Hepatocellular adenoma
'A new perspective'

Susanna Maria van Aalten

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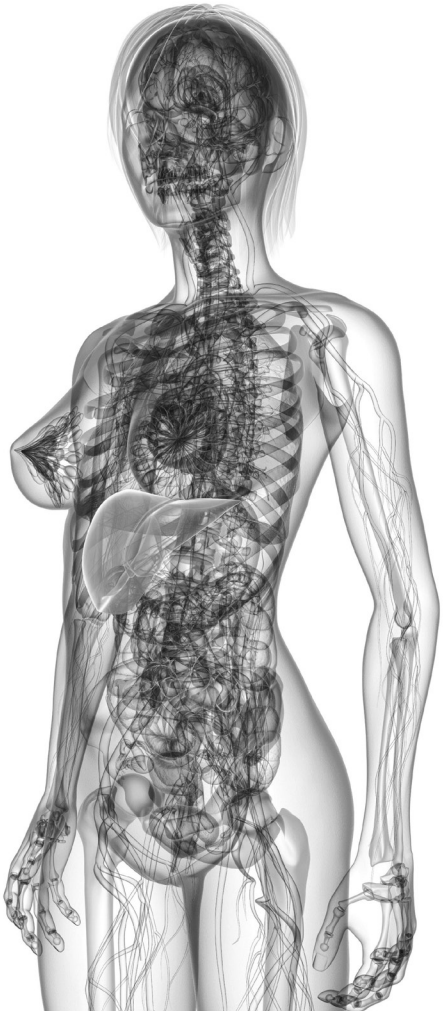
Chapter 1

General introduction



INTRODUCTION

Since the introduction and widespread use of abdominal imaging technologies there has been an increase in the frequency of detection of space-occupying lesions in the liver. In particular due to the use of ultrasound imaging which is frequently used because of its safety and non-invasive nature and its accessibility [1]. Liver tumors that are found by incidence are defined as findings unrelated to the clinical indication for which the imaging examination was performed. To decide which of these tumors needs therapy further characterization with highly advanced imaging modalities (magnetic resonance imaging (MRI)) or needle biopsy is needed. Core needle biopsy is still accepted as the gold standard for diagnosing tumors in various organs. However, there is an increasing role for radiology in the diagnosis of focal liver tumors, especially by the use of state-of-the-art MRI. Moreover, most hepatic tumors can be diagnosed with confidence by the use state-of-the-art MRI, which may have consequences for the role of needle biopsy during work-up of focal liver lesions [2].

A tumor is a space occupying mass of tissue. The word tumor is not synonymous with cancer, because a tumor may be either benign or malignant. Malignant primary liver tumors can spread to other areas of the body and can be fatal. Malignant liver tumors frequently need therapy or long term follow-up. Benign liver tumors do not spread to other areas of the body and are generally not life-threatening. Various benign focal liver lesions can occur in patients. The most common benign liver lesions are hemangiomas (masses of blood vessels), simple cysts (fluid-filled cavities), focal nodular hyperplasia (FNH) and hepatocellular adenomas (HCA). In most cases, benign liver tumors are not detected because they cause no symptoms and these masses are typically found during a routine examination. The indication for the treatment of benign liver tumors frequently depends on their size, presence of symptoms and the type of tumor. In this thesis we focus on solid benign liver tumors, in particular HCA.

HEPATOCELLULAR ADENOMA

Complex situations may arise in case of HCA with confusion for doctors and patients. HCA is a rare benign tumor of the liver that typically presents in women within their reproductive years. Although the etiology and pathogenesis of HCA is unknown, an association of HCA with the use of estrogen containing oral contraceptives (OC) was first described in 1973 [3]. In subsequent years many authors supported the hypothesis of an association between OC and HCA [4-8]. It should be noted that HCA were rarely reported before the commercial introduction of OC in the 1960s. Regression of HCA may occur

when OC are withdrawn [9-12]. The mechanism by which estrogen or other steroids contributes to the development of HCA is still not understood.

Despites its benign character, HCA can be complicated by hormone induced growth and rupture and bleeding of the tumor. Moreover, malignant transformation has been reported in rare instances [13]. Symptomatic patients with HCA present with right upper quadrant abdominal pain or discomfort secondary to bleeding within the HCA, elevated liver enzymes and symptoms of life treating hemorrhage into the peritoneal cavity. But most patients with HCA are asymptomatic and present as an incidental finding during ultrasonographic examination of the abdomen for unrelated reasons or are noted during laparoscopic cholecystectomy.

HCA can be solitary or multiple. In 1985, Flejou et al. defined more than 10 nodules found in an otherwise normal liver parenchyma as liver adenomatosis. Macroscopically the HCA lesion is smooth and soft on palpation. Microscopic examination shows well-circumscribed tumors with cords of hepatocytes having a glycogen and lipid content and showing loss of the normal lobular architecture with absence of portal tracts and hepatic veins. The hepatic plate may be two or more cells thick separated by dilated sinusoids. Bile ductules are absent, a key histologic feature that helps distinguish it from FNH [14, 15]. The cut surface of the adenoma has a characteristic yellow appearance, which comes from the lipid accumulation. A proportion of HCA also shows cytonuclear atypia. It may be difficult to distinguish HCA from other benign or malignant liver tumors. The differential diagnosis of HCA includes FNH and well differentiated hepatocellular carcinoma. FNH is a benign solid tumor of the liver of vascular etiology, usually observed in female patients. Microscopically there is a central scar that contains larger arteries and smaller bile ducts surrounded by regenerative hepatocyte nodules [16, 17]. Differentiation may also be difficult based on radiological imaging because both tumors have radiological similarities. Many imaging modalities are available to detect benign liver tumors, however state-of-the-art MRI provides the most comprehensive and non-invasive imaging work-up of patients with suspected HCA [18].

Unlike FNH, HCA frequently requires treatment because of possible life-threatening complications in case of large tumors and in case there is a pregnancy wish in women with child bearing potential. Women with HCA seem to be at greater risk of bleeding during pregnancy. The debate whether to manage HCA by surveillance or surgical resection continues. Conservative management of HCA frequently implies cessation of the use of OC and intermittent follow-up by radiological imaging. Whereas aggressive treatment may include surgical resection of the tumor(s), transarterial embolization

(selective occlusion of blood vessels) or radiofrequency ablation therapy (destroys tissue by application of interstitial hyperthermia resulting in coagulative necrosis).

AIM OF THE THESIS

The overall aim of this thesis was to analyze the clinical, pathologic and radiologic characteristics of patients presenting with HCA and to establish a decision-making model for the management of HCA.

The management of HCA may pose clinical dilemmas since there is a lack of standardized protocols. The debate whether to manage solitary adenomas by surveillance or surgical resection continues. **Chapter 2** describes the present day-to-day management of HCA in the Netherlands based on expert opinions on diagnosis and treatment of HCA.

The Bordeaux group established a pathological and molecular classification system for HCA. HCA were divided into four different subgroups based on morphological criteria, molecular characteristics and by the use of an immunohistochemical panel of markers. In **chapter 3** we asked ourselves the following questions: Is it possible to distinguish subgroups of HCA based on pathological findings and is it possible to correlate pathological findings with imaging characteristics on state-of-the-art MRI?

HCA in pregnant women requires special considerations because of the risk of hormone induced growth and spontaneous rupture, due to increased levels of steroid hormones during pregnancy that may threaten the life of both mother and child. Most experts advocate that women with HCA should not get pregnant or advise surgical resection before pregnancy [19, 20]. **Chapter 4** describes the management of HCA during pregnancy and a proposal is made for a multicenter prospective study to give more insight in the behavior of HCA during pregnancy. We hypothesized that pregnancy may be allowed in case of one or more known HCA < 5 cm, because HCA < 5 cm will not disturb the course of pregnancy.

