2). An additional five patients did not undergo laparotomy due to disease progression detected on imaging after SL. Exploratory laparotomy for the remaining 47 patients showed 6 (13%) additional unresectable tumors due to advanced tumor (n = 5) or nodal metastases (n = 1). Consequently, the yield of SL was 7% (95% confidence interval, 3–17%), and the accuracy was 27% (95% CI, 11–52%). A biopsy of the contralateral liver was performed for 45 patients who underwent SL, leading to changes in management for 4 patients (17%) with cirrhosis.

CONCLUSION

The overall yield of SL for HCC was 7%, and the accuracy was 27%. When accurate imaging methods are available and additional percutaneous liver biopsy is implemented as a standard procedure in the preoperative workup of patients with HCC, the benefit of SL will become even less.

INTRODUCTION

Hepatocellular carcinoma (HCC), the sixth most common malignancy worldwide [1, 2], varies greatly in geographic occurrence and corresponding risk profile. Chronic hepatitis B and C are predominant risk factors in the development of HCC, but the strongest correlation between underlying disease and HCC development is seen with the cirrhotic liver, in which 80% of HCCs occur [1], making this the greatest predisposing factor (Table 1). The Barcelona-Clinic Liver Cancer (BCLC) classification [4] generally used as the standard classification for HCC was endorsed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) [5, 6]. The AASLD has established a set of criteria for the diagnosis of HCC. The current guidelines recommend radiologic imaging, such as computed tomography (CT) and magnetic resonance imaging (MR) imaging. When both of these imaging methods show a hypervascular lesion in the arterial phase with signs of washout during the portal or late phase, an HCC is most likely. Subsequently, this classification offers a link between the tumor stage and its treatment strategy. The preferred treatment for early-stage HCC is surgical resection, liver transplantation, or percutaneous ablation with curative intent [7, 8], depending on the size and number of lesions and the liver function. The long-term outcome for this group of patients is good, with a 5-year survival rate of 50–70% [3, 9]. Although radiologic imaging is a noninvasive method for the staging of malignant disease, additional staging laparoscopy (SL) still is used for a variety of malignancies including esophageal cancers [10], gastric cancers [11, 12], adenocarcinoma of the pancreas [13, 14], and hilar cholangiocarcinoma [15, 16]. In the case of hepatic lesions, SL could offer the additional benefit of a nontumorous liver parenchyma biopsy for assessment of fibrosis and cirrhosis. Based on additional findings, SL may change the treatment strategy for patients with HCC and patients found to be unresectable, avoiding an unnecessary laparotomy and thereby decreasing operative morbidity, complications, and length of hospital stay [17]. Therefore, studies from the University of Hong Kong supported the use of laparoscopic staging procedures before a planned laparotomy for HCC patients [18–21]. Patients with HCC that appears to be resectable on preoperative imaging may benefit from SL for evaluation of the location, size, and number of hepatic lesions; the presence of metastases; and the assessment of cirrhosis and fibrosis. However, this procedure is not regularly used for patients with HCC, and no criteria are currently known to increase the yield of SL. Therefore, this study aimed to assess the outcomes of SL in the management of HCC to determine whether this procedure still is useful for patients with HCC.
METHODS

The study analyzed 1,156 consecutive patients with HCC who underwent SL between January 1999 and December 20. All the patients undergoing SL were believed to have resectable tumors after initial imaging. The patients’ demographics, preoperative imaging studies, surgical findings, resectability, operative data, and histopathologic reports were analyzed. The diagnosis of HCC was confirmed in accordance with the guidelines of AASLD. These guidelines state that at least one imaging method (CT, MR imaging, or ultrasonography) should show arterial enhancement with subsequent loss of contrast during the venous or portal phase of imaging (“washout sign”). This is especially true for lesions occurring in the background of hepatitis, hemochromatosis, and cirrhosis, with or without elevated serum alpha-fetoprotein levels.

The standard diagnostic workup included a multiphase CT scan, MR imaging, or dynamic ultrasound of the liver as required. The diagnosis was defined by CT scan using a four-phase (blanc, arterial, portal, and late venous phase) 2.5-mm, thin-slice, contrast-enhanced CT or multiphase MR imaging with dynamic T1 contrast sequence (arterial, portal, and late venous phase [VIBE]), T2 and diffusion weighted sequences. No official imaging criteria exist for the detection of cirrhosis and fibrosis. A multidisciplinary team consisting of a liver surgeon, hepatologist, gastroenterologist, and (interventional) radiologist evaluated the imaging studies and came up with a proposal for the treatment of patients with HCC. In general, liver resection was not indicated for patients with extrahepatic or nodal metastases, main portal trunk or inferior vena cava invasion or thrombus, or multicentric bilobar HCC. Most patients with Child-Pugh B and all patients with Child-Pugh C were excluded from resection. If the aforementioned criteria were met, and the patient was in overall good condition to undergo resection, the HCC lesions considered for resection included one lesion involving no more than one liver lobe without vascular involvement of the remaining liver lobes and up to three lesions smaller than 3 cm (including lesions suitable for curative radiofrequency ablation in the contralateral segments). Preoperative assessment of future remnant liver volume and function included respectively CT volumetry and Tc-labeled mebrofenin hepatobiliary scintigraphy (HBS) with single-photon emission computed tomography (SPECT) [22]. The volumes of the total liver (TLV), tumor (TV), and future remnant liver (FRLV) were assessed preoperatively. The percentage of FRL then was calculated according to the following formula: FRLV x 100 / (TLV - TV). If the FRLV was more than 30% in healthy liver parenchyma or more than 40% in cirrhotic parenchyma (Child-Pugh A and B), the patient was considered eligible for surgery. Otherwise, portal vein embolization was chosen to be performed after SL. A cutoff value for an FRL function of 2.69%/min/m2 identified patients at risk for the development of postoperative liver failure [23].

With the patient under general anesthesia, SL was performed as a separate procedure, and the patient was positioned in the supine position. A TrocDoc trocar was inserted through a semicircular, subumbilical incision for optimal visualization of the entire liver. Carbon dioxide (CO2) pneumoperitoneum at 14 mmHg was instituted, and two additional 5-mm trocars were positioned in the right and left subcostal spaces. Both the right and left lobes of the liver were systematically examined to identify any suspicious lesions. Additionally, distant sites were examined for metastases. Laparoscopic ultrasound also was performed for further location of hepatic lesions and for exploration of metastases.

However, this imaging method was used only in the beginning of the study because it was found later to be less useful. For suspicious lesions, biopsies were taken and microscopically analyzed by the pathologist. If no metastases or other signs of unresectability were found, liver resection was planned.

Major liver resections were defined as resections of three or more Couinaud segments. Minor resections were hepatectomies of fewer than three liver segments, including wedge resections and metastectomies. Hematoxylin and eosin (H&E) sections of the resection specimens were thoroughly examined by an experienced liver pathologist for assessment of well-differentiated or poorly differentiated HCC in addition to determination of fibrosis/cirrhosis of the liver parenchyma. In case of uncertainty, slides were evaluated with immunohistochemical staining using keratin 19 for poorly differentiated HCC.

STATISTICAL ANALYSIS

The data were analyzed using statistical software (SPSS 18.0; SPSS, Chicago, IL, USA). Yield was defined as the total of avoided laparotomies divided by the total number of patients undergoing SL. Accuracy was assessed by dividing the total of avoided laparotomies by all the patients with unresectable disease. Data are presented as mean ± standard deviation unless otherwise stated. The results were considered statistically significant when P was lower than 0.05.
RESULTS

A total of 56 patients (34 men and 22 women) with a mean age of 60 ± 14 years underwent SL. All 56 patients had undergone preoperative CT scans. An MR image of the liver was obtained for 15 patients (27%). For 56 patients (64%) a Tc-labeled mebrofenin HBS with SPECT was performed preoperatively to assess liver functional reserve. Based on the preoperative imaging results, cirrhosis was predicted for 15 (26.8%) of the 56 patients and fibrosis for 2 of the patients (3.6%). All the patients were discussed in a multidisciplinary conference and deemed potentially resectable.

STAGING LAPAROSCOPY

The patients for whom surgical treatment was planned are summarized in Fig. 1. For 2 (3.6%) of the 56 patients, SL was unsuccessful because of intraabdominal adhesions. For 4 (7.1%) of the 56 patients, SL showed unresectability because of metastases (n = 1), tumor progression in patients with unexpected severe cirrhosis (n = 1), or severe cirrhosis, particularly in the non–tumor-bearing contralateral lobe (n = 2). Laparoscopic ultrasound was performed for 8 (14.3%) of the 56 patients. For two of these patients, severe cirrhosis of the liver was confirmed by ultrasonography. This did not result in a change in treatment strategy. A biopsy of the liver parenchyma on the nontumorous lobe was performed for 45 (80.4%) of the 56 patients during SL. Of these 45 patients, 23 (51.1%) showed cirrhosis and 28 (62.2%) showed fibrosis, leading to changes in management for 4 (17.4%) of the 23 patients with cirrhosis.

One complication, urinary retention, recorded after laparoscopy was managed by transurethral catheterization and bladder training. None of the patients experienced postoperative ascites as a result of SL. No in-hospital mortality was observed. The median hospital stay for laparoscopy was 3 days (range, 2–6 days). Subsequent laparotomy was cancelled for five patients because of disease progression based on imaging studies after SL. The median interval between SL and subsequent imaging was 39 days (range, 8–73 days). The median time between laparoscopy and explorative laparotomy was 37 days (range, 0–112 days; n = 47).

LAPAROTOMY

Exploratory laparoscopy for the remaining 47 patients showed resection to be impossible in an additional 6 cases (13%, Fig. 1) due to peritoneal seeding (n = 1), advanced tumor (n = 4), or distant nodal metastases (n = 1). Consequently, the accuracy of SL was 77% (47/60; 95% confidence interval [CI], 71–83%), and the yield was 74% (47/60; 95% CI, 63–85%). Histopathologic examination confirmed the diagnosis of HCC for all the resected patients (n = 41). Microscopic examination of the liver parenchyma in the resection specimens showed fibrosis (n = 19), steatosis (n = 23), cholestasis (n = 4), or cirrhosis (n = 23). The pathology outcomes for cirrhosis were in accordance with the results of biopsies during laparoscopy showing cirrhosis. Staging laparoscopy showed 23 patients with cirrhosis, leading to treatment changes for 4 patients. For the remaining 19 patients, microscopic examination of the resection specimens similarly showed cirrhosis. Cirrhosis was found in biopsies taken during laparotomy for another four patients. Microscopic examination of the specimen after surgery showed fibrosis in 19 patients. For 16 of these patients, fibrosis was already visible in the biopsies taken during SL. Fibrosis was detected in the biopsies of three patients taken at laparotomy. Hepatitis B was shown in 5 patients, and for 11 patients a diagnosis of hepatitis C was determined. In 10 (24%) of 41 patients, recurrent or metastatic disease was detected after a median follow-up period of 15 months (range, 3–28 months). Five of nine patients who showed recurrence of the primary tumor presented with local recurrence, and the four remaining patients had new lesions. Two patients also showed lung or lymph node metastases. Only one patient showed lung metastases. No recurrence of primary tumor or metastases was found in 31 (76%) of 41 patients during the median follow-up period of 10 months (range, 3–47 months).

Because liver resection is the only curative treatment option for HCC, adequate staging and selection for putative resection are mandatory. Although preoperative staging for malignancies is readily achieved by conventional imaging studies, a considerable number of unresectable disease is still detected at laparotomy. Staging laparoscopy is used to avoid these unnecessary laparotomies. This study examined the additional value of SL for patients with a diagnosis of HCC. The findings show that in the end, laparotomy was not indicated for 27% (15/56) of cases and that only 7% (4/56) of the unresectable cases were detected by SL. We therefore conclude that although SL is safe for patients with HCC, its use in clinical practice is questionable because of its low yield and poor accuracy.
The amount and quality of the available literature on staging SL in HCC is limited. Two studies reported that 40–70% of patients with liver malignancies showed unresectable disease at laparotomy [24, 25]. In 1994, Babineau et al. [26] found that 48% (14/29) of patients with liver malignancies were not resectable at laparoscopy due to metastases (n = 10) or cirrhosis (n = 4), including six patients with HCC. Based on these results, the authors advised that diagnostic laparoscopy should be performed before laparotomy. The findings of Lo et al. [19, 20] a few years later were in line with this statement. These authors concluded that laparoscopy with laparoscopic ultrasonography should precede a planned exploratory laparotomy for HCC. Another study in 2008 arrived at the same conclusion that laparoscopy and laparoscopic ultrasound can identify surgically unresectable disease and thus can select optimal treatment [18].

In contrast to these reports, we showed in the current series that SL found only 7% of the patients to be unresectable. This rate is too low to justify routine performance of the procedure. This discrepancy with others suggests that SL is applicable only for a selected group of patients. An explanation for the low yield in our patients may be the increased accuracy of imaging methods for detection and staging of HCC in recent years, resulting in more accurate selection of resectable disease during the diagnostic workup in the ASLD guidelines. As the diagnostic workup is performed before laparotomy, the histopathologic results were consistent with the typical vascular enhancement pattern on contrast-enhanced CT or MR imaging is sufficient to confirm the diagnosis of HCC. The Asian Oncology Summit statement does not have the size limitation and applies the same criteria also to smaller lesions [27]. Diagnosis therefore leans heavily on arterial enhancement, with subsequent washout of the HCC lesion during portovenous or a late phase of scanning. A major limitation lies in the smaller HCC that presents without typical enhancement given the fact that early HCC often is hypovascular [28]. New and improved imaging tools have been implemented to increase the accuracy of detection. The multiphase CT scan currently is mostly performed with a 64 detector row unit, making more detailed evaluation of the lesion possible. Ultrasonography also has become more accurate in recent years, especially since the introduction of contrast-enhanced ultrasonography [26]. The most progressive innovations have been made with MR imaging. First, detection of fat, glycogen, copper, and iron content in the lesion is possible with MR imaging, which helps to discriminate between liver lesions [30]. Also, small lesions (<2 cm), which might remain undetected by CT scanning, are depicted with the diffusion weighted MR images [31, 32]. Overall, improved imaging methods have increased the accuracy of HCC detection and staging, rendering SL an inefficient, additional invasive procedure in the absence of careful patient selection.

At the onset of our study, SL was thought to have an additional value in terms of assessment of (the grade of) fibrosis and cirrhosis. In our study, imaging techniques identified only 15 patients (26.8%) with cirrhosis and 2 patients (3.6%) with fibrosis before laparoscopy, although at SL, 23 (51.1%) and 28 (62.2%) patients, respectively, showed these compromised livers. Biopsies of the nontumorous liver parenchyma taken during SL also proved reliable because the histopathologic results were consistent with the final diagnoses made in the resection specimens performed during explorative laparotomy. However, a histologic diagnosis of parenchymal disease also may be obtained by percutaneous core biopsy of the nontumorous liver parenchyma, which in this series was omitted because the scheduled SL would provide biopsies anyway. In addition, a recent study with transient elastography showed promising results for non-invasive assessment of fibrosis and cirrhosis in patients with compromised livers. Hence, if the diagnostic workup includes accurate imaging methods and a preoperative percutaneous liver biopsy for histologic diagnosis of parenchymal disease is implemented in the workup, the benefit of performing SL before resection will become even less.

Our study had some limitations. First, the study contained only a small number of patients. Second, the AASDL criteria were gradually implemented in our center after 2008. Therefore, not all patients followed the same diagnostic protocol, and the diagnosis occasionally was based on one conclusive imaging method or biopsy of the tumor. Third, the median interval between SL and liver resection was 36 days (range, 0–88 days) for patients undergoing resection (n = 41), during which time tumors may have progressed. This delay was mostly related to intercurrent infectious complications (urinary tract infection or pneumonia) or preoperative preparation (portal vein embolization, n = 1). We initially performed SL for all HPB tumors. Routine SL was abandoned first for pancreatic tumors because of decreased yield and accuracy, largely due to improved imaging techniques, especially thin-sliced, contrastenhanced CT [33]. Next, we stopped performing routine SL in hilar cholangiocarcinoma for the same reasons [34]. Currently, we finish our evaluation of SL in HCC with the same conclusions. This overview of studies leads us to conclude that in this era, routine SL for HPB tumors should no longer be performed. Another point to consider is that laparoscopic liver resections currently are used increasingly, also for HCC in cirrhotics [35]. Examination of the intraperitoneal cavity and the liver with laparoscopic ultrasonography then would obviously precede resection in the same session.

In conclusion, the overall yield and accuracy of SL for HCC were 7 and 27%, respectively. When accurate imaging methods are available and additional percutaneous liver biopsy is implemented as a standard procedure in the preoperative workup of patients with HCC, the benefit of SL will become even less.


Outcomes of treatment of patients with hepatocellular carcinoma in a Dutch, non-liver-transplant center

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Dave Sprengers
Joanne Verheij
Thomas M. van Gulik
Otto van Delden
OBJECTIVE

In the Netherlands hepatocellular carcinoma (HCC) has shown an increased incidence in the past decades. The aim of this study was to assess the HCC patient population along with outcomes of treatment in a single tertiary, non-livertransplant medical center. Survival of patients treated with TACE was assessed.

SUBJECTS AND METHODS

Retrospective, single tertiary center study including data from consecutive patients with HCC collected from pathology, radiology and surgery records. Patient demographics and characteristics were recorded. A multi-disciplinary team evaluated patient data and results of (additional) investigations to institute appropriate treatment according to European guidelines. First and second treatment was noted, follow-up and outcome was assessed.

RESULTS

From February 1999 to February 2012 a total of 224 patients were included with definitive diagnosis of HCC. Median age was 62 years (male/female 172/56). Patients had cirrhosis in 156/224 (70%) of cases. Fifty-two (23%) patients were enrolled in an HCC screening program. Patients treated with curative intent had a median 2-year survival of 80%, patients treated with palliative intent had a median 2-year survival of 26%. Patients undergoing transarterial embolization (TACE) had a median 2-year survival of 35% (n = 80). Factors associated with overall survival after multivariate analysis were elevated aspartate transaminase (AST), low albumine, ascites, size of the largest lesion, and macrovascular involvement (P = 0.003, P = 0.042, P = 0.020, P < 0.001 and P < 0.001 respectively).

CONCLUSION

Our series of HCC patients in a Dutch non-liver-transplant center shows similar survival as the current literature. Factors associated with survival were elevated AST, low albumine, presence of ascites, macrovascular involvement, and size of the largest HCC lesion.

INTRODUCTION

Any condition causing cirrhosis, fibrosis, inflammation and loss of normal hepatic parenchyma can eventually lead to hepatocellular carcinoma [1-4]. The specific risk factors explain the unique distribution of HCC worldwide [5-8]. Hepatitis B virus (HBV) is the dominant risk factor resulting in a high prevalence of HCC especially in Asia and Africa [7]. This in contrary to Europe, were hepatitis C virus (HCV) is the main risk factor [6].

The management of HCC in the Netherlands has evolved in the last decade, as patients in high risk groups now undergo routine screening, potentially leading to detection of disease in an early stage. Furthermore, imaging work-up has been improved and local treatment has become more readily available. The number of patients diagnosed with primary liver carcinoma or intra-hepatic cholangiocarcinoma increased with 60% over the past decade from 340 new patients in 2001 to 544 in 2011 [10; 11].

A multidisciplinary tumor board has therefore been installed in 2008 at our tertiary referral center for gastro-intestinal oncology center. Based on prognostic factors for survival, various guidelines and algorithms for diagnosis and treatment have been established to improve care for the increasing group of patients [12; 13]. Diagnosis of HCC in Europe is based on criteria defined by the ‘European association for the study of the liver’ (EASL) [12; 14]. In combination with the criteria composed by the Barcelona-Clinic Liver Cancer (BCLC) group diagnosis leads to a treatment plan with expected prognosis for specific patient groups with HCC [15]. In the BCLC algorithm approximately 30% of patients are eligible for curative treatment using liver transplantation, resection of the lesion(s), and/or radio frequency ablation (RFA). For the remaining patients palliative treatment options to improve survival include transarterial chemoembolization (TACE) [16], selective internal radiation therapy (SIRT), or medical treatment with Sorafenib [17].

Local therapy with TACE, with or without additional systemic drug therapy [18], is the preferred first step in treatment for patients who are not amenable to curative treatment options, or as a bridge to transplantation. Only patients who have limited tumor burden, absence of macrovascular invasion, no extrahepatic disease and preserved liver function are eligible for this minimally invasive technique [19]. A chemotherapeutical agent is selectively injected into the feeding branches of the hepatic artery to the tumor combined with embolization material. This technique combines high dose local chemotherapy with occlusion of the arterial blood supply to induce tumor necrosis. TACE has shown to improve overall survival in patients with HCC who have limited tumor burden, absence of macro-vascular invasion, no extrahepatic disease and preserved liver function (intermediate dis-
sases according to the BCLC schedule) [20]. When the tumor does not respond to TACE, progresses during consecutive TACE treatments or is beyond treatment criteria for TACE, systemic therapy (sorafenib) may be indicated, depending on liver function. In the end stage of the disease, with extrahepatic extent, extensive hepatic disease, or no response to systemic treatment patients will undergo symptomatic treatment only.

The aim of this retrospective study was to assess the characteristics of the patient population with hepatocellular carcinoma seen in our center, along with the outcomes of curative and palliative treatment, and to compare this Dutch patient cohort with patient cohorts from high incidence countries.

In this retrospective single center study consecutive patients who were suspected of having HCC between February 1999 and February 2012 were included. Data of patients older than 18 years of age, were analysed from patient records of the department of pathology, (interventional) radiology, hepatology, gastroenterology, and medical oncology. Time of death was checked in the database of the governmental civil registration and patients who were not registered in this database were excluded from survival analyses. The following patient characteristics were noted: demographics, patient history (including underlying parenchymal disease and cirrhosis), ethnicity, presentation of the disease, alcohol use (positive defined as female patients consuming 2 units per day and male 4), patients enrolled in a screening program (at least one ultrasound in the year before diagnosis), and Child-Pugh score.

METHODS

Diagnosis & Treatment

The diagnosis HCC was made on histology, using data from the Dutch pathology database or based on imaging techniques including multiphase CT imaging, dynamic contrast-enhanced MR imaging and ultrasound. In absence of histopathology imaging used as primary diagnostic modality. Diagnostic guidelines changed during the years of this study: Until 2012 two imaging modalities with suspicion of HCC were necessary for diagnosis [14]. Today, only one dynamic imaging study with suspicion of HCC is sufficient for diagnosis. Typical characteristics of HCC include: hyperintensity on arterial phase of imaging, with subsequent loss of contrast in the portal-venous phase (wash-out)[12]. Patient data collected from the medical files were ascites on imaging, hepatic steatosis on MR imaging, and cirrhosis was assessed with histopathology or fibroscan. No radiological screening for bone lesions was performed as part of standard work-up. Laboratory tests included liver transaminases (AST, ALT), gamma glutamyl transferase (yGT), alkaline phosphatase (Alk phos), alpha fetoprotein (AFP), and total bilirubin. A multi-disciplinary tumor board consisting of a liver surgeon, hepatologist, medical oncologist, pathologist, and (interventional) radiologist evaluated diagnosis, staging, and treatment. Patients fitting Milan criteria [21] were referred to a transplant centre and when indicated, received treatment of the lesion(s) as a bridge to transplantation with radio frequency ablation (RFA) and/or transarterial chemoembolization (TACE). Patients with more extensive disease were treated with palliative care including RFA, TACE, sorafenib, or selective internal radiation therapy (SIRT). Patients who were beyond that stage were treated according to their symptoms. Most patients underwent more than one treatment and analysis was performed on an intention to treat basis: patients were considered as either undergoing curative or palliative treatment.

A total of 249 patients were included in the overall, initial primary liver carcinoma database. All patients with another diagnosis than HCC, or inconclusive diagnosis of HCC based on the EASL criteria from 2001 or 2012 depending of time of diagnosis were excluded (n = 25). A remaining total of 224 patients were included with definitive diagnosis of HCC from February 1999 to February 2012 (Figure 1). Patient characteristics are shown in Table 1. Median age was 63 years (range 18-88 years), male 168 and female 56. Patients had cirrhosis in 156/224 (70%) of cases. Alcohol abuse was noted in 60/224 (27%) patients with or without other underlying risk factors. 42 patients (19%) had hepatitis B (HBV) and 61 (27%) hepatitis C (HVC). Fifty-two (23%) patients were enrolled in a screening program because of risk factors for HCC.

First treatment is summarized in Figure 1 (Flowchart). Curative treatment was performed in 81/224 (37%) of patients. Cirrhosis was present in 57/83 (69%) of these patients: Child A: 51 and Child B: 6 patients. 29/83 (35%) patients were enrolled in a screening program for HCC. Resection was performed in 49/83 (60%) patients, resection and RFA in 3 (4%), RFA in 16 (20%). Of the 14 (17%) patients who were on the waiting-list for liver transplantation, 7 patients underwent TACE as a treatment of the lesion(s) as a bridge to transplantation with radio frequency ablation (RFA) and/or transarterial chemoembolization (TACE). Patients with more extensive disease were treated with palliative care including RFA, TACE, sorafenib, or selective internal radiation therapy (SIRT). Patients who were beyond that stage were treated according to their symptoms. Most patients underwent more than one treatment and analysis was performed on an intention to treat basis: patients were considered as either undergoing curative or palliative treatment.

Statistical analysis was performed using SPSS 20 (IBM Corporation, Chicago, IL). Descriptive statistics were used for patients’ demographics. Mann Whitney, ANOVA, uni- and multivariate test were used to analyse continuous data. Pearson’s Chi square and the Fisher’s exact test were used for categorical data analyses. If during a specific analysis missing values were encountered, the variable was excluded from analysis. Survival was assessed with the Kaplan Meier and the Cox regression analysis. Statistical tests were evaluated at the 5% level of significance.

Results

Diagnosis, Staging & Treatment
Curative treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection</td>
<td>50</td>
</tr>
<tr>
<td>RFA + Resection</td>
<td>3</td>
</tr>
<tr>
<td>RFA</td>
<td>16</td>
</tr>
</tbody>
</table>

Palliative treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACE</td>
<td>80</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>25</td>
</tr>
<tr>
<td>Ethanol injection</td>
<td>2</td>
</tr>
</tbody>
</table>

Symptomatic treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Frequency</th>
</tr>
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</table>

The remaining 141/224 (63%) patients underwent palliative or symptomatic treatment. Cirrhosis was present in 99/141 (70%) patients, and 22/141 (16%) patients were enrolled in an HCC screening program. Patients underwent the following first treatment: 80/141 (57%) underwent TACE, 24 sorafenib (17%), 2 ethanol injection (1%), and 35 symptomatic (25%) treatment. Secondary treatment consisted of: 7 resection (these patients were down staged with local therapy and became resectable), 54 TACE, 1 SIRT, 11 sorafenib, 6 RFA, 25 symptomatic, and 35 patients received no additional treatment.

The subset of 80 patients who underwent TACE as first treatment had a median age of 67 years (44-88 years), and patient characteristics (age, sex and ethnicity) were similar compared to patients treated with curative intent. Patient had cirrhosis in 67/80 cases (83%: Child A 56, Child B 18, and Child C 6), with a median lesion size of 51 mm (13-140mm). Complications of TACE occurred in 14/80 patients: 3 patients had abdominal discomfort leading to prolonged hospital stay, 6 patients had fever (1 had additional shortness of breath, 1 delirium), leading to prolonged hospital stay. One patient had decompensated cirrhosis, requiring change of drug treatment. One patient had pleural effusion, one had a false aneurysm in the common femoral artery, and one patient had a biloma requiring drainage, and one patient had peritonitis; all patient required prolonged hospital stay.

In the overall HCC patient group the median survival was 622 days, with a 2-year survival of 44%, and a 5-year survival of 25%. Patients enrolled in a screening or surveillance programme were associated with better survival (P = 0.002). Other factors influencing survival were the following (details are mentioned in Table 2): elevated AFP (>20 U/L) P = 0.004; elevated AST/AIk phos/yGT, and bilirubine (P<0.001/ P <0.001/ P = 0.002/ P= 0.001 respectively); albumine < 35 g/L (P<0.001); Child-Pugh score B or C (P < 0.001); size of the largest lesion (Figure 2; P < 0.001);
Figure 2

A: Shows the cumulative survival of all patients included in the study in association with the size of the largest lesion per patient: 51 patients had <3cm lesion(s); 75 had 3-5cm; 45 had 5-8cm, and 44 patients had lesion(s) larger than 8cm. With increase in size of the largest lesion, survival decreases; P < 0.001.

B: This association was lost in the group of patients treated with curative intent: most patients had a low tumor load: 34 patients had <3cm lesion(s); 23 had 3-5cm; 12 had 5-8cm, and 5 patients had lesion(s) larger than 8cm.

C: Most patients with high tumor load will undergo palliative treatment or symptomatic care and size was highly associated with survival in this patient group: 17 patients had <3cm lesion(s); 32 had 3-5cm; 33 had 5-8cm, and 39 patients had lesion(s) larger than 8cm.

presence of ascites on imaging (P < 0.001), and finally macro-vascular involvement was associated with survival (P = 0.009). After multivariate analysis AST, albumine, ascites, size of the largest lesion, and macrovascular involvement remained associated with survival (P = 0.003, P = 0.042, P = 0.020, P < 0.001 and P < 0.001 respectively).

Patients treated with curative intent (n = 83) had a median survival of 1508 days, a 2-year survival of 80%, and a 5-year survival of 40% (plotted in the Kaplan Meier curve in figure 3). In this patient group survival was associated with the presence of elevated levels of AST (P = 0.01); Albumine <35g/L (P = 0.001); INR >1.7 (P = 0.009) and Child score (P = 0.047). Size of the lesions was not associated with survival: as only patients with relatively small lesions are treated with curative intent according to the standard of care. After multivariate analysis elevated AST and low albumine were associated with survival in this patient group (details are shown in supplement Table 3).