Treatment is indicated in selective cases. The management of HCA might become complex in patients with centrally located HCA or multiple HCA in both lobes of the liver. In **chapter 5** the safety and efficacy of radiofrequency ablation (RFA) for the treatment of HCA and liver adenomatosis is investigated. RFA destroys tissue by application of interstitial hyperthermia resulting in coagulative necrosis.

Although HCA is a benign tumor of the liver, the diagnosis has a great impact on the lives of young women. HCA can be complicated by hormone induced growth and subsequently spontaneous rupture. **Chapter 6** of this thesis gives a systematic review of the literature on the risk on hemorrhage and rupture of HCA.

In **chapter 7** the current knowledge about diagnosis and treatment modalities of HCA is discussed and a decision-making model for the management of HCA is proposed.

Finally, in **chapter 8** the results of the studies performed in this thesis are summarized and discussed.

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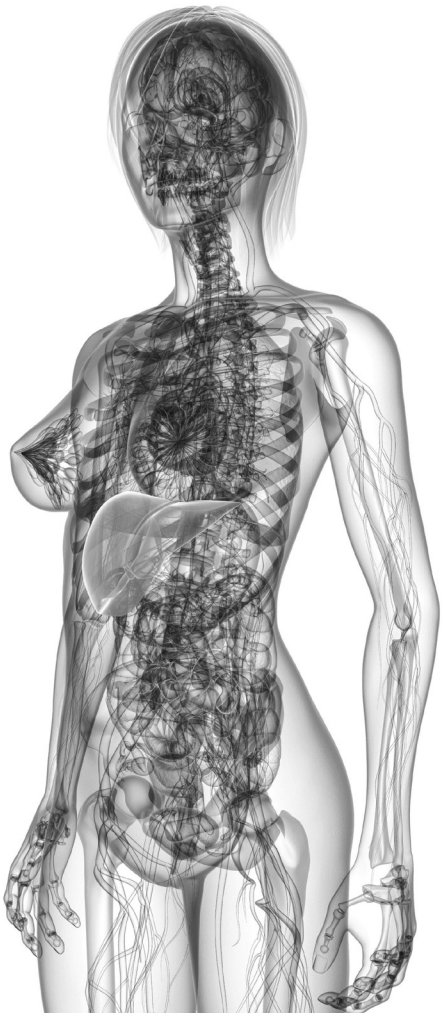
Chapter 2

Diagnosis and treatment of hepatocellular adenoma in the Netherlands: Similarities and differences



Digestive Surgery, 2010; 27(1):61-7

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ABSTRACT

Background: The diagnosis of hepatocellular adenoma (HCA) has a great impact on the lives of young women and may pose clinical dilemmas to the clinician since there are no standardized protocols to follow. We aimed to establish expert opinions on diagnosis and treatment of HCA by collecting data from a nationwide questionnaire in the Netherlands.

Methods: A questionnaire was sent to 20 Dutch hospitals known to offer hepatologic and surgical experience on liver tumours.

Results: 17 hospitals (85%) responded to the questionnaire. Annually, a median of 52 patients presented with a solid liver tumour. In 15 (88%) hospitals, hepatic adenomas were diagnosed with contrast-enhanced, multiphase spiral CT or MRI. In 2 (12%) hospitals, histology was required as part of a management protocol. Surveillance after withdrawal of oral contraceptives was the initial policy in all clinics. MRI, CT or ultrasound was used for follow-up. Criteria for surgical resection were a tumour size > 5 cm and abdominal complaints. In 5 (29%) hospitals, patients were dismissed from follow-up after surgery. In complex cases (e.g. large, multiple or centrally localized lesions, a wish for pregnancy), the treatment policy was highly variable. Pregnancy was not discouraged in 15 hospitals, but in 11 (65%) of these, strictly defined conditions were noted: frequent follow-up, peripheral tumour localization that makes surgery easier if necessary, stable tumour size, and a good informed consent.

Conclusion: The management of HCAs in the Netherlands is rather uniform, except in complex cases in which multiple factors may influence policy.

INTRODUCTION

The diagnosis of hepatocellular adenoma (HCA) has a great impact on the lives of young women. HCA is a benign tumour that usually presents as a solitary nodule; in a minority, multiple lesions are seen. This tumour is mostly detected in females within their reproductive years, associated with a long-term use of oral contraceptives (OC). The incidence is low, estimated to be 3–4/100,000 in long-term OC users [1]. During pregnancy the presence of HCA can be complicated by growth and rupture which is induced by elevated hormone levels. Rupture and bleeding is associated with high maternal and fetal mortality [2–5]. Malignant transformation of HCA to hepatocellular carcinoma (HCC) occurs rarely, but the true incidence of malignancy arising within HCA is not known [6, 7]. Patients with HCA may present with right upper quadrant abdominal pain secondary to bleeding, elevated liver enzymes and symptoms of life-threatening haemorrhage. However, most patients are asymptomatic. Since the introduction and widespread use of highly advanced imaging modalities, the number of solitary nodules that are found by accident has greatly increased in the last decennium [8].

The debate whether to manage solitary adenomas by surveillance or surgical resection continues. Conservative management of HCA frequently implies cessation of the use of OC, intermittent follow-up by radiological imaging and negative advice regarding pregnancy. Surgical treatment of HCA is associated with a risk of morbidity and mortality and does not guarantee relief of complaints. The most important reason for surgery is size of the lesion, since rupture as well as malignant transformation is seldom reported in lesions <5 cm [7]. Patients with an adenoma which is <5 cm and who do have a wish for pregnancy might also benefit from an early intervention in order to avoid an invasive treatment during pregnancy [9]. In practice, management strategy is not only determined by the size of the HCA, but may also depend on complaints, the number and localization of nodules, a wish for pregnancy and surgical risks. Therefore, the policy for HCA should be standardized while there is a place for a custom-made approach when considering these factors. For this purpose, we collected data by a nationwide questionnaire in order to establish the most common approach in diagnosis and treatment of HCA in the Netherlands.

METHODS

In January 2005, a questionnaire was sent to 20 Dutch university centres and hospitals with a large programme of hepatobiliary surgery (Table 1). Hepatobiliary surgeons in these hospitals all participate in the Dutch Liver Surgery Working Group of which is a division of the Dutch Society for Surgery. Both the departments of surgery and gastroin-

Table 1. Summary of questionnaire concerning policy in case of HCA held in The Netherlands

Incidence
Are patients with solid liver tumours registered?
How many liver tumours are seen each year?
How many of them are benign?
Is there a multidisciplinary consultation team to determine treatment policy?
Diagnosis
Which imaging tools are being used for diagnosis?
Is there a role for liver biopsy in diagnosis of hepatocellular adenoma?
Are patients being tested for hepatitis B or C infection?
Therapy
Define surveillance
What are criteria to switch to invasive therapy?
What would be the first option?
Is the histological diagnosis of the resected specimen always conform preoperative histological diagnosis?
Follow-up
Is there a follow-up after conservative management?
Is there a follow-up after surgery?
What kind of follow-up is being used and for how long?
What are the reasons for follow-up?
Pregnancy
What do you advise a patient with a wish for pregnancy?
Did you ever had a pregnant patient with an adenoma in situ?

testinal diseases were invited to take part in this questionnaire. In May 2005, a reminder was sent to those who had not responded. The questionnaire included multiple-choice questions concerning incidence, diagnosis, treatment and follow-up of HCA in the Netherlands. There was a possibility to add a comment next to each question. Specialists were asked what they would advise a women with a HCA and a wish for pregnancy. In questions concerning treatment, we proposed that a conservative policy was followed initially. Thereafter, the question was asked on what criteria invasive treatment could have been chosen. Clinical dilemmas on HCA were discussed on the basis of 5 imaginary cases. These cases had an open-answer option. Statistical data were analyzed using SPSS for Windows Version 13.0 (SPSS, Chicago, Ill., USA).

RESULTS

Of the 20 hospitals (8 university centres and 9 general hospitals), 17 (85%) responded. In 8 (47%) of these 17 hospitals, data on incidence were from prospective databases. Data from the remaining hospitals were based on retrospective analyses or estimates by specialists.