Table 2 - Features associated with survival in the overall patient group with HCC

<table>
<thead>
<tr>
<th>Mortality (n=123)</th>
<th>Alive (n=84)</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>63 (±12)</td>
<td>62 (±11)</td>
<td>0.98-1.01</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>96 (36)</td>
<td>65 (19)</td>
<td>0.71-1.52</td>
</tr>
<tr>
<td>Viral hepatitis (B and C)</td>
<td>54 (41%)</td>
<td>52 (62%)</td>
<td>0.451-0.926</td>
</tr>
<tr>
<td>Surveillance programme</td>
<td>20 (15%)</td>
<td>30 (35%)</td>
<td>1.32-3.43</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>67 (±54)</td>
<td>68 (±50)</td>
<td>0.997-1.003</td>
</tr>
<tr>
<td>ALT &gt;50 U/L</td>
<td>67 (51%)</td>
<td>45 (54%)</td>
<td>1.000-1.001</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>107 (497)</td>
<td>76 (499)</td>
<td>1.000-1.001</td>
</tr>
<tr>
<td>AST &gt;50 U/L</td>
<td>98 (74%)</td>
<td>49 (58%)</td>
<td>1.570-3.883</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>237 (±463)</td>
<td>128 (±86)</td>
<td>1.000-3.277</td>
</tr>
<tr>
<td>yGT</td>
<td>273 (±307)</td>
<td>223 (±220)</td>
<td>1.000-1.001</td>
</tr>
<tr>
<td>Bilirubine</td>
<td>23 (±23)</td>
<td>18 (±17)</td>
<td>1.01-1.02</td>
</tr>
<tr>
<td>Albumine</td>
<td>37 (±6)</td>
<td>41 (±5)</td>
<td>1.01-1.02</td>
</tr>
<tr>
<td>Albumine &gt;35 g/L</td>
<td>40 (30%)</td>
<td>12 (14%)</td>
<td>1.01-1.02</td>
</tr>
<tr>
<td>Alpha-fetoprotein (U/L)</td>
<td>2387</td>
<td>3436</td>
<td>1.01-1.02</td>
</tr>
<tr>
<td>Alpha-fetoprotein (&gt;20 U/L)</td>
<td>78 (59%)</td>
<td>36 (43%)</td>
<td>1.01-1.02</td>
</tr>
<tr>
<td>INR &gt;1.7</td>
<td>1.5 (±1.8)</td>
<td>1.1 (±0.3)</td>
<td>0.897-1.149</td>
</tr>
<tr>
<td>Child-Pugh score (0-9)</td>
<td>21 (16%)</td>
<td>9 (11%)</td>
<td>0.789-1.651</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT &gt;50 U/L</td>
<td>1.42-5.67</td>
<td>0.003</td>
<td>1.02-3.00</td>
</tr>
<tr>
<td>Albumine</td>
<td>1.07-2.16</td>
<td>0.020</td>
<td>1.01-1.02</td>
</tr>
<tr>
<td>Ascites</td>
<td>0.17-0.59</td>
<td>&lt;0.001</td>
<td>0.17-0.59</td>
</tr>
</tbody>
</table>

**Table 2**
The subgroup of 80 patients who underwent TACE as first treatment had a median 2-year survival of 35%. In this patient group survival was associated with Alk phos levels (P = 0.002); albumine <35 g/L (P < 0.001); AFP levels (P = 0.015); Child score (P = 0.035); and size of the largest lesion P < 0.001 (Figure 2C). After multivariate analysis the following features remained associated with survival in this patient group: Alk phos, albumine, AFP, and size of the largest lesion (P = 0.001, P < 0.001, P = 0.041, P < 0.001 respectively). Details are found in supplementary Table 5.

Survival of patients treated with TACE was better compared to patients beyond TACE who were treated with Sorafenib (P < 0.001); median overall survival for TACE was 18 months (2-year survival 35%); for patients treated with Sorafenib median survival was 8 months. A subgroup of 10 patients treated with TACE showed complete (radiological) response to treatment and median 2-year survival was 80%. Compared to the overall TACE patient group characteristics were similar (age, sex, presence of cirrhosis, Child score, AFP, presence of ascites, size of the largest HCC lesion, macro-vascular invasion, or port thrombosis), except liver transamina levels (P = 0.040) and bi-lobar spread of disease (P = 0.022). Four patients did not undergo second treatment because there was no residual tumor tissue detected, 3 patients developed a new hepatic HCC lesion and underwent TACE treatment of this lesion, liver transplantation was performed in 2 and one patient was eventually lost to follow-up. Additional statistical analyses could not be performed due to the small number of patients.

Survival of patients treated with TACE was better compared to patients beyond TACE who were treated with Sorafenib (P < 0.001); median overall survival for TACE was 18 months (2-year survival 35%); for patients treated with Sorafenib median survival was 8 months. A subgroup of 10 patients treated with TACE showed complete (radiological) response to treatment and median 2-year survival was 80%. Compared to the overall TACE patient group characteristics were similar (age, sex, presence of cirrhosis, Child score, AFP, presence of ascites, size of the largest HCC lesion, macro-vascular invasion, or port thrombosis), except liver transamina levels (P = 0.040) and bi-lobar spread of disease (P = 0.022). Four patients did not undergo second treatment because there was no residual tumor tissue detected, 3 patients developed a new hepatic HCC lesion and underwent TACE treatment of this lesion, liver transplantation was performed in 2 and one patient was eventually lost to follow-up. Additional statistical analyses could not be performed due to the small number of patients.

**FIGURE 3**

**Table 3**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Mortality (n = 30)</th>
<th>Alive (n = 50)</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>62 (±12)</td>
<td>60 (±11)</td>
<td>0.95-1.02</td>
<td>0.366</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>19 (11)</td>
<td>43.7</td>
<td>0.28-1.30</td>
<td>0.187</td>
</tr>
<tr>
<td>Viral hepatitis (B and C)</td>
<td>14 (47%)</td>
<td>38 (76%)</td>
<td>0.85-1.10</td>
<td>0.600</td>
</tr>
<tr>
<td>Surveillance programme</td>
<td>8 (27%)</td>
<td>22 (42%)</td>
<td>0.59-3.05</td>
<td>0.485</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>84 (±80)</td>
<td>74 (±54)</td>
<td>0.92-4.25</td>
<td>0.079</td>
</tr>
<tr>
<td>ALB &gt;50 U/L</td>
<td>16 (53%)</td>
<td>29 (58%)</td>
<td>1.00-1.01</td>
<td>0.318</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>107 (±119)</td>
<td>79 (±53)</td>
<td>1.25-7.93</td>
<td>0.011</td>
</tr>
<tr>
<td>AST &gt;50 U/L</td>
<td>20 (67%)</td>
<td>28 (56%)</td>
<td>1.00-1.00</td>
<td>0.638</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>128 (±158)</td>
<td>130 (±101)</td>
<td>0.97-1.03</td>
<td>0.953</td>
</tr>
<tr>
<td>yGT</td>
<td>151 (±117)</td>
<td>226 (±254)</td>
<td>1.67-9.07</td>
<td>0.001</td>
</tr>
<tr>
<td>Bilirubine</td>
<td>15 (±9)</td>
<td>16 (±16)</td>
<td>1.40 (±0.55)</td>
<td>0.10 (±0.14)</td>
</tr>
<tr>
<td>Albumine &lt;35 g/L</td>
<td>6 (20%)</td>
<td>8 (16%)</td>
<td>1.23-11.10</td>
<td>0.009</td>
</tr>
<tr>
<td>Alpha-fetoprotein (U/L)</td>
<td>2652</td>
<td>1075</td>
<td>1.00-2.66</td>
<td>0.047</td>
</tr>
<tr>
<td>Alpha-fetoprotein (&gt;20 U/L)</td>
<td>10 (33%)</td>
<td>20 (40%)</td>
<td>1.00-1.02</td>
<td>0.191</td>
</tr>
<tr>
<td>INR</td>
<td>6 (20%)</td>
<td>4 (8%)</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
<tr>
<td>Child-Pugh score (0-9)</td>
<td>6 (±1)</td>
<td>5 (±1)</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
<tr>
<td>Child A</td>
<td>26 (87%)</td>
<td>43 (86%)</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
<tr>
<td>Child B</td>
<td>4 (13%)</td>
<td>7 (14%)</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
<tr>
<td>Child C</td>
<td>0</td>
<td>0</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
<tr>
<td>Size of largest lesion (mm)</td>
<td>52 (±49)</td>
<td>35 (±20)</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
<tr>
<td>&lt;35mm</td>
<td>15 (50%)</td>
<td>30 (60%)</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
<tr>
<td>35-50mm</td>
<td>3 (10%)</td>
<td>8 (16%)</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
<tr>
<td>50-80mm</td>
<td>5 (17%)</td>
<td>8 (16%)</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
<tr>
<td>80mm&lt;</td>
<td>4 (13%)</td>
<td>1 (2%)</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
<tr>
<td>Presence of ascites on imaging</td>
<td>1 (3%)</td>
<td>4 (8%)</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>20 (67%)</td>
<td>35 (70%)</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
<tr>
<td>Bilirubulin</td>
<td>4 (13%)</td>
<td>7 (14%)</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
<tr>
<td>Macrovascular involvement</td>
<td>0</td>
<td>3 (6%)</td>
<td>1.00-1.02</td>
<td>0.383</td>
</tr>
</tbody>
</table>

**Multivariate analysis**

- **AST >50 U/L**: 1.15-7.58 | 0.024
- **Albumine <35 g/L**: 1.04-8.04 | 0.041
### Supplement Table 4  Features associated with survival in patients treated with palliative or symptomatic treatment

<table>
<thead>
<tr>
<th></th>
<th>Mortality (n=102)</th>
<th>Alive (n=34)</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>63 (±12)</td>
<td>66 (±9)</td>
<td>0.97-1.01</td>
<td>0.134</td>
</tr>
<tr>
<td>Sex</td>
<td>77 (77%)</td>
<td>22 (12%)</td>
<td>0.88-2.18</td>
<td>0.155</td>
</tr>
<tr>
<td>Viral hepatitis (B and C)</td>
<td>40 (39%)</td>
<td>14 (41%)</td>
<td>0.97-1.066</td>
<td>0.406</td>
</tr>
<tr>
<td>Surveillance programme</td>
<td>12 (12%)</td>
<td>8 (24%)</td>
<td>1.01-3.38</td>
<td>0.044</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>61 (±42)</td>
<td>60 (±42)</td>
<td>0.75-1.67</td>
<td>0.570</td>
</tr>
<tr>
<td>ALT &gt;50 U/L</td>
<td>51 (50%)</td>
<td>16 (47%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aspartate aminotransferase</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>107 (90)</td>
<td>71 (±43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>78 (77%)</td>
<td>21 (62%)</td>
<td>1.17-3.30</td>
<td>0.010</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>271 (±320)</td>
<td>124 (±58)</td>
<td>1.00-1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>yGT</td>
<td>308 (±336)</td>
<td>218 (±159)</td>
<td>1.00-1.00</td>
<td>0.011</td>
</tr>
<tr>
<td>Bilirubine</td>
<td>25 (±25)</td>
<td>20 (±18)</td>
<td>1.00-1.02</td>
<td>0.006</td>
</tr>
<tr>
<td>Albumin</td>
<td>37 (±5.6)</td>
<td>40 (±4.9)</td>
<td>0.37-2.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumine &lt;35 g/L</td>
<td>34 (33%)</td>
<td>4 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-fetoprotein (U/L)</td>
<td>30201</td>
<td>6586</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-fetoprotein (&lt;20 U/L)</td>
<td>68 (67%)</td>
<td>16 (47%)</td>
<td>1.18-2.94</td>
<td>0.005</td>
</tr>
<tr>
<td>INR</td>
<td>1.54 (±1.94)</td>
<td>1.23 (±0.41)</td>
<td>1.00-1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INR=1.7</td>
<td>15 (15%)</td>
<td>5 (14%)</td>
<td>0.60-1.38</td>
<td>0.654</td>
</tr>
<tr>
<td>Child-Pugh score (0-9)</td>
<td>6 (5-10)</td>
<td>6 (5-10)</td>
<td>1.14-1.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Child A</td>
<td>67 (66%)</td>
<td>27 (79%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child B</td>
<td>26 (20%)</td>
<td>3 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child C</td>
<td>9 (9%)</td>
<td>4 (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size of largest lesion (mm)</td>
<td>79 (±45)</td>
<td>45 (±26)</td>
<td>1.01-1.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;35mm</td>
<td>11 (11%)</td>
<td>14 (41%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-50mm</td>
<td>16 (16%)</td>
<td>8 (24%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-80mm</td>
<td>25 (25%)</td>
<td>8 (24%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80mm</td>
<td>36 (35%)</td>
<td>3 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of ascites on imaging</td>
<td>29 (29%)</td>
<td>5 (14%)</td>
<td>1.18-1.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>66 (65%)</td>
<td>30 (88%)</td>
<td>0.322-0.736</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bilobular</td>
<td>50 (49%)</td>
<td>12 (35%)</td>
<td>1.08-2.41</td>
<td>0.020</td>
</tr>
<tr>
<td>Multivariates involvement</td>
<td>21 (21%)</td>
<td>4 (12%)</td>
<td>0.96-2.59</td>
<td>0.106</td>
</tr>
</tbody>
</table>

### Supplement Table 5  Features associated with survival (Cox regression analysis) in patients treated with TACE for HCC.

<table>
<thead>
<tr>
<th></th>
<th>Mortality (n=51)</th>
<th>Alive (n=27)</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>93 (±84)</td>
<td>74 (±47)</td>
<td>0.87-3.34</td>
<td>0.115</td>
</tr>
<tr>
<td>AST &gt;50 U/L</td>
<td>34 (67%)</td>
<td>17 (63%)</td>
<td>1.00-1.01</td>
<td>0.002</td>
</tr>
<tr>
<td>yGT</td>
<td>259 (±232)</td>
<td>227 (±169)</td>
<td>1.00-1.00</td>
<td>0.017</td>
</tr>
<tr>
<td>Bilirubine</td>
<td>24 (±16)</td>
<td>21 (±19)</td>
<td>0.99-1.03</td>
<td>0.314</td>
</tr>
<tr>
<td>Albumin</td>
<td>36 (±6)</td>
<td>40 (±4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Albumine &lt;35 g/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-fetoprotein (U/L)</td>
<td>12318</td>
<td>460</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-fetoprotein (&gt;20 U/L)</td>
<td>30 (60%)</td>
<td>12 (44%)</td>
<td>1.15-4.04</td>
<td>0.015</td>
</tr>
<tr>
<td>Child-Pugh score (0-9)</td>
<td>6 (±1)</td>
<td>6 (±1)</td>
<td>1.01-1.52</td>
<td>0.035</td>
</tr>
<tr>
<td>Child A</td>
<td>34 (67%)</td>
<td>21 (78%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child B</td>
<td>14 (28%)</td>
<td>3 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child C</td>
<td>3 (6%)</td>
<td>3 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size of largest lesion (mm)</td>
<td>63 (±30)</td>
<td>37 (±16)</td>
<td>1.02-1.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;35mm</td>
<td>6 (12%)</td>
<td>13 (48%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-50mm</td>
<td>9 (18%)</td>
<td>8 (30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-80mm</td>
<td>18 (35%)</td>
<td>5 (19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80mm</td>
<td>9 (18%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of ascites on imaging</td>
<td>12 (22%)</td>
<td>4 (15%)</td>
<td>0.97-1.77</td>
<td>0.074</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>40 (78%)</td>
<td>25 (93%)</td>
<td>0.28-1.06</td>
<td>0.067</td>
</tr>
<tr>
<td>Bilobular</td>
<td>16 (31%)</td>
<td>8 (30%)</td>
<td>1.25-2.30</td>
<td>0.474</td>
</tr>
<tr>
<td>Macrovahascular involvement</td>
<td>6 (12%)</td>
<td>3 (11%)</td>
<td>0.42-2.31</td>
<td>0.904</td>
</tr>
</tbody>
</table>

### Multivariates analysis

<table>
<thead>
<tr>
<th></th>
<th>Mortality (n=102)</th>
<th>Alive (n=34)</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>1.06-4.67</td>
<td>1.01-1.02</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
This study reports treatment outcomes in a patient population with HCC presenting in a Dutch tertiary, non-liver transplant center. Diagnosis and treatment were performed according to the guidelines in that era [12;14]. After multivariate analysis survival in the overall patient group was associated with AST, albumin, presence of ascites, macrovascular involvement, and size of the largest HCC lesion. In the patients group treated with curative intent survival was associated with elevated AST and lowalbumine. For patients treated with palliative intent AST and size of the largest lesion were associated with survival, while the subgroup of patients treated with TACE showed an association with Alk phos, albumin, AFP, and size of the largest HCC lesion.

Two-year survival of patients with HCC in the Netherlands was 19% between 2001 and 2005 compared to 44% in the present study [10]. This probably relates to improved surveillance of patients with hepatitis and cirrhosis in our study resulting in detection of the disease in an earlier stage with better chances for treatment [11]. In this study we treated 37% of patients with curative intent. World-wide between 30-60% of patients can be treated with curative intent [12]. The reason is especially true in countries with a high burden of HCC (18% in our study) and 40-45% has HCV (27% in our study). These numbers are very different in most comparable with Northern America where HBV accounts for 10-15% of HCC [26] (similar to the 18% in our study) and 54% of patients have HCC smaller than 2cm [22] compared to only 8% in our study. At this moment most Western countries still see the bulk of patients with HCC in intermediate, advanced and late stage of the disease. Like Japan, we should work towards a shift to detection of HCC in an early stage, thereby improving curative opportunities. Improvements should be made in all treatment categories. In this study we treated 48% of patients with TACE or Sorafenib as first treatment. Recent studies by Chung et al. and Bai et al. suggest that the combination of both treatments improves overall survival with an additional 2 months [18; 23]. However, predicting which patients will respond to TACE treatment is not always possible. If at treatment evaluation viable tumor tissue is present at imaging, additional treatment(s) with TACE is indicated when liver function is good enough. Sieghart et al. published the ‘ART score’ to identify patients who may or may not profit from additional treatment [24] and such models may help us in the future to determine in which patients additional TACE should or should not be performed. They proposed a scoring system based on AST levels, Child score and the absence of tumor response after treatment. The first criterion, AST, was also significant for survival in our study population.

As mentioned above elevated AST, but also low albumine were associated with decreased survival in the overall patient group. Comparing survival of our patient cohort with other studies has limited value because the heterogeneity of the patient cohort. However, Torzilli et al. retrospectively evaluated data from 10 centers worldwide of patients undergoing resection for HCC [28]. For patients treated with curative intent (BCLC 0-A) overall survival at 1, 3 and 5 years was 88%, 71%, and 57%. Our results at 1 and 3 years were 80% and 40% after treatment with curative intent. The 5-year survival is not similar, however, due to the small number of patients in our cohort, no survival analysis was performed for every BCLC stage; analysis was performed according to treatment intent. Features associated with survival in multivariate analysis were bilirubine, tumor size ≤5cm, macrovascular invasion, cirrhosis, and esophageal varices. Our study showed elevated AST and low albumine as features associated with survival after multivariate analysis. Recent study by Colombo et al [29] give a European perspective on treatment of HCC. They state that TACE prolongs survival in patients with advanced stage of the disease and after treatment they have a survival of 20 months (similar to the 18 months in our study). This statement is not supported by the Cochrane systematic review by Oliveri et al who report that the beneficial effect of TACE on survival is not evident [30]. Recent meta-analysis by Raoul et al. shows that it is difficult to compare studies on TACE because of heterogeneous patient populations and different treatment strategies [31]. Data from Europe and the US show the benefit of Sorafenib on overall survival of patients in advanced stage of the disease with median survival of 10.7 months (SHARP trial [32]) and results from a similar trial from Asia [27] reported median survival of 6.5 months. A limited number of patients treated with Sorafenib were analyzed in our study with median survival of 8 months.

In this study the presence of cirrhosis was in favour of overall better survival in the palliative patient group. However, the presence of cirrhosis is associated with decreased survival as it negatively influences the function of the liver [28; 33]. The contradictory findings in our study can probably be explained by the high number of patients with no underlying parenchymal disease. These patients were not included in a surveillance program and they usually presented with symptoms in a late stage of the disease with corresponding bad prognosis. This study is limited by its retrospective design in a single medical center. The number of patients is low in the subgroup analyses of patients treated with TACE. The patient population was heterogeneous and had missing data therefore not all analyses could be performed. Histopathological evaluation of HCC specimen was not prospectively performed and macrovascular involvement and differentiation grade of the tumor are of prognostic value [34-36]. Future studies and (meta) analysis should focus on prospective evaluation of patients with HCC treated with curative and palliative intent in an attempt to identify factors prognostic of good outcome after treatment. This will ultimately lead to better selection of patients who potentially are candidates for curative treatment, candidates for secondary curative treatment after RFA or TACE, and candidates for additional palliative treatment.

In conclusion, this retrospective study shows results consistent with literature of patients with HCC in low-incidence countries. Factors associated with survival are elevated AST, low albumine, presence of ascites, macrovascular involvement, and size of the largest HCC lesions.


Case-Studies on Hepatic Hypervascular Tumors

Hepatoblastoma & $^{18}$F-FCH PET/CT

Hepatocellular adenomas & Hepatic granulomas.

Giant liver hemangiomas: an update

Von Meyenburg complexes mimicking metastatic disease
HEPATOBLASTOMA EVALUATED BY 18F-FLUOROMETHYL CHOLINE PET/CT

AN INTERESTING IMAGE
Hepatoblastoma is a rare carcinoma mostly seen in children. Neo-adjuvant chemotherapy followed by resection and adjuvant chemotherapy is the optimal treatment. We present the case of an 18-year-old woman who presented with abdominal pain, nausea, bloating, and fatigue. MRI showed 3 hepatic lesions with high signal intensity on arterial phase T1-weighted images and slight washout on the late phase, suggestive for hepatocellular carcinoma. Laboratory examinations revealed plasma α-feto-protein of 114,745 Kg/L. Subsequent baseline and posttreatment 18F-fluoromethyl choline PET/CT were performed to possibly evaluate extent of the disease and assess disease response after neo-adjuvant chemotherapy. PET/CT with 18F-fluoromethyl choline (18F-FCH) is used to detect local prostate cancer and distant metastases [2].

**Figure 1**

An 18-year-old woman presented with abdominal pain, nausea, bloating, and fatigue, all features consistent with an abdominal mass. Physical examination revealed an enlarged liver with tenderness in the epigastrium region. Plasma α-feto-protein was highly elevated (3100,000 Kg/L). Postcontrast gadolinium MRI showed 3 hyperintense inhomogeneous hepatic lesions on T1-weighted arterial images; the largest lesion measured 9 cm (A, B). Subsequent portal phase showed slight washout with enhancement of the rim of the lesions, consistent with hepatocellular carcinoma (HCC) or hepatoblastoma (C, D). The largest lesion showed hypodense central areas suggestive of bleeding or necrosis. Histopathological biopsy of the lesions was advised to determine the appropriate treatment, resulting in a slight preference for hepatoblastoma, based on histomorphology and the overexpression of alpha-fetoprotein within the lesion. Therefore, treatment with neoadjuvant cisplatin was started to downsize the tumor [1].

Based on 18F-FCH uptake high-grade gliomas [3], benign lesions and metastases can be detected in the brain [4, 5], and concerning the liver, differentiation of focal nodular hyperplasia from hepatocellular adenomas is possible [6]. Furthermore, Talbot et al [7] reported promising results with the use of 18F-FCH PET/CT in evaluation of HCCs [8]. Hepatoblastoma is a malignant hepatocyte proliferation, closely related to HCC, and therefore, we hypothesized 18F-FCH PET/CT to be of potential use in this patient. The patient subsequently underwent an extended left hemihepatectomy,9 and diagnosis of hepatoblastoma was confirmed at the histopathological examination of the surgical specimen. One year after surgery, no recurrent or metastatic disease was found, and the patient has resumed school and work. In all, 18F-FCH PET/CT is a promising additional imaging tool for hepatoblastomas and proved useful for staging and assessment of treatment response in our patient.
HEPATOCELLULAR ADENOMAS ASSOCIATED WITH HEPATIC GRANULOMAS:
EXPERIENCES IN FIVE CASES
A 36-year-old woman with a history of diabetes mellitus (DM) and 15 years of oral contraceptive (OC) use was referred to the surgical department. She presented with acute upper abdominal pain caused by bleeding of a hepatic lesion (12.5 cm) during the 19th week of pregnancy, which was treated by selective arterial embolization of the branches of the feeding hepatic arteries in segment 2 and 3 (fig. 1a). One year later, the patient presented with abdominal pain similar to the pain during the previous episode of bleeding, and imaging showed signs of recurrent bleeding (fig. 1b). At laparotomy the liver surface appeared macroscopically inhomogeneous with disseminated pale lesions of approximately 0.5-1.0 cm with a tendency to confluence (fig. 1c, d). A diffusely metastasized malignancy was suspected, however intraoperative frozen sections of these lesions revealed granulomas. Histopathological examination showed multiple HCA: hepatocellular proliferation without cytonuclear atypia, but with the presence of thick-walled vessels, areas of necrosis, hemorrhage, and in some vessels embolization material (fig. 1e). These HCA included unclassified as liver fatty acid binding protein (LFABP), glutamine synthetase (GS), C-reactive protein (CRP) and serum amyloid A (SAA) did not show any aberrant expression patterns [8]. Throughout the HCA lesions and liver, tissue was disrupted by epithelioid granulomas with a necrotic center containing multinucleated giant cells (fig. 1f). Ziehl-Neelsen, PAS and Grocott staining were negative. At the outpatient clinic no evidence of sarcoidosis, bacterial or fungal infection was found. Three months after surgery, the patient had fully recovered and resumed work.

### Summary of patient and lesion characteristics

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age, years</th>
<th>Sex</th>
<th>DM</th>
<th>BMI</th>
<th>OC, years</th>
<th>HCA, n</th>
<th>HCA location</th>
<th>HCA subtype</th>
<th>Location of hepatic granulomas</th>
<th>Characteristics of hepatic granulomas</th>
</tr>
</thead>
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<tr>
<td>This report (case 1)</td>
<td>36</td>
<td>f</td>
<td>II</td>
<td>27</td>
<td>15</td>
<td>7</td>
<td>diffuse</td>
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<td>diffuse</td>
<td>epithelioid, necrotizing; multinucleated giant cells; diffuse hilar lymphadenopathy</td>
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<tr>
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<td>29</td>
<td>f</td>
<td>I</td>
<td>31</td>
<td>10</td>
<td>&gt;10</td>
<td>diffuse</td>
<td>IHCA</td>
<td>border T and NT</td>
<td>epithelioid; non-casinging</td>
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<tr>
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<td>f</td>
<td>II</td>
<td>27</td>
<td>18</td>
<td>6</td>
<td>diffuse</td>
<td>IHCA</td>
<td>T</td>
<td>epithelioid; non-casinging; multinucleated giant cells</td>
</tr>
<tr>
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<td>28</td>
<td>23</td>
<td>4</td>
<td>right</td>
<td>IHCA</td>
<td>T</td>
<td></td>
</tr>
<tr>
<td>This report (case 5)</td>
<td>32</td>
<td>m</td>
<td>I</td>
<td>NA</td>
<td>1</td>
<td>left</td>
<td>IHCA</td>
<td>border T and NT</td>
<td>epithelioid</td>
<td></td>
</tr>
<tr>
<td>Martin-Blondel et al., 2010 [7]</td>
<td>39</td>
<td>f</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>diffuse</td>
<td></td>
<td></td>
<td>epithelioid; non-necrotizing</td>
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<td>28</td>
<td>f</td>
<td></td>
<td>5/9</td>
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<td></td>
<td></td>
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<tr>
<td>Malatjatian and Graham, 1982 [10]</td>
<td>31</td>
<td>f</td>
<td></td>
<td>7</td>
<td>1</td>
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<td>border T and NT</td>
<td></td>
<td></td>
<td>epithelioid; non-casinging; multinucleated giant cells</td>
</tr>
<tr>
<td>Le Bail et al., 1992 [5]</td>
<td>39</td>
<td>f</td>
<td></td>
<td>12</td>
<td>1</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Grazzi et al., 2007 [6]</td>
<td>26</td>
<td>f</td>
<td></td>
<td>10</td>
<td>2</td>
<td>III &amp; IV-V</td>
<td></td>
<td></td>
<td></td>
<td>multinucleated giant cells; diffuse hilar lymphadenopathy</td>
</tr>
</tbody>
</table>

A 29-year-old woman was referred to the surgical department. Patient history included 10 years of OC use, DM type I with diabetic nephropathy (creatinine 147 μmol/l; normal 90 μmol/l), and severe hypertension (up to 220/100 mm Hg) which caused encephalopathy (table 1). Preoperative liver biopsy confirmed the diagnosis of HCA and showed hepatic granulomas in the biopsy specimen. The left-lateral segments of the liver were resected and local excision of the lesion in segment 6 was performed. The lesions were consistent with inflammatory HCA, with hemorrhagic changes, sinusoidal dilatation, infiltr of inflammatory cells and irregular, thick blood vessels. Immunohistochemical staining showed overexpression of CRP and SAA. Beta-catenin, GS and LFABP expression were not aberrant. Within the HCA lesions and liver, tissue was disrupted by epithelioid granulomas with a necrotic center containing multinucleated giant cells (fig. 1f). Ziehl-Neelsen, PAS and Grocott staining were negative. At the outpatient clinic no evidence of sarcoidosis, bacterial or fungal infection was found. Three months after surgery, the patient had fully recovered and resumed work.

### Table 1

**Patient characteristics in cluded: age, sex, diabetes, mel- litus (DM type I or II); body mass index (BMI); years of oral contraceptive use (OC).** lesion characteristics include: number and location of HCA WITHIN THE LIVER; subtype of HCA − INFLAM- MATORY (IHCA) AND UNCLASSIFIED; LOCATION OF HEPATIC GRANULOMAS (DIFFUSE THROUGHOUT THE LIVER AND LESION − WITHIN THE TUMOR (T) − BORDER AREA OF TUMORAL (T) TO NON-NECROTIC (N) PARENCHYMA); CHARACTERISTICS OF HG, * previously re- ported [5].

---

**1ST PATIENT**

A 29-year-old woman was referred to the surgical department. Patient history included 10 years of OC use, DM type I with diabetic nephropathy (creatinine 147 μmol/l; normal 90 μmol/l), and severe hypertension (up to 220/100 mm Hg) which caused encephalopathy (table 1). Preoperative liver biopsy confirmed the diagnosis of HCA and showed hepatic granulomas in the biopsy specimen. The left-lateral segments of the liver were resected and local excision of the lesion in segment 6 was performed. The lesions were consistent with inflammatory HCA, with hemorrhagic changes, sinusoidal dilatation, infiltr of inflammatory cells and irregular, thick blood vessels. Immunohistochemical staining showed overexpression of CRP and SAA. Beta-catenin, GS and LFABP expression were not aberrant. Within the HCA lesions and liver, tissue was disrupted by epithelioid granulomas with a necrotic center containing multinucleated giant cells (fig. 1f). Ziehl-Neelsen, PAS and Grocott staining were negative. At the outpatient clinic no evidence of sarcoidosis, bacterial or fungal infection was found. Three months after surgery, the patient had fully recovered and resumed work.
at the border of tumorous and non-tumorous tissue, an influx of epithelioid granulomas was found. There were no signs of sarcoidosis or opportunistic infections, and Ziehl-Neelsen and PAS staining were negative. No peri- or postoperative complications occurred and the patient could be discharged on day 7. Six months after surgery the patient was in good condition.