Incidence

A median of 52 patients with a solid liver tumour presented annually per hospital (range 3–415). Between 1 and 40% of these patients had benign lesions with a differential diagnosis of adenoma, focal nodular hyperplasia, and haemangioma.

Diagnostics

In 16 (94%) hospitals the policy for individual patients was determined by a multidisciplinary consultation of a surgeon, hepatologist, radiologist, oncologist and pathologist. The diagnosis of HCA was usually based on imaging modalities. Multiphase spiral CT series were performed in 12 (71%) hospitals. Multiphase contrast-enhanced MRI series were also applied in 12 hospitals. These data show that in 15 (88%) hospitals HCAs were diagnosed with contrast-enhanced, multiphase spiral CT or MRI series. In 2 (12%) hospitals a liver biopsy was required for histological diagnosis. 13 (76%) hospitals followed the standard policy to test patients with a solid nodule for hepatitis B and C. Additional tests included serum analyses for iron overload (8 (53%) hospitals), α_1-antitrypsin deficiency and alcohol consumption (both in 2 (12%) hospitals).

Treatment

In 12 (71%) hospitals the policy for HCA was not structured in a protocol. Surveillance was the initial strategy in all hospitals. This policy consisted of withdrawal of OC and outpatient control by an imaging modality at least once. The kind of imaging tool that was used varied; MRI, CT or ultrasound was performed for follow-up in respectively 7 (41%), 10 (59%) and 8 (47%) hospitals. The interval between follow-up episodes also varied. Follow-up after 6 months was mentioned in 10 (59%) hospitals, but intervals of 3, 4, or 12 months were also reported. Another question concerned the situation in which a patient could resume the use of OC. This was assumed to be possible in 8 (47%) hospitals. Six hospitals reported that in patients who did not show a regression of the lesion up to 1 year after stopping, the use of OC could be resumed. Comments were made that patients tended not to resume the use of OC and often wanted to have imaging information about renewed growth. Major criteria for surgical resection were a tumour size >5 cm (16 (94%) hospitals) and abdominal complaints (15 clinics, 88%). In those cases the decision for radical resection of the liver tumour was unanimous. In case of multiple adenomas the motivation for surgical intervention was determined by the pattern of complaints, size and localization of the lesions, opportunities to treat all tumours and the availability and use of alternative treatments such as radiofrequency ablation. Other criteria were a wish for pregnancy, signs of malignancy, tumour growth, diagnostic doubt and localization in respectively 7 (41%), 10 (59%), 4 (24%), 5 (29%) and 7 (41%) of all hospitals. In 14 (82%) hospitals it had occurred that histological analysis of the resected specimen showed another diagnosis compared to the preoperative

diagnosis. Most of these cases were focal nodular hyperplasia. Five (29%) hospitals mentioned a few cases in which a HCC was diagnosed after resection.

Follow-Up

Patients who were managed by surveillance were followed for a median period of 4 years (range 1–10) in all hospitals. In 14 (82%) of the 17 hospitals, radiological tools were used to monitor growth and malignant transformation. After surgical resection, in 5 (29%) hospitals follow-up was not considered necessary. In the other cases, patients were followed for a median period of 2 years (range 1–5). Growth or residual lesions were monitored. Pregnancy was not discouraged in 15 hospitals, but in 11 (65%) of these, strictly defined conditions such as frequent follow-up (4 hospitals), a peripheral tumour localization that makes surgery easier if necessary (2 hospitals), a stable tumour size (2 hospitals), and a good informed consent about the risks in case of pregnancy (2 hospitals) were noted. No restrictions in patients with HCA were imposed in 4 hospitals. In only 1 hospital, 1 patient was advised to postpone pregnancy until a surgical resection had been performed. Seven hospitals reported 1 or more patient(s) who presented with an adenoma during pregnancy; growth of the tumour occurred in 4 cases. Three of them fulfilled their pregnancy without complications. In 1 hospital, 1 patient underwent a surgical resection during the first trimester of pregnancy and another patient underwent a premature caesarean section in the third trimester because of a rapidly growing adenoma.

Imaginary Cases

Clinical dilemmas on HCA were investigated on the basis of 5 imaginary cases (Table 2). Small asymptomatic adenomas were managed by surveillance. In case of a large adenoma which was located centrally in the liver, the choice between surveillance and surgical resection was difficult to make and answers varied widely on this point. In 6 hospitals an additional biopsy was preferred in case of multiple adenomas in order to exclude malignancy.

DISCUSSION

Data obtained from this survey show that most Dutch specialists who responded to the questionnaire rely on multiphase contrast-enhanced CT or MRI series to confirm the diagnosis of HCA. Using these techniques it is usually possible to differentiate adenomas from other benign lesions such as focal nodular hyperplasia and haemangioma as well as from malignancies [10–12]. No strict consensus for the optimal imaging work-up of liver lesions was found. Most often, MRI was applied to characterize liver lesions by using

Table 2. Imaginary cases and answers of specialists from 17 hospitals with expertise in hepatobiliary surgery

Case	Policy	Hospitals, n
48-year-old female with a hilar-located adenoma of 8 cm and signs of intrahepatic bleeding	Resection if possible Arterial embolisation RFA Observation	7 (41%) 4 (24%) 1 (6%) 5 (29%)
23-year-old female with an incidentally found adenoma located in the middle of the right lobe; she uses OC and has a clear wish for pregnancy in future	Surveillance Surveillance, invasive treatment in case of growth or no regression RFA	11 (65%) 4 (24%) 2 (12%)
40-year-old obese female diagnosed with 4 lesions suspected for adenoma: 2 are located in the right liver (diameter 6 and 2 cm) and two in the left (diameter 2 and 3 cm)	Surveillance Resection of largest one Resection of largest adenoma and RFA of other lesions RFA of largest lesion	7 (41%) 4 (24%) 5 (29%) 1 (6%)
Female patient with an adenoma of 8 cm; regression occurred after stopping OC; the tumour now measures 4 cm and she wants to become pregnant	Resection before pregnancy RFA before pregnancy Good informed consent and surveillance during pregnancy	10 (59%) 2 (12%) 5 (29%)
Female patient with an adenoma of 4 cm, which did not show regression after stopping OC; she wants to be pregnant	Frequent surveillance during pregnancy Resection or RFA before pregnancy Informed consent; the patient has to decide for surveillance, surgery or RFA	8 (47%) 7 (41%) 2 (12%)

RFA = Radiofrequency ablation; OC = Oral contraceptives

multiphase dynamic contrast-enhanced techniques. The availability of tissue-specific contrast media in MRI, e.g. gadobenate dimeglumine, which is one of the most recently used agents in hepatic imaging, permits lesion characterisation based on its cellular composition, enhancement pattern and morphological features [13]. The use of this highly advanced imaging modality during differential diagnosis of a focal liver lesion will prevent unnecessary liver biopsy or surgery. The role of ultrasound-guided percutaneous liver biopsy is debatable as various studies indicate that histology on needle biopsies may not be conclusive regarding HCA, focal nodular hyperplasia and well-differentiated HCC [14–16]. Only 2 hospitals in our questionnaire indicated that a biopsy was required to establish the diagnosis of HCA. Conservative management, including imaging surveillance and discontinuation of OC, was the initial policy in all hospitals (Figure. 1). This strategy is in accordance with several studies advocating a conservative approach [14, 15, 17, 18]. Some authors emphasize the possibility of malignant transformation in large lesions [17, 19, 20] and tend to resect HCAs >5 cm. The relationship between tumour size and bleeding risk is unclear. After rupture or bleeding of HCAs it is difficult to identify the size of the original tumour as a haematoma may disturb imaging reliability. While most patients with an adenoma are asymptomatic, up to 60% of those who present with symptoms do have signs of bleeding [15, 19, 21]. Although tumour size is the most