A 52-year-old woman with a history of type II diabetes was referred to the liver surgical department for resection of multiple hepatic lesions, as previously reported [5]. The patient had had three normal pregnancies after which she had taken OC for 18 years. In a period of 6 years, the tumor in segments 6/7 enlarged from 2 cm to 7 cm. Ultrasound showed 5 additional smaller nodules measuring 2–3 cm: 4 in the right liver and 1 in segment 2. A right hepatectomy and enucleation of the lesion in segment 2 was performed. All 6 lesions had the same histopathological characteristics consistent with inflammatory HCA. Immunohistochemical staining revealed an overexpression of SAA and CRP, without abnormalities for LFABP, GS and beta-catenin staining. In addition, there were numerous non-necrotizing granulomas inside all tumors which were not present in the non-tumoral liver. The granulomas were composed of lymphocytes, epithelioid cells and multinucleated giant cells, occasionally containing as- teroid bodies. There was no argument for opportunistic infections and the following stainings were negative: Ziehl-Neelsen, PAS, Grocott and Warthin-Starry. The non-tumoral liver parenchyma was normal.

This 39-year-old woman was referred for resection of a 7 cm hepatic lesion in the right liver lobe discovered by hepatic ultrasound that was carried out for evaluation of elevated serum yGT (560 U/l; normal <40 U/l). Patient history revealed three normal pregnancies, one miscarriage and one abortion, OC use during 23 years, and DM type II. MRI showed a large subcapsular tumor with central necrosis in the right liver, and 2 hemangiomas in the left lobe. A right hemihepatectomy was performed. On histopathological examination a benign hepatocellular proliferation with necrotic and hemorrhagic changes was found, consistent with HCA. Three small nodules were discovered at some distance from the larger tumor, measuring between 1 and 2 cm. All lesions showed typical features of inflammatory HCA by standard microscopy, confirmed by additional immunohistochemistry with overexpression of SAA and CRP, whereas LFABP, GS and beta-catenin were normally expressed. In addition, small epithelioid granulomas were observed within the tumor mixed with inflammatory infiltrates. The non-tumoral liver was mildly steatotic without granulomas.

A 32-year-old man with DM type I was admitted to the liver surgical department after discovery by ultrasound of a 10 cm lesion in the left liver lobe. Serum alpha-fetoprotein was normal (<7 U/l) and there were no indications for primary or secondary malignant disease on additional imaging. A left hemihepatectomy was performed. The tumor, bulging from the posterior side of segment 3 of the liver, was well circumscribed and presented with congestive and hemorrhagic areas. In addition to a typical aspect of inflammatory HCA, there were numerous large epithelioid granulomas dispersed inside the tumor and in the immediate peritumoral parenchyma. The non-tumoral liver at distance was normal, except for many glycogenated nuclei. Immunohistochemical staining showed an overexpression of SAA and CRP inside the tumor, confirming inflammatory HCA. Follow-up after resection was uneventful.

**Figure 1**

**3rd Patient:** Imaging and histopathology. A: MR image of a 36-year-old woman who presented with acute abdominal pain. The transverse T2-weighted fat-suppressed image shows a lesion in the left liver (A) with hypodense areas consistent with bleeding (arrow). Furthermore, multiple hyperintense lesions compared to the surrounding liver parenchyma are shown (arrowheads). B: CT image of the same patient 1 year after the bleeding when she presented with recurrent upper abdominal pain. The transverse image of the arterial phase shows the shrunken lesion in the left liver (A) with a new hypodense area consistent with recent bleeding. Based on the symptoms of upper abdominal pain and the signs of bleeding on imaging, the patient was advised to undergo resection of the lesion. C: Macroscopic appearance of the liver at laparotomy, revealing an inhomogeneous liver surface, disseminated pale lesions of approximately 60 cm with a tendency to confluence, and a large well-circumscribed lesion in the left liver lobe (arrow). D: Intraoperative ultrasound shows the HCA lesion (arrow) and multiple, atypical, small hypodense lesions throughout the liver (arrowheads). E: Microscopic appearance of the resected HCA in the left liver lobe. This specimen shows the benign hepatocellular proliferation growing in sheets of cords, without pseudoglandular growth patterns. Solitary arteries (arrow) are seen and portal tracts are lacking (hematoxylin-eosin, 4×). F: Microscopic appearance of the surrounding liver parenchyma with a granuloma containing multinucleated giant cells (arrow) (hematoxylin-eosin, 10×).
Conclusions

Finally, chronic OC use might also be an underlying etiological factor in both HCA and hepatic granulomas. OCs are listed as one of many drugs known to cause GH [5, 13]. This drug is also associated with growth and development of HCA [13, 14]. Therefore chronic OC use may be a common etiological factor in the formation of HCA and hepatic granulomas in our female patients. The first case presented with multiple HCAs and diffuse granulomatous infiltration in both the existing HCA and the entire liver. This case was not an inflammatory HCA, but remained unclassified. The extensive GH likely reflects a systemic cause. All previously reported cases in literature (table 1) presented with a history of chronic OC use. Interestingly, in the patient described by Neuberger et al. [15] in whom a GH was diagnosed in association with OC use, the liver biopsy performed 6 months after discontinuation of OC revealed no granulomas, which supports this hypothesis.

In conclusion, little has been reported on hepatic granulomas in association with HCA. We found, along with HCA, granulomas in (peri)tumorous tissue, but also diffusely infiltrated in the entire liver. We propose that the hepatic granulomas in these cases are a response to persistent inflammation caused by (inflammatory) HCA, a local reaction to a neoplasm, chronic use of OCs, or a combination of these factors.

Discussion

The presented cases share many similarities, and we therefore propose three possible correlations between HCA and the formation of granulomas. First of all, the chronic inflammatory stress caused by inflammatory HCA might trigger granuloma formation. Inflammatory HCA is more often seen in patients with DM and obesity, and is the most frequent subtype with an incidence of 55–60% [9]; all our cases had a history of DM with a BMI ≥27. The hepatic lesions of 4/5 patients were histologically confirmed to be typical inflammatory HCA [1]. The chronic irritation and inflammatory stress caused by (inflammatory) HCA may cause activation of a cascade of inflammatory mediators and result in the formation of granulomas. This was also suggested by Martin-Blondel et al. [7] in their case study of GH and HCA. After resection of HCA the stressor theoretically subsides, which will subsequently result in the disappearance of the granulomas. This was reported in the case of Malatjalian and Graham [10] where a liver biopsy of the remnant liver was performed 6.5 years after resection of the HCA, revealing no evidence of granulomas anymore. However, no report was made about imaging findings and the biopsy was a single specimen, limiting the conclusion drawn from this investigation.

Second, a known cause of hepatic granulomas is the presence of a neoplasm, e.g. Hodgkin’s disease or hepatocellular carcinoma [11, 12]. Although HCA is a benign lesion, the liver is likely to respond in a same manner to the presence of the abnormal tumoral tissue.

Finally, chronic OC use might also be an underlying etiological factor in both HCA and hepatic granulomas. OCs are listed as one of many drugs known to cause GH [5, 13]. This drug is also associated with growth and development of HCA [13, 14]. Therefore chronic OC use may be a common etiological factor in the formation of HCA and hepatic granulomas in our female patients. The first case presented with multiple HCAs and diffuse granulomatous infiltration in both the existing HCA and the entire liver. This case was not an inflammatory HCA, but remained unclassified. The extensive GH likely reflects a systemic cause. All previously reported cases in literature (table 1) presented with a history of chronic OC use. Interestingly, in the patient described by Neuberger et al. [15] in whom a GH was diagnosed in association with OC use, the liver biopsy performed 6 months after discontinuation of OC revealed no granulomas, which supports this hypothesis.
Management of Giant Liver Hemangiomas:
An Update

Case Study 3

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Deha Erdogan
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Ulrich H.W. Beuers
Thomas M. van Gulik
Bieze M, van

Expert Rev Gastroenterol Hepatol 2013;7(3)
INTRODUCTION

Hemangiomas are the most common benign tumors affecting the liver, occurring in the general population with incidences ranging from 0.4 to 20% [1]. Hemangiomas are composed of multiple, large vessels lined by a single layer of endothelial cells within a thin fibrous stroma. Most hemangiomas are discovered between the thirs and fifth decade, with a mean age of 50 years at diagnosis [2] and are seen more often in females (female: male ratio = 5:1) [3]. The etiology is not understood, although a congenital anomaly has been suspected [1, 3]. Differential diagnosis include other hypervascular tumors, such as hepatocellular adenoma, hepatocellular carcinoma, metastasis of a neuroendocrine tumor or renal cell carcinoma. Most hemangiomas are small, asymptomatic and are usually incidental findings. Since the lesion is benign, these hemangiomas usually require no treatment of follow-up. Giant liver hemangiomas are defined by a diameter larger than 5 cm. In literature, there is no consensus regarding the optimal management of giant hepatic hemangiomas, be it a nonsurgical approach or resection, enucleation or selective embolization of the feeding hepatic artery.

The aim of this study is to review the current evidence concerning treatment strategies in giant hepatic hemangiomas, in combination with evaluation of management strategies for giant hemangiomas in our department. A systematic search of the literature was undertaken in PubMed, EMBASE, Ovid Medline (Ovid Technologies New York, NY, USA), and the Cochrane library database (Cochrana Database of Systematic Review) using the key words and medical subject headings 'treatment' and 'giant hemangioma' (figure 1). Two authors independently assessed study titles, abstracts and full texts, and selection was based on their relevance for the subject. The reference lists of all relevant articles appearing in the search results were scanned to check for additional publications. Only English articles were used for this study. No unpublished data were encountered.

DIAGNOSTIC IMAGING

The ultrasonographic appearance is highly suggestive of a liver hemangioma if a homogeneous, round or oval lesion is seen, which is hyperechoic, well defined and may exhibit posterior acoustic enhancement. Other imaging techniques, such as contrast-enhanced computed tomography (CT) or magnetic resonance (MR) imaging, are recommended for confirmation in case of inconclusive ultrasonographic results, or if a giant hemangioma requiring treatment is dealt with [4-6]. Characteristic, late, peripheral filling is seen after contrast administration, since the blood circulation within the tumor vessels is slow [1]. Another imaging option is the tagged red blood cell study for the characterization of hemangiomas [7]. Because of technical improvements of multiphase CT and MR imaging, liver scintigraphy, however, no longer used as routine imaging in clinical practice [8]. Frequent follow-up of imaging is not advised in patients with giant hepatic hemangiomas, since spontaneous changes are rare [9]. Previous studies have shown that the mean size of giant liver hemangiomas (n = 90) in patients who were observed, did not increase significantly, with an initial value of 7.4 ± 3.3 cm as compared with 7.6 ± 3.5 cm (P = 0.32) after a follow-up time of 5.1 ± 4.4 years [10]. A diagnostic biopsy to differentiate a hemangioma from a malignant lesion is not recommended because of the risk of hemorrhage in 1.8% of patients and the difficulty to obtain a definite diagnosis [2, 8].

Despite size, most patients with a giant hepatic hemangioma are asymptomatic. A hemangioma increases in size in 10-20% of patients [11, 12] and, because it may occupy space and displace other organs, may become symptomatic with pain in the right upper quadrant of the abdomen, nausea and vomiting, mainly seen in left-sided giant hemangiomas of the liver [3]. Occasional episodes of fever are reported in patients with giant hepatic hemangiomas, with high plasma infection parameters as a result of thrombosis and necrosis in the hemangioma [12, 13]. Typical abdominal pain is seen in 23-57% of patients with giant hemangiomas in the liver [14]. Schnell and others reported chronic abdominal pain, occasionally associated with fever and elevated white blood cell count, in patients with giant liver hemangiomas [14].

Related symptoms & complications

TABLE 1

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<td>Exclusion (n = 265)</td>
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Management of giant liver hemangiomas is controversial. Several treatment strategies are available, including percutaneous radiofrequency ablation (RFA), which in a number of case series, resulted in reduction in size of the lesion [19-22]. Even laparoscopic RFA has been reported to show promising results for the treatment of giant hepatic hemangiomas [23]. In addition, transarterial embolization (TACE) can be applied to relieve symptoms of giant hepatic hemangioma, as well as in cases of disseminated intravascular coagulation. A decrease in size of the hemangioma is usually the result; however, recurrence is common because of vascular recanalization [24].

Surgical intervention
The preference for (laparoscopic) enucleation or resection of a giant hepatic hemangioma is dependent on the obtained certainty of diagnosis, localization, size and number of lesions, and growth pattern of the hemangioma [4, 25]. Enucleation versus resection
Several authors prefer enucleation of a giant hepatic hemangioma rather than resection [17, 25, 26]. Enucleation without a margin of normal liver parenchyma is a justified treatment, since hemangiomas are benign lesions. Other reported advantages of enucleation are: less intraoperative blood loss (enucleation: 400 mL vs resection: 1330 mL; P = 0.004) [17], less risk of bile leakage (enucleation: 0% vs resection: 8-17%) [25, 26], maximum preservation of functional liver parenchyma and less overall complications [3, 16, 25-27]. No randomized controlled trials have been published that compare enucleation and resection.

Enucleation versus resection
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have been published that compare enucleation and resection. With enucleation, the risk of injury of bile ducts and vessels is minimal, since enucleation is performed just outside of the fibrous capsule surrounding the hemangioma, which is composed of compressed liver parenchyma. Belli et al. showed positive results after enucleation of giant hepatic hemangiomas in four patients, with preservation of sufficient normal liver parenchyma [28]. In addition, Singh et al. reported that enucleation of giant hemangiomas in the liver is safer and quicker, with less morbidity (enucleation: zero out of nine versus resection: five out of 12 patients; \( P = 0.045 \)) [26]. Kuo et al. compared patients with giant hepatic hemangiomas who underwent enucleation (n = 10) with a control group (liver resection, n = 10) [29]. Patients in the enucleation group showed 49% less blood loss (400 ± 129 mL vs 742 ± 116 mL; \( P < 0.05 \)) with less blood transfusions (two vs six). They concluded that enucleation is a safe alternative compared with resection for liver hemangiomas [29]. Mortality rates after liver resection for giant hemangiomas are low (0-4.3%) [30]. However, severe complications can develop after liver resection, of which intraoperative bleeding is life threatening [11, 31]. Other complications are bile leakage and infection. Postoperative insufficiency of the remnant liver is less important, since relatively little liver parenchyma is removed with resection of a giant hepatic hemangioma.

Liver tumors can also be resected by laparoscopic approach, depending on size and localization. This method can be considered in patients with hemangiomas in the left liver lobe or ventral segments. However, many surgeons are reluctant to perform laparoscopic resection in patients with large hemangiomas because of the risk of bleeding. Main case reports on laparoscopic surgery of liver hemangiomas have been described [31, 32]. Laparoscopic surgery has many advantages, such as smaller wounds and a faster return to full activity. Laparoscopic resection of giant hepatic hemangiomas will remain challenging, and is preferably performed by surgeons with a lot of experience in (open) liver surgery as well as in laparoscopic surgery [33].

Management of hemangiomas in the AMC

In our department, 22 patients with giant hepatic hemangiomas were evaluated (1991-2011). Figure 2 shows all patients classified according to size of hemangiomas. In this patient group, 73% of patients presented with abdominal pain. Surgical enucleation or resection was performed in 14 patients (64%) after a period of observation of 30.2 months (range: 4-96 months). The mean age of these patients was 44 ± 10.4 years (all women). Progressive abdominal pain was the indication for surgery in 12 patients. Enucleation was performed in 4 patients, a bi-segmentectomy in 6 patients, a right hemihepatectomy in 2 patients, a left hemihepatectomy in 1 patient. It should be noted that most giant hemangiomas were removed by resection, as with enucleation of these large, space occupying lesions, little parenchyma of the tumor-bearing segments would have been spared.

The mean size of resected giant hemangiomas was 13.0 cm (range 6.5-20 cm) compared with 9.5 cm (range 5.0-11.0 cm) in patients that did not undergo resection (\( P = 0.037 \)). Abdominal complications were resolved after resection in 92% (11 out of 12) of patients with symptomatic giant hepatic hemangiomas. However, one patient had persistent complaints of pain in the right abdomen 18 months after partial liver resection for a giant hepatic hemangioma of 8.0 cm. This was possibly due to a nonspecific form of neuralgia of the abdominal wall. The median hospital stay was 8 days (range 3-21). Figure 3 shows the findings of one of our patients (female 30 years of age).
age), in whom a giant hepatic hemangioma was discovered during follow-up of treatment for hepatitis B. Because this patient did not have complaints, clinical observation was justified with outpatient follow-up. Repeated ultrasonography 6 years later showed an increase in size reported abdominal complaints. A right hemihepatectomy was decided and histological examination confirmed a cavernous hemangioma. A CT scan repeated 2 years postoperatively showed a marked hypertrophy response of the remaining, left liver lobe. The image of figure 4 are of a 54-year-old female with morbid obesity, who presented with fatigue and upper abdominal complaints, enucleation of the larger left hemangioma was performed. In conclusion, liver hemangiomas are the most benign liver tumors. Hemangiomas of the liver are readily demonstrated by abdominal ultrasonography or enhanced CT or MR imaging. Giant liver hemangiomas are defined by a diameter larger than 5 cm. As complications are rare, observation is justified in the absence of symptoms. Surgical resection is indicated in patients with abdominal (mechanical) complaints or complications, or when diagnosis remains inconclusive. Enucleation is the preferred surgical method according to existing literature and the authors’ own experience.

EXPERT COMMENTARY

Hemangiomas are the most common benign tumors affecting the liver. Although the usually do not requiring any treatment, there is a great deal of confusion regarding the complications and treatment of giant hepatic hemangiomas (> 5 cm). Additionally, there is no consensus in the literature regarding optimal management of these large tumors. Expert information, therefore, is necessary concerning complications of giant hepatic hemangiomas, diagnostic imaging and treatment options.

The surgical risks of liver resection have greatly decreased in the past decade in specialized centers. Whereas benign tumors, even when large and symptomatic, would previously have been declined for resection, patients can now undergo safe liver resections with zero mortality in many centers. Giant hepatic hemangiomas (> 5 cm) are more likely to give rise to complaints and are readily demonstrated by contrast enhanced CT or MR imaging.

5 YEAR VIEW

In 5 years time, the field will evolve, resulting in even more accurate imaging of giant liver hemangiomas and a tailored surgical approach. We suggest that enucleation will be the surgical method of choice and that with increasing experience, more giant liver hemangiomas are amenable to a laparoscopic approach.

Preoperative CT scan of a 54-year-old female patient with a giant hepatic hemangioma. The scan demonstrated that the left liver lobe was almost totally occupied by one giant lesion (18 x 11 cm). A & B: A similar, hypodense lesion was seen in the right liver lobe. C: Intraoperative image of the giant hepatic hemangioma in the left liver lobe, which had a weight of 810 g after resection. D: CT scan after enucleation of the left giant liver hemangioma showed an unchanged size of the hemangioma in the remnant, right liver lobe.
Liver hemangiomas are the most common benign liver tumors, and are usually incidental findings.

Liver hemangiomas are readily demonstrated by abdominal ultrasonography, computed tomography or magnetic resonance imaging.

Differential diagnoses include other hypervascular tumors, such as hepatocellular adenoma, hepatocellular carcinoma, metastasis of a neuroendocrine tumor or renal cell carcinoma.

Giant liver hemangiomas are defined by a diameter larger than 5 cm.

In patients with a giant liver hemangioma, observation is justified in the absence of symptoms.

Surgical resection is indicated in patients with abdominal (mechanical) complaints or when diagnosis remains inconclusive. Enucleation is the preferred surgical method according to existing literature and our own experience.

Spontaneous or traumatic rupture of a giant hepatic hemangioma is rare, however, the mortality rate is high (16-39%).

An uncommon complication of a giant hemangioma is disseminated intravascular coagulation (Kasabach-Merritt syndrome); intervention is then required.
Von Meyenburg complexes mimicking metastatic disease at laparotomy for focal nodular hyperplasia
A 44-year-old woman presented with symptoms of fatigue and increasing abdominal discomfort. MR imaging with the hepatobiliary contrast Gd-EOB-DTPA (Primovist®) was performed showing a 6cm lesion in segment 2/3 of the liver typical for focal nodular hyperplasia. Because of severe complaints attributed to the lesion, the patient was scheduled for resection. At laparotomy multiple small white lesions were found throughout the liver with enlarged loco-regional lymph nodes. Macroscopically, the findings were consistent with widespread metastases and the surgeon felt compelled to determine the nature of these lesions before continuing resection. Final diagnosis revealed multiple bile duct hamartomas and an FNH lesion as was expected.

**PRESENTATION**

A 44-year-old woman presented with symptoms of fatigue and increasing abdominal discomfort. Patient history included hypothyroidism (medically treated with Thyrox) and a cholecystectomy. Diagnostic imaging was performed and a 6cm focal nodular hyperplasia (FNH) was diagnosed in segment 2/3 of the liver. Laboratory results showed elevated yGT 228 U/L (normal 40-120) and alkaline phosphatase 141 U/L (normal 40-120). Tumormarkers were normal: carcinoembryonic antigen 1.6μg (normal <5.5) and alpha-fetoprotein 4μg (normal <7). Additional MR imaging with the hepatobiliary contrast Gd-EOB-DTPA (Primovist®) was performed showing a lobulated hypervascular 6cm lesion in segment 2/3 of the liver (Figure 1A). The hypodense area within the lesion was consistent with a central scar, which is typical for FNH. Furthermore, the hepatobiliary phase 20 minutes post injection of contrast showed accumulation of contrast within the lesion, also consistent with FNH. Hepatocellular adenoma and (fibrolamellar carcinoma) were considered. However, the typical central scar made hepatocellular adenoma less likely. The lesion did not show typical findings for malignancies including ‘wash-out’: loss of contrast during veno-portal phase of dynamic imaging.

**TREATMENT**

Because of severe complaints attributed to the lesion, the patient was scheduled for resection of segment 2/3. At laparotomy multiple small white lesions (<0.5 cm) were found throughout the liver (Figure 2A) with enlarged loco-regional lymph nodes. Macroscopically, the findings could be consistent with widespread metastases or granulomatous hepatitis and the surgeon felt compelled to first determine the nature of these lesions before continuing resection. Frozen section examinations of liver biopsies revealed bile duct hamartomas, whereas the lymph nodes revealed only reactive changes, without signs of malignancy. Final histopathological diagnoses revealed an FNH (5.5 x 6cm; Figure 2B, Figure 3A), of which the diagnosis was confirmed with an additional GS staining, showing a typical ‘map-like’
staining pattern (Figure 3B) [1]. The other lesions consisted of multiple bile duct hamartomas (Von-Meyenburg complexes) in the surrounding liver parenchyma (Figure 4) and reactive changes in the resected lymph nodes. No signs of malignancy, granulomatous hepatitis, tuberculosis, or sarcoidosis were found. After resection, the patient was relieved of her symptoms. However, during follow-up the patient developed a cicatrical hernia, for which she underwent surgical repair.

**DISCUSSION**

FNH are benign liver lesions with no risk of bleeding or malignant transformation [1]. Therefore, FNH are only considered for resection if discomfort perceived by the patient is severe, other possible causes of complaints are excluded, and risk of surgery versus complaints is well evaluated. The exact etiology of FNH is unknown, but one hypothesis is vascular damage resulting in a hyperplastic and fibrotic response. The etiology of Von-Meyenburg complexes, or bile ducts hamartomas, is better known and is thought to be a developmental malformation with persistence of the ductal plate configuration. [2, 3]. The two cystic lesions larger than 5mm were depicted on pre-operative MR imaging and were described as simple cysts (Figure 1). However, like in most cases with hamartomas, the majority of hamartomas in our patient was small and only in retrospect detected as hyperintense irregular lesions on T2w series and low signal intensity on T1w series of the MR (Figure 1).

FNH and hamartomas are most likely to co-exist based on pure chance and no causal relation between both entities has been substantiated in literature. However, the co-existence might cause confusion as it mimics metastatic disease.

**LEARNING POINTS & TAKE HOME MESSAGE**

- FNH is a rare, benign liver tumor which may give rise to symptoms, relieved by excision of the lesion.
- Characteristic features of FNH on imaging are a central scar, without signs of wash-out of the lesion on veno-portal phase of dynamic imaging.
- Because bile duct hamartomas are usually small, they are often not detected on cross-sectional imaging studies.
- Bile duct hamartomas may mimick metastatic disease of the liver.
- Bile duct hamartomas may coincide with any other type of liver tumor, benign or malignant. An association of bile duct hamartomas with FNH is not apparent.
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Discussion & Summary

Chapter 11

Matthanja Bieze
PART I | CHAPTER 1 of this thesis provides an appraisal of the colourful history of medical imaging and an introduction to the hypervascular hepatic tumors discussed in this thesis: hepatocellular adenoma; focal nodular hyperplasia, hepatocellular carcinoma, and hepatic hemangioma. The general application of imaging modalities has long been established. However, fine-tuning of these techniques to specific diseases and abnormalities is still an ongoing process.

PART II discusses imaging and clinical management of hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH). Benign liver lesions do not always display typical characteristics for diagnosis and with that mindset; CHAPTER 2 discusses dynamic MR imaging with Primovist® for HCA and FNH. Accurate diagnosis is essential, because FNH and HCA have opposing therapeutic consequences. The risk of complications, such as bleeding or even malignant transformation, are known to occur in HCAs larger than 5 cm, unlike in FNH. This MRI technique proved highly accurate and makes invasive liver biopsy redundant. The study was designed to differentiate between HCA and FNH with Primovist® for differentiation of HCA and FNH, this modality will probably be impractical in many centers as a special cyclotron is necessary to synthesize 18F-FCH in close proximity to the hospital. Furthermore, as is discussed in CHAPTER 2, the 18F-FCH PET/CT as described in CHAPTER 3 can be used as an additional tool when MR imaging with Primovist® remains inconclusive. Even with accuracy higher than MR imaging with Primovist® for differentiation of HCA and FNH, this modality will probably be impractical in many centers as a special cyclotron is necessary to synthesize 18F-FCH in close proximity to the hospital. Furthermore, as is discussed in CHAPTER 2, the 18F-FCH PET/CT is useful in detection of hepatocellular carcinoma (HCC). Therefore, when HCC is not in the differential diagnosis the 18F-FCH PET/CT can be used to differentiate HCA from FNH. When dynamic MR imaging can be accurately incorporated in the process of imaging, two very accurate imaging modalities can be combined with less impact for the patient. In CHAPTER 4, the fine line between indicated surgical interventions against non-invasive care is discussed. Benign lesions will only need intervention when medically indicated by their associated risk factors and decreased quality of life expressed by the patient. In CHAPTER 5, the fine line between indicated surgical interventions against non-invasive care is discussed. Benign lesions will only need intervention when medically indicated by their associated risk factors and decreased quality of life expressed by the patient.

PART III discusses hepatocellular carcinomas (HCC) and unlike HCA and FNH this lesion has the potential to be life threatening. It is essential to detect HCC as early as possible to be able to remove and obtain curation. Multiple HCC lesions over 3 cm intrahepatically or extrhepatic spread of the disease means that curative treatment will no longer be possible [11]. Therefore, accurate staging of the disease is crucial for appropriate treatment implementations. In that respect, CHAPTER 7 shows the additional value of 18F-FCH PET/CT imaging in staging and detection of extrahepatic disease with direct treatment implication in a third of the patients of the study. Even though this imaging modality has been highly accurate and of additional value to diagnosis and treatment plans; logistics and associated costs make its general use controversial. 18F-FCH has to be specially synthesized and the specific risk factors for lesional bleeding and associated costs make its general use controversial. 18F-FCH has to be especially synthesized and has a half-life time of 110 minutes. Therefore, the cyclotron cannot be located far from the medical center where the patients undergo the imaging. However, if it is a high-volume medical center regarding HCC patients or involved in a HCC screening program, the 18F-FCH PET/CT will be of clear additional value. The additional value of the 18F-FCH PET/CT for HCC lies in accurate whole body assessment in regards to the extent of disease, which has direct implications for staging and treatment decisions. Further studies need to determine its place in diagnostic work-up and show which patients will profit most from the 18F-FCH PET/CT.

Another possibility to assess local extent of the disease is by staging laparoscopy (SL). A laparoscopy can be performed in the work-up prior to hepatic resection to assess local extent of disease and the overall condition of the liver (cirrhosis and fibrosis) by biopsy of non-tumorous tissue with consecutive histopathological evaluation. CHAPTER 8 shows that staging laparoscopy is outdated as curately assessed, clinical implications should be assessed in large patient group to provide a treatment algorithm.

Malignant transformation of HCA occurs in an estimated 4.3% of the patients with HCA larger than 5 cm [8] and is overshadowed by the risk of lesional bleeding. Bleeding is more frequent and demands emergency care with transarterial embolization in case of active bleeding or severe intra-abdominal Grade III bleeding as discussed in CHAPTER 5. The specific risk factors for lesional bleeding in HCA were identified in CHAPTER 6, being: patients with obesity, HCA size >35 mm, HCA protruding from the liver (exophytic growth), HCA located in the left liver lobe, and HCA with radiological presence of central or peripheral arteries. HCA located deeper in the liver might have a lower risk of severe bleeding as none of the intrahepatic lesions showed extrahepatic bleeding (n = 82) and only 11% showed Grade I or II bleeding. Based on these findings, preventive treatment can be better focused on the patients who are at risk. However, the best method of preventive treatment remains under debate. A preventive surgical intervention, even laparoscopically, in a patient with a benign liver tumor could be regarded as somewhat excessive. On the other hand, radio frequency ablation has been shown to be a safe alternative in small lesions and studies have shown that HCA under 3 cm can be completely and safely ablated [9, 10]. Another less invasive treatment could be transarterial embolization (TAE).
imaging modalities are of such quality that ‘an initial peek’ with more invasive laparoscopy holds no additional value. In this retrospective evaluation of patients undergoing staging laparoscopy prior to hepatic resection the yield was only 7%. Therefore, only in cases in which local or distant metastases are suspected SL can still be considered. In light of CHAPTER 7, the 18F-FCH PET/CT might however be a more elegant non-invasive tool to assess extent of disease. An overview and discussion of the patients with HCC seen at the Academic Medical Center of Amsterdam, a non-liver-transplant center is presented in CHAPTER 9. Overall survival in patients treated with curative intent and with palliative or symptomatic treatment is similar to data from literature. Transarterial chemoembolization is highlighted as this treatment is the most commonly used local treatment in the palliative setting for HCC and in some patients complete response to treatment occurs with subsequent high survival. Further study into TACE and optimal (re)treatment will have to be conducted in a center with a high patient load to determine the best possible outcome for the individual patient with HCC requiring palliative TACE.