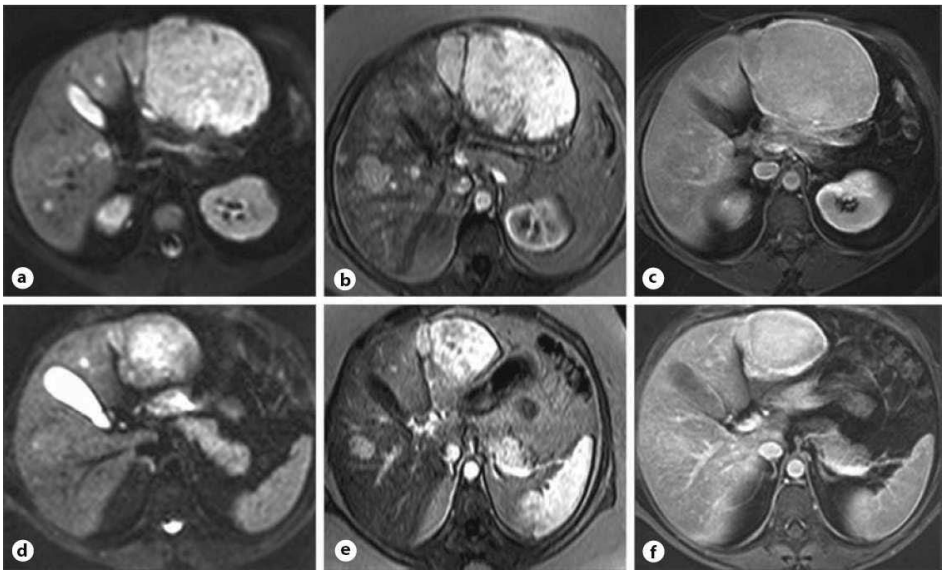

Figure 1. Contrast-enhanced multiphase MRI series of patient with HCA: **(a)** T2-weighted, **(b)** arterial phase, **(c)** delayed phase during use of OC, **(d)** T2-weighted, **(e)** arterial phase, and **(f)** delayed phase after stopping use of OC.

important factor to decide whether to manage by observation or to perform a surgical resection, abdominal pain was an equally important determinant. Surgical resection of HCA is described as an effective method to reduce complaints. However, various experts stress that it should be ascertained that symptoms are related to the HCA [15]. Abdominal pain often arises due to the sudden increase in volume of a haematoma. Bleeding can be managed conservatively and resorption of a haematoma can equally reduce symptoms. Many experts answered to favour a wait-and-see policy in dynamically stable patients [22]. The localization of a HCA and the surgical risks determine whether a surgical approach is feasible. If there are doubts about radiological diagnosis, specialists are more likely to favour surgical resection, i.e. to exclude HCC. Clinical dilemmas occur when multiple factors mentioned above are to be considered. In these situations it is complex to define an appropriate treatment strategy and comments varied considerably between specialists. The use of imaging modalities is essential during follow-up of HCA, since there is a large discrepancy between clinical signs of patients and the size or growth of the adenoma. It has to be noted that it is a difficult decision to discourage pregnancy in otherwise healthy young women. Pregnancy was not discouraged in most of the clinics, but in most of the imaginary cases, a majority of experts wanted to exclude the risk of bleeding by resection before pregnancy. In a recently published review of 27 women who were pregnant with a HCA in situ, rupture occurred in 16 of them, leading to death of mother or child in 7 cases [5]. However, it has to be noted that all of these case reports were published in the 1970s or 1980s. In this period, the

routine use of ultrasonography was less frequent and there might have been a delay in diagnosis because of confusion with other pregnancy-related diseases like preeclampsia or pulmonary embolism. When women are informed about the potential risks, it is safe to allow pregnancy, especially if the lesion is accessible for limited surgical resection. It seems unjustified to discourage all women with HCAs from pregnancy. In women with a clear diagnosis of a single HCA with a diameter <5 cm and without complaints, most experts advise a conservative policy. After discontinuation of OC, HCA does not seem to grow and the likelihood of bleeding decreases [23]. If the diagnosis of HCA is uncertain and the diagnosis HCC remains in differential diagnosis, radical resection of the tumour is recommended. At our centre, surgical treatment of solitary adenomas is restricted to patients having lesions that measure ≥5 cm, in those patients in which malignancy cannot be excluded and to lesions that do not show adequate regression after discontinuation of OC, especially in case of women with a wish for pregnancy [9, 15]. However, due to the invasive nature of hepatic surgery and the risk of postoperative morbidity, other treatment strategies are needed. Several authors have described the successful application of minimal invasive strategies such as transarterial (chemo)embolization and radiofrequency ablation [24–28] . The role of these alternative treatments in case of HCA still needs to be established in clinical studies. Recent identification of gene mutations, such as mutations in hepatocyte nuclear factor 1α and β-catenin that seem to be correlated to the phenotype of HCA, will create a basis for a new genotype/phenotype classification of HCAs. These developments will hopefully permit significant improvements in liver biopsy interpretation, creating the possibility to predict the risk of bleeding and malignant transformation and the ability to propose better guidelines in terms of surveillance and treatment [29, 30]. We conclude that the management of HCAs in the Netherlands is rather uniform. However, in complex situations where multiple factors may play a role in determining the management strategy, such as pregnancy or multiple adenomas, respondents' opinions are very variable regarding treatment and follow-up. Because evidence-based data are scarce in the literature, it is recommended that Dutch specialists exchange knowledge and data of patients with HCA to develop the most adequate guidelines in complex situations, justifying a custom-made approach. This will prevent unnecessary surgery and may offer well-balanced advice on pregnancy in case of more complex cases.

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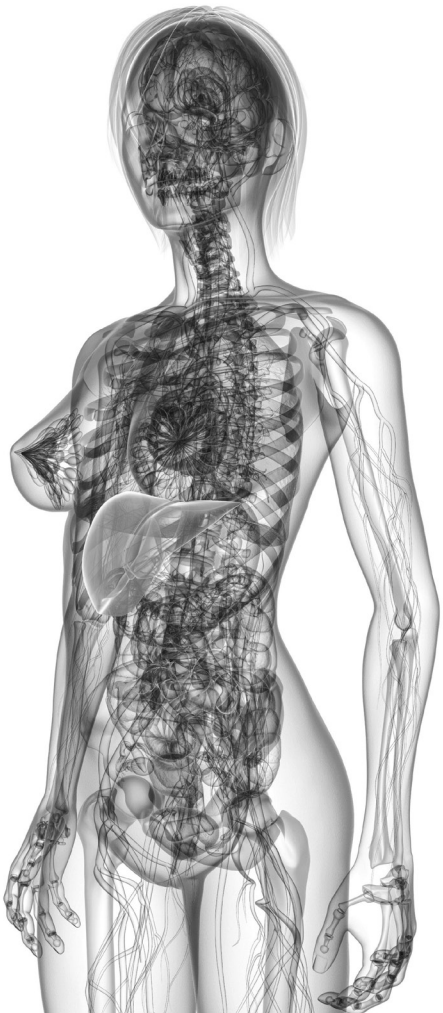
Chapter 3.1

Validation of a liver adenoma classification system in a tertiary referral centre: Implications for clinical practice



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ABSTRACT

Background & Aims: A molecular and pathological classification system for hepatocellular adenomas (HCA) was recently introduced and four major subgroups were identified. We aimed to validate this adenoma classification system and to determine the clinical relevance of the subtypes for surgical management.

Methods: Paraffin fixed liver tissue slides and resection specimens of patients radiologically diagnosed as HCA were retrieved from the department of pathology. Immunostainings included liver-fatty acid binding protein (L-FABP), serum amyloid A (SAA), C-reactive protein (CRP), glutamine synthetase (GS) and β-catenin.