The differential diagnosis of hypervascular liver tumors is multifold. PART IV discusses 4 different case studies of hepatic tumors. Many hepatic tumors can have an atypical presentation and these cases are fine examples. The 1st CASE presents a young female patient (18 years old) suspected of having HCC. An 18F-FCH PET/CT was performed to assess extent of disease as described in CHAPTER 7, and 18F-FCH PET imaging showed four hepatic tumors without extrahepatic disease. However, histopathology after resection of the lesion showed hepatoblastoma. With this patient we showed that the 18F-FCH PET/CT can detect a hepatic hepatoblastoma. The 2nd CASE study discusses the co-existence of HCA and hepatic granulomas. We proposed that the hepatic granulomas in these cases are a response to persistent inflammation caused by (inflammatory) HCA, a local reaction to a neoplasm, chronic use of oral contraceptives, or a combination of these factors. The 3rd CASE discussed diagnosis is the most common benign hepatic tumor: hemangiomas. Invasive treatment is only indicated when abdominal complaints impair quality of life. These symptoms usually only occur in giant hemangioma larger than 5cm. Intervention is also required when, although rare, a complication of disseminated intravascular coagulation (Kasabach-Merritt syndrome) occurs. Surgical enucleation has proven effective in relief of symptoms. The 4th CASE study shows images of a patient with FNH with severe abdominal complaints in whom resection was decided. At laparotomy a liver with multiple greyish lesions was found similar to metastatic disease. This was not expected as FNH is a benign lesion and no other signs of malignant disease were present. Frozen sections showed bile duct hamartomas, and resection of the FNH was continued as planned.

**References**

IMAGING OF HEPATIC HYPERVASCULAR TUMORS &
CLINICAL IMPLICATIONS

SUMMARY

Matthanja Bieze

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PART I of this thesis is the introduction of the hypervascular hepatic tumors discussed in this thesis.

PART II discusses imaging of benign hypervascular hepatic tumors and clinical implications. Consecutive patients with suspected hepatocellular adenoma (HCA) or focal nodular hyperplasia (FNH) were enrolled in a prospective study designed to test whether improvements in diagnosis and management can be made. CHAPTER 2 evaluates the additional value of the hepatobiliary phase of Gd-EOB-DTPA (Primovist®) magnetic resonance (MR) imaging compared to standard MR imaging. The accuracy of standard MR imaging for HCA was 50% (12/24) and for FNH 68% (19/28). After reviewing the hepatobiliary phase the accuracy for HCA improved to 96% (23/24) and accuracy for FNH to 96% (27/28). Lesional features with predictive value for diagnosis in HCA included bleeding, fat, and glycogen. The presence of a central scar was highly predictive for FNH. This study shows high accuracy of the Gd-EOB-DTPA enhanced MRI when standard contrast enhanced series are combined with the hepatobiliary phase for differentiation of HCA and FNH in lesions larger than 2 cm. In the same patient cohort the additional value of positron emission tomography (PET) computed tomography (CT) with 18F-fluoromethylcholine (18F-FCH) as a novel diagnostic approach in the differentiation of HCA and FNH is discussed.

CHAPTER 3 evaluates the additional value of the hepatobiliary phase of Gd-EOB-DTPA (Primovist®) magnetic resonance (MR) imaging compared to standard MR imaging. The accuracy of standard MR imaging for HCA was 50% (12/24) and for FNH 68% (19/28). After reviewing the hepatobiliary phase the accuracy for HCA improved to 96% (23/24) and accuracy for FNH to 96% (27/28). Lesional features with predictive value for diagnosis in HCA included bleeding, fat, and glycogen. The presence of a central scar was highly predictive for FNH. This study shows high accuracy of the Gd-EOB-DTPA enhanced MRI when standard contrast enhanced series are combined with the hepatobiliary phase for differentiation of HCA and FNH in lesions larger than 2 cm. In the same patient cohort the additional value of positron emission tomography (PET) computed tomography (CT) with 18F-fluoromethylcholine (18F-FCH) as a novel diagnostic approach in the differentiation of HCA and FNH is discussed.

CHAPTER 3. Evaluation of PET imaging was done with a ratio: the maximum standard uptake value (SUV) of the lesion, divided by the mean SUV of the surrounding liver. The mean SUV ratio for FNH was 1.67±0.31 (mean ±SD, n=28), resulting in a positive likelihood ratio of 32.3 for PET-positive FNH. The mean SUV ratio for HCA was 0.82±0.17 (n=32), with a likelihood ratio of ≈100 for PET-negative HCA. Receiver operating characteristic curve analysis revealed an optimal SUV ratio cut-off value of 1.13, which reached 100% sensitivity and 97% specificity in differentiating FNH from HCA. This prospective study shows that PET/CT with 18F-FCH can accurately differentiate HCA from FNH and may become a valuable diagnostic tool when conventional imaging techniques fail to do so. CHAPTER 4 discusses the controversy of management of hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH), especially with respect to patient selection for surgery. This was the final study of the full cohort of 110 patients in which 51 patients with HCA and 59 with FNH were included. If patients with HCA and FNH require surgery, limited resection or enucleation of the lesion can be carried out with low morbidity and without mortality, using either an open or laparoscopic approach. Patients with preoperative symptoms show a high rate of postoperative symptom relief. The debate about invasive (preventive) treatment of HCA is further discussed in CHAPTER 5 & 6. Even though HCA is a benign hepatic lesion it does carry the risk of spontaneous bleeding. Bleeding was scored and graded on CT and/or MR imaging: intralesional (Grade I), infrahepatic (Grade II), or extrhepatic (Grade III). Treatment of bleeding consisted of observation in hemodynamically stable patients and selective transarterial embolization (TAE) in patients whom required blood transfusion. We propose a grading system of bleeding HCA in which Grade I and II with bleeding-areas larger than 6cm, and preferably all Grade III bleedings are treated with TAE. Additional care, being follow-up or preventive treatment, is advised in patients with exophytic adenomas.

CHAPTER 5. In CHAPTER 6 we aimed to assess risk factors for bleeding in patients with HCA. Standard of reference for diagnosis was histopathology, or dynamic CT and/or MR imaging. Bleeding was scored and evaluated on CT and/or MR imaging. As mentioned in CHAPTER 5 bleeding was seen in 29 (64%) patients and in 42 (22%) lesions. Patients with a body mass index (BMI) >25 showed
an increased risk for severe bleeding Grade II and III. In lesions >35mm, exophytic lesions, lesions in segments 2-3, and lesions with peripheral or central arteries the risk of bleeding is increased.

PART III of the thesis discusses hepatocellular carcinoma (HCC); a hypervascular, malignant hepatic tumor. In the past two decades an increasing incidence of HCC was noticed in Western Europe, including in The Netherlands. At the Academic Medical Center a special dedicated team (GIOSA: gastrointestinal oncology center Amsterdam) has taken responsibility for the management of the patients presenting with liver lesions suspected for malignant disease, including HCC. Whereas diagnosis of HCC primarily involves imaging, the aim of Chapter 7 was to assess the advantage of \(^{18}\)F-FCH PET/CT for detection of HCC and evaluation of the extent of disease. Similar to Chapter 3 the SUV ratio was used to evaluate PET images. Intrahepatic lesions on \(^{18}\)F-FCH PET/CT imaging were positive with an SUV ratio of 1.95 ± 0.66 and an accuracy of 88%. Eighteen intrahepatic lesions showed \(^{18}\)F-FCH uptake on PET/CT while uptake was absent in 3 confirmed non-HCC lesions by additional investigation, resulting in an accuracy of 100%. In 17 of 19 patients additional lesions were found on PET/CT imaging, with implications for treatment in 15 patients. The \(^{18}\)F-FCH PET/CT has implications for staging, management, and treatment evaluation, due to accurate assessment of extrahepatic disease. While imaging modalities have become more and more of importance as shown above, the 17 cases of this series show the advantage of \(^{18}\)F-FCH PET/CT in assessing the extent of disease in patients with HCC. In these cases, enucleation of a 6cm lesion in segment 2-3 of the liver typical of focal nodular hyperplasia. Because of severe complaints attributed to the lesion, the patient was scheduled for resection. During the laparotomy multiple small white lesions were found throughout the liver with enlarged locoregional lymph nodes. Macroscopically, the findings could be consistent with widespread metastases and the surgeon felt compelled to determine the nature of these lesions before continuing the resection. The final diagnosis revealed multiple bile duct hamartomas. The 2nd CASE study presents five cases in whom two rare lesions were simultaneously found within the liver, i.e. HCA and hepatic granulomas. The coexistence of both entities in these patients confused diagnosis. HCA and especially the inflammatory subtype may cause formation of granulomas in (peri-)tumorous tissue as a local response to persistent inflammation and/or the presence of a tumor. Both HCA and hepatic granulomas have also been associated with oral contraceptive use and was thought to be (partially) causative in these patients. We suggested that HCAs associated with hepatic granulomas derive from a local response to (inflammatory) HCA or neoplasm, chronic use of oral contraceptives, or a combination of these factors. The 3rd CASE study addressed the most common benign hepatic lesion: the liver hemangioma. Fortunately liver hemangiomas are readily detected by abdominal ultrasonography, contrast enhanced CT or MR imaging on which giant liver hemangiomas are defined by a diameter larger than 5 cm. In asymptomatic patients with a giant liver hemangioma observation is justified. However, surgical resection is indicated in patients with (mechanical) abdominal complaints, or when diagnosis remains inconclusive. In these cases, enucleation is the preferred surgical method, according to existing literature and our own experience. Finally a rare coexistence of two benign hepatic lesions was presented in the 4th CASE: FNH and hepatic bile duct hamartomas. MR imaging with the hepatobiliary contrast Gd-EOB-DTPA, Primovist® was performed showing a 6cm lesion in segment 2-3 of the liver. Fortunately liver hemangiomas are readily detected by abdominal ultrasonography, contrast enhanced CT or MR imaging on which giant liver hemangiomas are defined by a diameter larger than 5 cm. In asymptomatic patients with a giant liver hemangioma observation is justified. However, surgical resection is indicated in patients with (mechanical) abdominal complaints, or when diagnosis remains inconclusive. In these cases, enucleation is the preferred surgical method, according to existing literature and our own experience. Finally a rare coexistence of two benign hepatic lesions was presented in the 4th CASE: FNH and hepatic bile duct hamartomas. MR imaging with the hepatobiliary contrast Gd-EOB-DTPA, Primovist®, was performed showing a 6cm lesion in segment 2-3 of the liver. Because of severe complaints attributed to the lesion, the patient was scheduled for resection. During the laparotomy multiple small white lesions were found throughout the liver with enlarged locoregional lymph nodes. Macroscopically, the findings could be consistent with widespread metastases and the surgeon felt compelled to determine the nature of these lesions before continuing the resection. The final diagnosis revealed multiple bile duct hamartomas and an FNH lesion as was expected.
The Gd-EOB-DTPA enhanced MRI shows high accuracy when standard contrast enhanced series are combined with the hepatobiliary phase for differentiation of HCA and FNH in lesions larger than 2 cm.

PET/CT imaging with \(^{18}\text{F-FCH}\) can accurately differentiate HCA from FNH and may become a valuable diagnostic tool when conventional imaging techniques fail to do so.

If patients with HCA and FNH require surgery, limited resection or enucleation of the lesion can be carried out with low morbidity and without mortality, using either an open or laparoscopic approach. Patients with preoperative symptoms show a high rate of postoperative symptom relief.

Bleeding HCA can be graded on which treatment can be based: Grade I and II with bleeding-areas larger than 6cm, and all Grade III bleedings are preferably treated with TAE. Additional care, being follow-up or preventive treatment, is advised in patients with exophytic adenomas.

Bleeding was seen in 64% patients and in 22% lesions. Patients with a body mass index >25 showed an increased risk for severe bleeding Grade II and III. Lesions >35mm, exophytic lesions, lesions in segments 2-3, and lesions with associated peripheral or central arteries have a higher risk for bleeding.

The \(^{18}\text{F-FCH PET/CT}\) has additional value for patients with HCC. The \(^{18}\text{F-FCH PET/CT}\) has implications for staging, management, and treatment evaluation due to accurate assessment of extrahepatic disease.

With the current accurate imaging methods and the implementation of additional percutaneous biopsy of non-tumorous parenchyma as a standard procedure in the pre-operative workup of patients with HCC, the benefit of staging laparoscopy is lost.

Overview of the cohort of hepatocellular carcinoma patients was similar to data of Western centers. Factors associated with survival of patients with HCC are AST, low albumine, presence of ascites, macrovascular involvement, and size of the largest HCC lesion.

\(^{18}\text{F-FCH PET/CT}\) proved to be a promising additional imaging tool for hepatoblastomas and useful for staging and assessment of treatment response of this patient.

We suggested that HCAs associated with hepatic granulomas derive from a local response to (inflammatory) HCA or neoplasm, chronic use of oral contraceptives, or a combination of these factors.

In asymptomatic patients with a giant liver hemangioma observation is justified. However, surgical resection is indicated in patients with (mechanical) abdominal complaints, or when diagnosis remains inconclusive. In these cases, enucleation is the preferred surgical method, according to existing literature and our own experience.

Looks can be deceiving: macroscopically, the findings could be consistent with widespread metastases, frozen section analysis revealed multiple bile duct hamartomas and a lesion as was expected.
Imaging of Hepatic Hypervascular Tumors & Clinical Implications

Samenvatting

Matthanja Bieze
Promotor: T.M. van Gulik, Chirurg
Co-promotors: R.J. Bennink, Nucl. Med., J. Verheij, Pathology

UVA; Academic Medical Center
Hoofdstuk 11

Deel I

Het leveradenoom, focale nodulaire dysplasie (FNH) en lever hemangiomen zijn goedkankende tumoren die vaak bij toeval in de lever worden gevonden. Van FNH worden geen complicaties gezien en van hemangiomen zijn complicaties heel zeldzaam, daarom worden deze tumoren alleen behandeld als de klachten opwegen tegen de risico’s die een eventuele ingrijpende behandeling. Het leveradenoom kent wel complicaties zoals bloeding en in zeldzame gevallen kan het kanker worden. Voor patiënten met leveradenomen zijn deze risico’s de reden waarom een operatie geadviseerd wordt. Als laatste wordt het hepatocellulair carcinoom (HCC), leverkanker besproken. Deze vorm van kanker wordt steeds vaker in Nederland gezien en als een patiënt zich presenteert met verdenking op leverkanker dan wordt een multidisciplinair team van specialisten ingezet om de diagnose en uitbreiding van de ziekte te evalueren om de behandeling zo snel mogelijk te kunnen starten.