Results: From 2000 to 2010, 58 cases (71 lesions) were surgically resected. Fourteen lesions were diagnosed as focal nodular hyperplasia with a characteristic map-like staining pattern of GS. Inflammatory HCA expressing CRP and SAA was documented in 36 of 57 adenomas (63%). Three of these inflammatory adenomas were also β-catenin positive as well as GS positive and only one was CRP and SAA and GS positive. We identified eleven L-FABP-negative HCA (19%) and four β-catenin positive HCA (7%), without expression of CRP and SAA and with normal L-FABP staining, one of which was also GS positive. Six HCA were unclassifiable (11%). In three patients multiple adenomas of different subtypes were found.

Conclusions: Morphology and additional immunohistochemical markers can discriminate between different types of HCA in >90% of cases and this classification, including the identification of β-catenin positive adenomas may have important implications in the decision for surveillance or treatment. Interpretation of nuclear staining for β-catenin can be difficult due to uneven staining distribution or focal nuclear staining and additional molecular biology may be required.

INTRODUCTION

Hepatocellular adenoma (HCA) is a rare benign tumor of the liver that occurs predominantly in women, in most cases within their reproductive years. The estimated incidence is about 1–1.3 per 1,000,000 in women who have never used oral contraceptives (OC), compared to a substantial higher incidence of 30–40 per 1,000,000 in long-term users [1,2]. These data refer to studies performed decades ago. Although to date the incidence may be lower due to reduced concentrations of OC, the detection rate may have increased due to better and more frequently applied imaging techniques [3,4].

Recently, a new molecular and pathological classification of HCA was introduced by Bioulac-Sage and colleagues who suggested that the identification of subtypes might be of great clinical importance [5]. They divided HCAs in four subgroups, based on morphological criteria, molecular characteristics and by the use of an immunohistochemical panel of markers. The first group, 35–40% of the HCA cases, was defined by the presence of mutations in the TCF1 gene that inactivate the hepatocyte nuclear factor 1α (HNF-1α). The second group, 10–15% of cases, showed the presence of β-catenin activating mutations. The third group, 50% of cases, showed inflammatory and/or telangiectatic HCAs with serum amyloid A (SAA) and C-reactive protein (CRP) expression. This group was histomorphologically characterized by the presence, with variable intensity, of inflammatory infiltrates, thick walled arteries, sinusoidal dilatation and ductular reaction. Finally, less than 10% of HCA are unclassified [6–8].

There are several interesting findings from this study. HNF-1α mutated HCA have a lack of liver-fatty acid binding protein (L-FABP) expression in the tumor and this subtype is most of the time highly steatotic, with steatosis grade 2 and 3 in 27% and 36%, respectively [7,9]. Liver adenomatosis (HCA >10) is most often found in HNF-1α mutated HCA [6]. Another finding is that patients with a high body mass index (BMI) and excessive alcohol consumption were more frequently observed in the inflammatory group [10,11]. β-Catenin activated lesions seem to have a higher risk of malignant transformation in patients with HCA bigger than 4–5 cm [9,10]. Therefore identifying a β-catenin mutation is of major interest. It is well known that, it can be very difficult to differentiate HCA from a well-differentiated hepatocellular carcinoma (HCC), especially when some cytonuclear atypia is present. Additional markers may have great relevance in helping to discriminate these lesions. Glutamine synthetase (GS) is another useful marker in tumor liver pathology. A strong and diffuse/homogeneous GS staining is shown in β-catenin mutated HCA. In focal nodular hyperplasia (FNH), a 'map-like' staining pattern is described [12].

The aim of this study was to validate the classification system and to determine the clinical relevance of the subtypes for surgical management.

MATERIALS AND METHODS

Patients

The Erasmus University Medical Centre Rotterdam in the Netherlands is a tertiary referral centre for focal liver lesions. From 2000 to 2010, 58 patients who were radiological diagnosed as HCA were treated by surgical resection. A total of 71 lesions were surgically excised. Clinical data for OC use, BMI and symptoms, radiological data for the number of lesions and follow-up data were retrospectively collected. The study was approved by the institutions review board.

Histopathological and immunohistochemical analysis

Paraffin fixed liver tissue slides were retrieved from the archives of the department of pathology, Erasmus University Medical Centre Rotterdam. For each lesion macroscopic characteristics (size, number of tumors) and microscopic features were noted by the liverpathologist. Non-tumoral liver tissue was evaluated for steatosis, sinusoidal dilatation, inflammatory infiltrates and fibrosis according to the classification of the METAVIR group as follows: F0 (no fibrosis); F1 (portal fibrosis), F2 (few bridges), F3 (many bridges) and F4 (cirrhosis) [13]. Steatosis was graded according to Kleiner et al.: Grade 1 (5–33% of the hepatocytes), grade 2 (33–66% of the hepatocytes), grade 3 (more than 66% of the hepatocytes). Steatosis, if not observed or <5% was graded as grade 0 [14]. Lesions were evaluated for the presence and degree of dystrophic and solitary arteries, inflammatory infiltrates, sinusoidal dilatation, ductular reaction, haemorrhage, presence of a fibrous tumor capsule, presence of fibrous bands, steatosis (grade as mentioned above), cytonuclear atypia and the formation of pseudoglands. Sinusoidal dilatation was graded as follows: up to one third (grade 1), up to two thirds (grade 2), and more than two thirds of the sinusoids affected (grade 3). Absence of sinusoidal dilatation was graded as grade 0. Immunohistochemistry was performed on paraffin sections representative of the tumor. Immunostainings included L-FABP (polyclonal antibody, 1:100 dilution, Bio-Connect), SAA (monoclonal mouse antibody, 1:200 dilution, Dako), CRP (mouse monoclonal antibody, 1:1600 dilution, Bio-Connect), GS (monoclonal mouse antibody, 1:3200 dilution, BD Biosciences) and β-catenin (monoclonal mouse antibody, 1:50 dilution, BD Biosciences). A nuclear staining for β-catenin, focal or diffuse, was considered positive. For each immunohistochemical staining a positive and negative control was used for quality control.

Statistical analysis

Continuous variables were summarized as mean and standard error in case of normal variances, or as the median with ranges in case of non-normal variances and categoric variables were summarized as frequency and percentages. Categorized variables were

compared with each other using the chi-square test or Fishers' exact test. The nonparametric Mann-Whitney test for unpaired data was used for continuous variables. All reported p values were based on 2-sided test of statistical significance. A p value of less than 0.05 was accepted as statistical significance.

RESULTS

Clinical and pathological features

From 2000 to 2010, in 58 patients, 71 lesions diagnosed as HCA by radiological imaging, were surgically resected. Fifty six patients (97%) were female using OC as documented in 50 women. The time of duration of OC use was known in 30 women, 27 women (90%) had been taking OC for ≥5 years. The median age at diagnosis was 36 years (range 15–64) and the median BMI was 26.6 (range 18.2–42.6). Acute abdominal pain was present in 30 cases (53%), in 7 patients these symptoms were caused by bleeding. Eight cases (14%) presented with specific symptoms. The remaining cases were discovered as an incidental finding during radiological examination of the abdomen for unrelated reasons. Haemorrhage was seen in 31 of 57 lesions (54%) with a final diagnosis of HCA. No haemorrhagic component was seen in 14 lesions with a final diagnosis of FNH. We identified HCA in 47 cases (57 lesions) and FNH in 11 cases (14 lesions), based on morphological criteria and with additional immunohistochemical analysis (see below).

Non-tumoral liver tissue was not available in three cases. Pathological analysis of the non-tumoral liver tissue showed steatosis grade 0 in 62% of cases, steatosis grade 1 or grade 2 in 33% of cases and steatosis grade 3 in 5% of cases. F0 was present in 78% of cases. All other patients presented F1 (20%) or F2 (2%). Forty-nine percent of cases presented with sinusoidal dilatation grade 1, 13% of cases presented with sinusoidal dilatation grade 2 and 2% of cases presented with sinusoidal dilatation grade 3. In 36% of cases there was no sinusoidal dilatation. Inflammatory infiltrates were present in 51% of cases. None of the patients had noted diseases known to be associated with HCA such as glycogenosis, familial adenomatous polyposis coli or aplastic anemia. Upon preoperative imaging, 25 HCA patients were considered to have a single HCA in the liver. Multiple adenomas (2–9 nodules) were found in 18 patients and adenomatosis (≥10 nodules) was present in 4 cases. (Table 1) Two patients presented with a simultaneous occurrence of HCA and FNH. Follow-up data were available in 53 patients. Median follow-up was 35 weeks (range 2–293 weeks). Two patients were followed elsewhere and three patients are still in follow-up (all <1 year). In 35 cases there was a complete resection of the lesions. In 23 patients there were nodules left in the surrounding liver (1–9 nodules), these nodules were stable in size during follow-up in 10 patients with a maximum diameter of 10–28 mm. In 9 patients regression of the lesions was observed; four patients were

Table 1. Clinical and pathological characteristics

Characteristics	Number (%)	Median	Range
Age, years		35.7	15-64
Sex			
Female	56 (96.6)		
Male	2 (3.4)		
BMI, kg/m^2	54	26.6	18.2-42.6
< 25	24 (44.4)		
≥ 25	30 (55.6)		
Missing	4		
OC use (females)	50		
No OC use	1		
Missing	5		
Number of HCA (radiological)			
Single	25 (53.2)		
> 1 to 10	18 (38.3)		
≥ 10	4 (8.5)		
Symptoms	57		
Acute abdominal pain	30 (52.6)		
Aspecific symptoms	8 (14.0)		
Symptom free	19 (32.8)		
Missing	1		
Size (mm) resected HCA		68.5	5-200
Size (mm) resected FNH		70	10-90
Haemorrhagic HCA	31 (54.4)		
Haemorrhagic FNH	0		

treated with radiofrequency ablation. After surgery, five patients became pregnant with an uneventful outcome and stable tumor size in all cases. During follow-up there were no complications including bleeding or malignant transformation. None of the patients died during follow-up.

Analysis according to subgroups

The immunohistochemical analysis allowed us to classify the adenomas in 4 subgroups.

First, inflammatory HCA with expression of both CRP and SAA is the most frequent subgroup and was documented in 36 of 57 adenomas (63%). Among this subgroup, 3 adenomas (8%) demonstrated focal positivity for β-catenin and demonstrated a diffuse and homogeneous staining pattern for GS (Figure 3) and one HCA (3%) demonstrated only a heterogeneous GS staining pattern (no nuclear β-catenin staining), involving a majority of hepatocytes and therefore considered as positive. Serum CRP levels before resection were available in 23 of 36 inflammatory adenomas. All patients, except two,

Table 2. Clinical characteristics according to subtype classification of HCA and FNH

Characteristics	Subtype classification of HCA (n = 57)				FNH (n = 14)
	L-FABP-negative (compatible with HNF-1α mutation)	Inflammatory type	β-catenin positive	Unclassified	
Number of lesions	11 (19%)	36 (63%)	4 (7%)	6 (11%)	14
BMI, kg/m^2					
< 25	6	11	4	1	7
≥ 25	5	22	0	5	5
Missing		3			3
Size (mm)*	70 (5-165)	65 (9-200)	45 (20-90)	67.5 (30-100)	70 (10-90)

* median (range)

showed elevated serum CRP levels (range 11–523 mg/l). The two male patients were found in the inflammatory group; one showed expression of CRP, SAA and a heterogeneous staining pattern for GS as mentioned before. Second, a lack of L-FABP expression, compatible with HNF-1α mutation, was present in 11 adenomas (19%), with steatosis grade 3 in 64% of these adenomas (Figure 1). All other cases (3) with a lack of L-FABP,

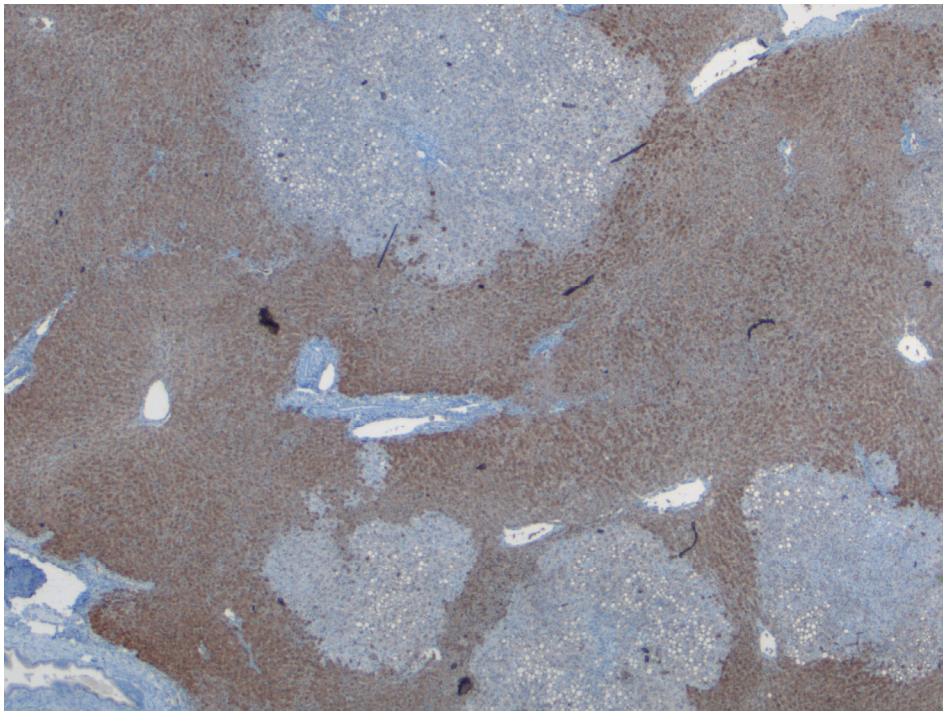

Figure 1. Liver-fatty acid binding protein (L-FABP) immunostaining in multiple steatotic HCA: lack of L-FABP expression in HCA in contrast with normal expression in non-tumoral liver.

showed steatosis grade 1 or grade 2. No steatosis was present in one case. Third, (some) nuclear staining of β-catenin was observed in 3 HCA, without expression of CRP, SAA and GS and with normal L-FABP staining pattern. All these lesions had cytological abnormalities. Nuclear staining of β-catenin with concomitant diffuse and homogeneous GS staining positivity was observed in one HCA. None of these tumors had steatosis within the lesion. The fourth subgroup is formed by so-called unclassifiable adenomas: 6 HCA were unclassifiable (11%) because they were CRP, SAA, β-catenin and GS negative, with a normal L-FABP staining pattern (Table 2). In three patients multiple resected adenomas (range 2–3) were of the same subtype: 3 steatotic adenomas in one patient and inflammatory adenomas in 2 patients (2 and 3, respectively). Two patients showed one unclassified and one inflammatory HCA, and another patient showed two β-catenin positive HCA and one unclassified HCA. As mentioned before, pathological signs of bleeding were seen in 31 of 57 HCA lesions (54%). Bleeding was more frequent in the L-FABP-negative group than in the inflammatory HCA group (73% vs. 50%, however the difference between the subgroups did not reach statistical significance). The median size of lesions, based on pathology, in the L-FABP-negative group was 70.0 mm (range 5-165 mm) compared to a median size of 65.0 mm (range 9-200 mm) in the inflammatory group; the difference between the subgroups did not reach statistical significance. The