Deel II

Bespreekt de beeldvorming van goedkankende hypervasculaire levertumoren en de klinische implicaties hiervan. Alle patiënten die verdacht werden van een leveradenoom of focale nodulaire dysplasie (FNH) werden gevraagd deel te nemen aan beeldvormende onderzoeken met het doel diagnose en behandeling van deze patiëntengroep te verbeteren. In Hoofdstuk 2 wordt het leverspecifieke contrastmateriaal Primovist® voorgesteld. Primovist® is een magnetische resonance imaging (MRI) contrastmateriaal dat wordt toegepast na intraveneuze inwerking van de standaard MRI scan met intraveneus contrast, voor de differentiatie van leveradenomen en FNH. De nauwkeurigheid van de standaard MRI voor leveradenomen was 59% en voor FNH 68%. Na het beoordelen van de leverspecifieke fase verbeterde de nauwkeurigheid van de MRI naar 96% voor leveradenomen en 96% voor FNH. Kenmerken van de lesies die van voorspellende waarde waren voor de diagnose van leveradenomen op de MRI zijn de aanwezigheid van bloeding, vet en glycogeen in de lesie. Een centraal litteken was sterk voorspellend voor FNH. Geconcludeerd werd dat de nauwkeurigheid van de MRI scan voor de differentiatie van leveradenomen en FNH sterk verbetert als het standaard MRI scan gecombineerd wordt met de leverspecifieke fase na toediening van Primovist®. In Hoofdstuk 3 wordt in het zelfde patiëntencohort de positie van leveradenomen en FNH van de SUV van het leveradenoom en/of FNH was gedeeld door de gemiddelde SUV van het omliggende (lever)weefsel. De gemiddelde SUV ratio van FNH was 1,67±0,91 (likelihood ratio van 33,3 voor PET-positieve FNH). De gemiddelde SUV ratio van leveradenomen was 0,82±0,17 (likelihood ratio van 1,0 voor PET-negatieve LA). De afwaard van de SUV ratio met de hoogste nauwkeurigheid voor differentiatie van leveradenomen en FNH kleef 1,13 lager dan 1,15 past bij leveradenomen en hoger bij FNH. Deze studie laat zien dat de SUV ratio/FET/CT nauwkeurig is voor het differentiëren van leveradenomen en FNH en dat het een aanvullende diagnostische waarde kan hebben wanneer conventionele beeldvormende technieken (MRI/scan) geen uitsluitend gegeven. Hoofdstuk 4 bespreekt de controverse rondom de behandeling van patiënten met leveradenomen en FNH, met name de indicatie voor chirurgische behandeling. Deze studie sluit de rij in studies uit het patiëntencohort met leveradenomen en FNH. Uiteindelijk zijn 71 patiënten met leveradenomen en 59 met FNH geïncludeerd. De indicaties voor resectie waren klachten als gevolg van de tumor, leveradenomen >5 cm (met toegenomen kans op bloeding of kwaadaardige ontaarding) of onzeker diagnose. Als chirurgische behandeling geïndiceerd is dan heeft een beperkte operatie of laparoscopische resectie de voorkeur. Deze operaties kunnen met een lage morbiditeit en zonder mortaliteit worden uitgevoerd. Patiënten die klachten hadden voor de operatie lieten een hoog percentage van symptoomverlichting zien na chirurgische behandeling. De discussie over (preventieve) behandelingen van leveradenomen wordt voortgezet in HOOFDSTUKKEN 5 & 6. Hoewel leveradenomen een goedkankende levertumor is wordt deze geïmkerken door een risico op spontane bloeding. Als een bloeding is opgetreden kan de uitbreiding op de volgende manier worden gegraad: op een CT of MRI scan beperkt het leveradenoom (graad I); in het leveradenoom + omgevende leverweefsel (graad II); in het leveradenoom + de lever doorbraak door het leverkapsel in de buik (graad III). Behandeling van bloeding bestaat uit observatie of hemodynamisch stabiele patiënten en selectieve transarteriële embolisatie (TAE) in patiënten met een actieve bloeding of patiënten die bloedtransfusie moeten ondergaan. In HOOFDSTUK 5 wordt het graderingssysteem gepresenteerd met betrekking tot de voorgestelde behandeling waarin alleen Graad I & II bloedingen met een bloedingsgebied van 6 cm of groter en bij voorkeur alle Graad III bloedingen, door middel van TAE behandeld worden. Gezien het verhoogde risico op bloeding, wordt extra zorg (controle of preventieve behandeling) geadviseerd in patiënten met leveradenomen die van de lever pulsen (exofytisch). Het doel van HOOFDSTUK 6 was risicofactoren voor bloeding in kaart te brengen in patiënten met leveradenomen. Bloeding werd gedefinieerd op CT en/of MRI zoals hierboven beschreven. In 64% van de patiënten met de diagnose leveradenomen werd een bloeding gezien in (minstens 1) leveradenoom. Indien alle leveradenomen in alle patiënten werden beoordeeld, werd in 22% van alle leveradenomen een bloeding gezien. Patiënten met een ‘body mass index’ (BMI) van meer dan 35 hebben een verhoogd risico op ernstige bloedings (Graad II & III). Leveradenomen van 5 cm of groter vertonen meer bloedings dan lesies die kleiner zijn, exofytische lesvies vertonen vaker bloeding dan lesions die intrahepatisch of subcapsular in de lever liggen. Lesies in de linker laterale leversectoren (segment 2-3) vaker vaten bloedingen dan lesies in de rechter lever. Tenslotte is het risico op bloeding groter als er perifere of centrale arteriële in de rond het leveradenoom voorkomen.

Deel III

Van dit proefschrift bespreekt leverkanker (hepatocellulair carcinoom; HCC). In de afgelopen decennia wordt een toenemende trend van het aantal patiënten met HCC in West Europa, inclusief Nederland. In het Academisch Medisch Centrum zijn een speciale polikliniek en multidisciplinair team (GIJOCA: gastro-intestinaal oncologisch centrum Amsterdam) opgezet die verantwoordelijk zijn voor diagnostiek en behandeling van patiënten met tumoren van het spijsverteringskanaal die verdacht zijn voor een kwaadaardige tumor zoals HCC. De diagnose HCC wordt meestal door beeldvorming gesteld en het doel van HOOFDSTUK 7 was in kaart te brengen of de ‘F-FCH PET/CT’ van toegevoegde waarde is voor detectie van HCC.
en voor evaluatie van de uitgebreidheid van de ziekte. Net als in HOOFDSTUK 3 werd gebruik gemaakt van de SUVratio om de PET beelden te evalueren. Intrahepatische HCC lesions waren positief op de $^{18}$F-FCH PET/CT met een nauwkeurigheid van 88% en een SUVratio van 1.95 ± 0.66 (bij een afzak waarden van 1.12). Achtentwintig manifestaties van HCC buiten het leverparenchym worden daardoor niet aangetoond. In HOOFDSTUK 3 werden enkele belangrijke aspecten van de preoperatieve evaluatie van HCC en eventuele metastasen. In HOOFDSTUK 8 werd de rol van diagnostisch onderzoek voor het hepatoblastoom en de evaluatie van behandeling in deze patiënt. De bevindingen op de $^{18}$F-FCH PET/CT lieten zien dat de behandeling van HCC, met name door de nauwkeurige detectie van extrahepatische ziekte, beeldvormende technieken zijn tegenwoordig diagnostisch voor HCC en eventuele metastasen. In HOOFDSTUK 8 wordt de rol van diagnostisch laparoscoope (DL) in patiënten met HCC onderzocht. In deze studie werden alle patiënten van HCC die een DL ondergingen tussen januari 1999 en december 2001 geïncludeerd. Zes patiënten ondergingen DL om de uitgebreidheid van het HCC en de kwaliteit van het leverparenchym in kaart te brengen. Een biopsie van de niet-aangedane lever werd verricht in 25 patiënten die een DL ondergingen en hetgeen leidde tot een verandering in behandeling in 4 patiënten met cirrose (17%). In slechts 7% van de patiënten had DL een toegevoegde waarde met een nauwkeurigheid van 95%. Met de huidige technieken in kaart brengen en voor evalueren van de uitgebreidheid van de ziekte is het dus van belang te weten welke technieken in kaart brengen en voor evalueren van de uitgebreidheid van de ziekte. In deze studie werden alle patiënten met HCC die een DL ondergingen tussen januari 1999 en december 2001 geïncludeerd. Zes patiënten ondergingen DL om de uitgebreidheid van het HCC en de kwaliteit van het leverparenchym in kaart te brengen. Een biopsie van de niet-aangedane lever werd verricht in 25 patiënten die een DL ondergingen en hetgeen leidde tot een verandering in behandeling in 4 patiënten met cirrose (17%). In slechts 7% van de patiënten had DL een toegevoegde waarde met een nauwkeurigheid van 95%. Met de huidige technieken in kaart brengen en voor evalueren van de uitgebreidheid van de ziekte is het dus van belang te weten welke technieken in kaart brengen en voor evalueren van de uitgebreidheid van de ziekte.
De Gd-EOB-DTPA MRI laat een hoge nauwkeurigheid zien wanneer standaard dynamische series gecombineerd worden met de hepatobiliaire fase voor de differentiatie van HCA en FNH in afwijkingen groter dan 2cm.

PET/CT met 18F-FCH kan een HCA accuraat onderscheiden van FNH en kan een waardevolle aanvullende techniek zijn als De Gd-EOB-DTPA MRI geen uitsluitkans geeft.

Wanneer in patiënten met HCA of FNH een chirurgische behandeling geïndiceerd is, kan een beperkte resectie of enucleatie uitgevoerd worden met lage morbiditeit en zonder mortaliteit. Hierbij kan gebruik worden gemaakt van een open of laparoscopische benadering. Patiënten met pre-operatieve klachten lieten een hoog percentage aan symptoomverlichting zien na chirurgische interventie.

Een graderingsysteem voor bloedingen in HCA wordt voorgesteld waarin Graad I & II bloedingen met een bloedingsgebied groter dan 6cm en alle Graad III bloedingen behandeld worden met transarteriële embolisatie. Extra zorg door middel van controle of preventief ingrijpen wordt geadviseerd in patiënten met exofytische lesies.

Bloedingen in HCA wordt gezien in 64% van patiënten en in 22% van alle HCA lesies. Patiënten met een ‘body mass index’ (BMI) van 25 of meer hebben een verhoogde kans op een ernstige Graad II&III bloeding. HCA groter dan 35mm, exofytische HCA, HCA in segment 2-3 van de lever en HCA met centrale of perifere voedende arteriën, hebben een hoger risico voor bloeding.

18F-FCH PET/CT heeft toegevoegde waarde in patiënten met HCC met implicaties voor stagering, behandeling en evaluatie van behandeling, door de accurate detectie van extrahepatische ziekte.

Met de huidige accurate beeldvorming en de implementatie van percutane biopsie van het niet-aangedane leverparenchym in de pre-operatieve work-up van patiënten met HCC, is het voordeel van een diagnostische laparoscopie weg gevallen.

Een overzicht van een cohort patiënten met HCC behandeld in het AMC kwam overeen met data van Westerse centra. Factoren die geassocieerd zijn met overleving van patiënten met HCC zijn ASAT, albumine, ascites, macrovasculaire betrokkenheid en de grootte van de tumor.

18F-FCH PET/CT bleek een veelbelovende aanvullende beeldvormende techniek voor het hepatoblastoom en bleek nuttig voor stagering van de ziekte en evaluatie van de behandeling.

Levergranulomen die simultaan met HCA voorkomen ontstaan waarschijnlijk door een lokale respons op een (inflammatoir) adenoom of neoplasma, chronische gebruik van de pil, of een combinatie van deze factoren.

In asymptomatische patiënten met een reuzenhe-mangioom van de lever is observatie gerechtvaardigd. Wanneer een patiënt mechanische klachten heeft, of wanneer de diagnose onzeker is, is chirurgische interventie geïndiceerd. In deze patiënten is enucleatie de aangewezen methode.

Eerste indruk kan bedriegen: macroscopisch kan een bevinding de indruk geven van uitgebreide metastasering, maar aanvullende vriescoupes kunnen de diagnose bevestigen wanneer nodig. In deze patient bleken multiple galgang hamartomen samen te gaan met een FNH.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>#F-FCH</td>
<td>*fluoromethylcholine</td>
</tr>
<tr>
<td>#F-FDG</td>
<td>*F-Fluorodeoxyglucose</td>
</tr>
<tr>
<td>AASLD</td>
<td>American Association for the Study of Liver Diseases</td>
</tr>
<tr>
<td>AF</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>AFP</td>
<td>Alpha fetoprotein</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>AMC</td>
<td>Academic Medical Center</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate transaminase</td>
</tr>
<tr>
<td>BCLC</td>
<td>Barcelona-Clinic Liver Cancer</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CDP</td>
<td>Cytidine diphosphocholine (Kennedy pathway)</td>
</tr>
<tr>
<td>CEA</td>
<td>Carcinoembryonic antigen</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CK7</td>
<td>Cytokeratin 7 (staining)</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>Computer Tomography</td>
</tr>
<tr>
<td>CUSA</td>
<td>Cavitron® Ultrasonic Surgical Aspirator</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
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<tr>
<td>EASL</td>
<td>European Association for the Study of the Liver</td>
</tr>
<tr>
<td>FISP</td>
<td>Fast imaging with steady-state precession</td>
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<tr>
<td>FNH</td>
<td>Focal nodular hyperplasia</td>
</tr>
<tr>
<td>FRLV</td>
<td>Future remnant liver volume</td>
</tr>
<tr>
<td>Gd</td>
<td>Gadoxetate disodium</td>
</tr>
<tr>
<td>Gd-EOB-DTPA</td>
<td>Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid</td>
</tr>
<tr>
<td>GH</td>
<td>Granulomatous hepatitis</td>
</tr>
<tr>
<td>GS</td>
<td>Glutamine synthetase</td>
</tr>
<tr>
<td>HBS</td>
<td>Tc-labeled mebrofenin hepatobiliary scintigraphy</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>HCA</td>
<td>Hepatocellular adenoma</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>HE</td>
<td>Haematoxyline-eosine (staining)</td>
</tr>
<tr>
<td>i.v.</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LA</td>
<td>Leveradenoom</td>
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<tr>
<td>LFABP</td>
<td>Liver–fatty acid-binding protein</td>
</tr>
<tr>
<td>LoS</td>
<td>Postoperative length of stay</td>
</tr>
<tr>
<td>LR</td>
<td>Likelihood ratio</td>
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<tr>
<td>MBq</td>
<td>Megabecquerel</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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</tbody>
</table>

NWC: Number of words count (S, sensory; A, affective; E, evaluation)
OC: Oral contraceptive
OCT1: Organic cation transporter 1
PC: Phosphocholine
PET/CT: Positron Emmision Tomography
PPV: Positive predictive value
PRI: Pain rating index (S, sensory; A, affective; E, evaluation).
RFA: Radiofrequency ablation
SAA: Serum amyloid A
SIRT: Selective internal radiation therapy
SL: Staging laparoscopy
SPECT: Single-photon emission computed tomography
SUV: Standard uptake value
SUVmax: Maximum standardized uptake value
SUVmean: Mean SUV of surrounding tissue
TAE: Transarterial embolization
TLV: Total Liver Volume
TV: Tumor Volume
VAS: Visual analogue scale
VIBE: Volumetric interpolated breath-hold examination
VLDL: Very-low-density-lipoproteins
yGT: Gamma glutamyl transpeptidase
Diagnostic accuracy of MRI in differentiating hepatocellular adenoma from focal nodular hyperplasia: prospective study of the additional value of gadoxetate disodium.  

Outcomes of liver resection in hepatocellular adenoma and focal nodular hyperplasia.  

The use of 18F-fluoromethylcholine PET/CT in differentiating focal nodular hyperplasia from hepatocellular adenoma: a prospective study of diagnostic accuracy.  

Hepatoblastoma evaluated by 18F-fluoromethyl choline PET/CT.  

Von Meyenburg complexes mimicking metastatic disease at laparotomy for focal nodular hyperplasia.  

Hepatocellular adenomas associated with hepatic granulomas: experience in five cases.  

Differentiation of hepatocellular adenoma and focal nodular hyperplasia using 18F-fluorocholine PET/CT.  

Skin autofluorescence is elevated in neovascular age-related macular degeneration.  

Management of giant liver hemangiomas: an update.  

Giant haemangioma of the liver: diagnosis and treatment.  
Staging laparoscopy in patients with hepatocellular carcinoma: is it useful? 

Fibrin sealant for prevention of resection surface-related complications after liver resection: a randomized controlled trial.
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Let’s have more dreams together.
1. **International Hepato-Pancreato-Biliary Association, Buenos Aires, Argentina** [2010]
   Differentiation of hepatocellular adenoma and focal nodular hyperplasia using 18F-fluorocholine PET/CT; preliminary results.
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