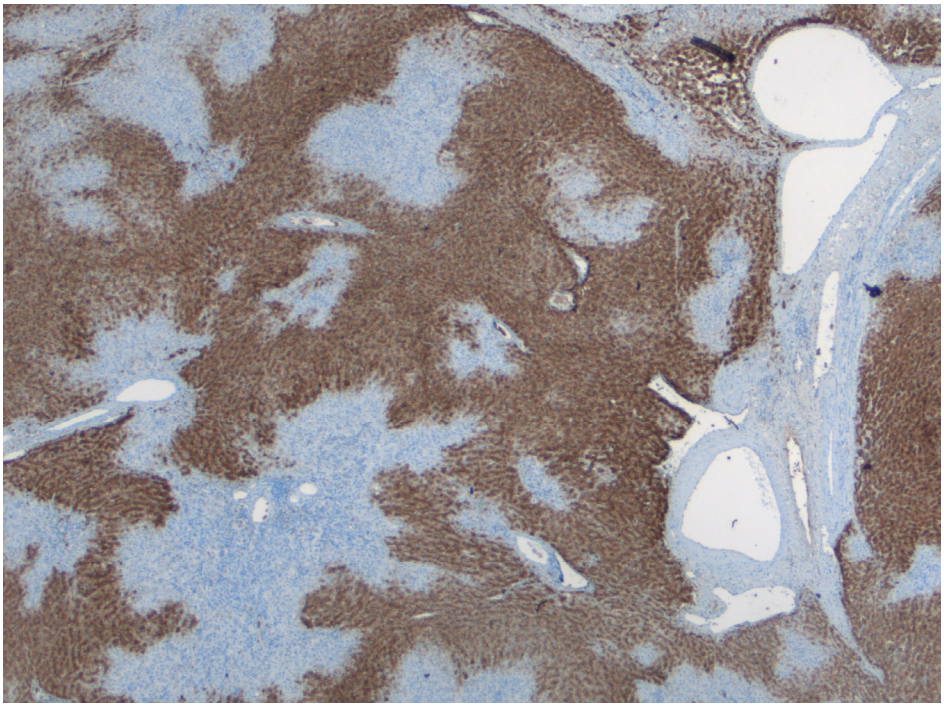

Figure 2. Map-like staining pattern of glutamine synthetase (GS) in FNH.

frequency of multiple adenomas based on radiological imaging was almost equivalent in the L-FABP-negative group and the inflammatory group (44% vs. 42%). Patients with inflammatory HCA were more obese: median BMI 28.7 (range 18.6-42.6) compared to the L-FABP-negative group with a median BMI of 24.5 (range 22.3–40.8); however, the difference between the subgroups did not reach statistical significance. Subtype classification was straightforward in more than 90% of HCA cases using immunohistochemical

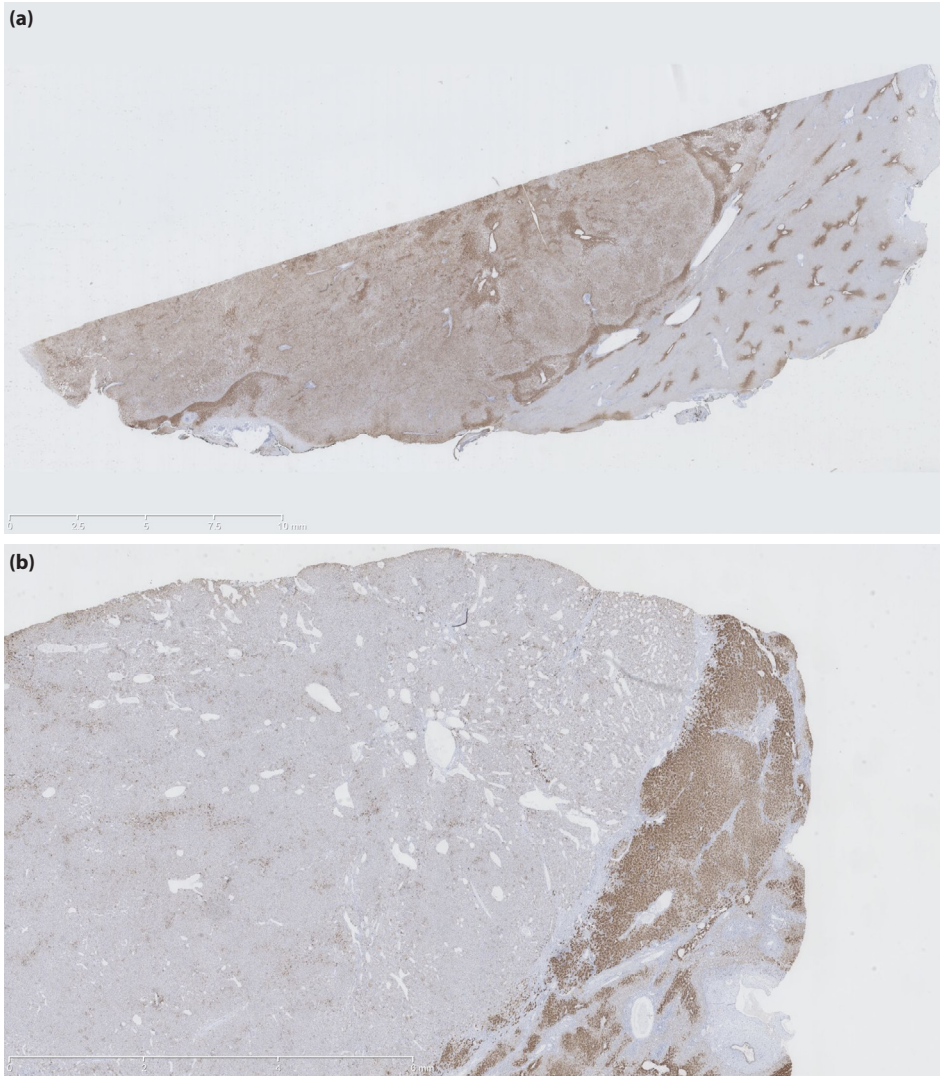

Figure 3. β-catenin positivity and glutamine synthetase (GS) positivity in two inflammatory HCAs. **(a)** Homogeneous GS immunostaining pattern of HCA (left) and perivenular (zone 3) staining restricted to 2 or 3 plates of hepatocytes in non-tumoral liver (right) **(b)** Area of GS positivity at the border of the tumor within a HCA (right). In this area, there was also nuclear positivity for β-catenin.

staining patterns and morphological criteria. In four cases the immunohistochemical markers were difficult to interpret. One case showed an inflammatory type HCA with a heterogeneous positivity of GS, which was not diffuse and not strong, except in some areas with a nuclear staining of β-catenin in these areas. In one case it was difficult to differentiate an area at the border of the tumor where cytonuclear atypia was seen within an adenoma, from a well-differentiated HCC. In this area β-catenin and GS were clearly positive (Figure 3). Additional staining with glypican-3 and HSP-70 could be of help in these situations [15]. Another inflammatory adenoma showed GS staining with a lot of background staining, however no nuclear staining of β-catenin was found. A third inflammatory HCA showed a heterogeneous GS staining and a doubtful nuclear staining of β-catenin. In these situations, molecular biology for the detection of β-catenin mutations may be required.

Fourteen lesions, morphological compatible with FNH, showed a characteristic map-like pattern of GS immunostaining (Figure 2). All FNH lesions were CRP, SAA and β-catenin negative, with a normal L-FABP staining. Microscopically all FNH lesions showed variable ductular reaction, fibrous septa, dystrophic arteries, intermingled with inflammatory cells. Haemorrhage and necrosis were not present.

DISCUSSION

Currently, in our hospital all female patients with HCA are advised to stop the use of OC and other hormone medication including hormone replacement therapy, as regression of HCA may occur when estrogens are withdrawn [16–19]. Observation should be the first choice of treatment for most patients with HCA [20]. The management of solitary adenomas by conservative treatment or continuous surgical resection is still a matter of debate. Most authors believe that surgical resection is required if the diameter exceeds 5 cm after 6 months of follow-up, if the lesion does not show adequate regression after discontinuation of OC or if bleeding occurs [21–24]. Surgical resection is also indicated if there is any suspicion on malignancy [25,26]. Immunohistochemical analysis may offer a helpful tool for HCA management strategy. The results of our series of 58 cases (71 lesions) are in accordance with data shown by Bioulage-Sage and colleagues and confirm that inflammatory HCA and L-FABP-negative HCA form the two main subgroups (83%) that differ on clinical and pathological grounds [6]. Morphology and immunohistochemistry allows subtyping of more than 90% of HCA. We observed 36 inflammatory HCA of which three demonstrated positivity for β-catenin and demonstrated a diffuse and homogeneous staining pattern for GS. Difficulties exist due to the fact that the number of β-catenin positive cells may be limited and staining may be focal (β-catenin expression was considered positive when the staining showed nuclear accumulation in the

neoplastic cells, sometimes with concomitant cytoplasmic staining). In our series, we did not find any patient with homogeneous nuclear staining of β-catenin throughout the lesion. The same counts for the subgroup that shows nuclear β-catenin staining without expression of CRP and SAA. These subgroups also showed focal β-catenin positivity and cytological atypia in all lesions. In agreement with the observations of Van der Borght et al., we noticed that β-catenin activated HCA had a complete absence of steatosis [27]. Inflammatory HCA occur more often in obese patients compared to the L-FABP-negative group. However, the difference between the subgroups did not reach statistical significance. Bleeding was more frequently found in the L-FABP-negative group compared to the inflammatory group and the median size of lesions in the L-FABP-negative group was larger compared to the median size of adenomas in the inflammatory group. However, these data did not reach statistical significance, which may be due to the small group of 11 L-FABP-negative adenomas. In six patients multiple adenomas were resected and were of the same subtype in three patients. We observed that the other three patients showed adenomas of two different subtypes; always an unclassified HCA and one or more HCA of one other subtype. One might hypothesize that unclassified HCA may develop with time into another subtype. On the other hand, it is conceivable that multiple adenomas of different subtypes may occur in the same patient.

HCA and FNH are the most frequent benign epithelial lesions of the liver observed in women during their reproductive years and are detected more frequent nowadays because of improvements in radiological modalities. Differentiation of HCA and FNH is important because FNH generally does not require treatment and follow-up, whereas HCA does. HCA can be complicated by life threatening rupture and bleeding or undergo malignant transformation necessitating treatment. In all our cases the morphological diagnosis of FNH was supported by the map-like staining pattern of GS [12]. When doubt remains about the diagnosis HCA (especially the inflammatory type that may contain inflammation as well as ductular reaction) or FNH, needle biopsy may be performed for the differential diagnosis and GS may be of help in this setting.

Whether the immunohistochemical markers will also be useful on biopsies from liver tumors, suspected of being HCA needs to be investigated. In most cases the identification of L-FABP-negative and inflammatory type adenomas with positive CRP and SAA staining should be feasible on a biopsy, because of the more or less homogeneous staining pattern. However, the interpretation of β-catenin staining may be difficult because of the heterogeneous and sometimes focal nuclear staining pattern and additional molecular biology may be required, since close relationships were found between genetic data and immunohistochemical data [28–30]. This was already mentioned as a potential problem by Bioulac-Sage and colleagues and this is confirmed by our data [6]. A concomitant staining with GS is warranted to increase sensitivity to detect a β-catenin mutation, especially in the case of a biopsy. However, as mentioned before, no data are

available about the success rate of the immunohistochemical markers to classify subgroups on biopsies and our present experience suggest that sampling error will remain a problem in this situation. Besides, the amount of material obtained by biopsy could be insufficient to achieve a reliable diagnosis [22].

So far, management of HCA is defined by clinical parameters. All women with HCA should be advised to stop the use of OC's and other hormone replacement therapy. Nodules >5 cm may be removed to avoid the risk of haemorrhage and the risk of malignant transformation. A decrease in size, documented by radiological imaging, after stopping OC may lead to a discharge or reduction in surveillance, particularly if no β-catenin mutation is detected. In the case of growth or β-catenin positivity, surgery may be required [6,8]. However, the possibility of immunohistochemical markers on biopsies needs to be investigated. To this date, the management of HCA requires a multidisciplinary approach.

CONCLUSION

Morphology and immunohistochemical markers are useful in subtyping adenomas in more than 90% of cases and this classification, including the identification of β-catenin positive adenomas may have important implications in the decision for surveillance or treatment. However, in some patients, due to the low number of positive cells and focal positivity, the identification of nuclear staining for β-catenin still remains difficult. In this situation additional molecular biology for the detection of β-catenin mutation may be required. The consequence for treatment and follow-up of the subclassification remains to be determined. The low incidence of HCA and the absence of well defined information on the potential danger of malignant transformation of β-catenin positive lesions warrant a European multicenter study. This way, the classification system may be correlated with a legitimized clinical management.

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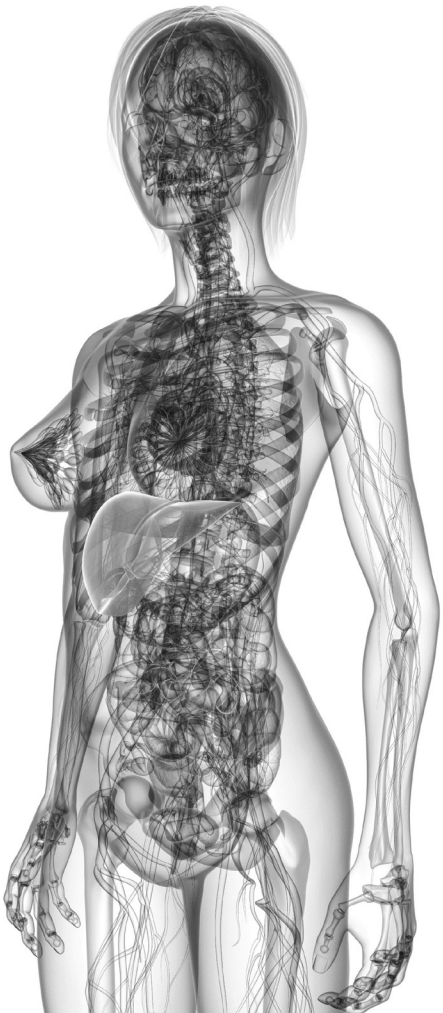
Chapter 3.2

Hepatocellular adenoma: Correlation of MR imaging findings with pathologic subtype classification



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ABSTRACT

Purpose: To investigate the correlation between magnetic resonance (MR) imaging findings and pathologic subtype classification of hepatocellular adenoma (HCA).

Materials and Methods: This retrospective study was approved by the institutional review board, and the requirement for informed consent was waived. MR imaging studies of 61 lesions (48 patients; median age, 36 years) were available and were independently reviewed by two radiologists. Consensus readings on all morphologic and signal-intensity imaging features were obtained. Previously, these lesions had been classified on the basis of pathologic findings and immunohistochemical analysis. Fisher exact and χ^2 tests were performed to compare the results between the different subtypes. A Bonferroni correction was applied to correct for multiple testing ($\alpha < .0033$).

Results: MR imaging signs of diffuse intratumoral fat deposition were present in seven (78%) of nine liver-fatty acid binding protein (L-FABP)-negative HCAs compared with five (17%) of 29 inflammatory HCAs ($P = .001$). Steatosis within the nontumoral liver was present in 11 (38%) of 29 inflammatory HCAs compared with none of the L-FABP-negative HCAs ($P = .038$). A characteristic atoll sign was only seen in the inflammatory group ($P = .027$). Presence of a typical vaguely defined type of scar was seen in five (71%) of seven β-catenin-positive HCAs ($P = .003$). No specific MR imaging features were identified for the unclassified cases.

Conclusion: L-FABP-negative, inflammatory, and β-catenin-positive HCAs were related to MR imaging signs of diffuse intratumoral fat deposition, an atoll sign, and a typical vaguely defined scar, respectively. Since β-catenin-positive HCAs are considered premalignant, closer follow-up with MR imaging or resection may be preferred.

INTRODUCTION

Hepatocellular adenoma (HCA) is an uncommon benign tumor of the liver that occurs particularly in young and middle-aged women (1). HCA can be complicated by life-threatening rupture and bleeding or undergo malignant transformation (2,3). Management of HCA frequently requires cessation of oral contraceptives, intermittent follow-up with radiologic imaging, and a recommendation to avoid pregnancy (4–6). Recently, the Bordeaux group established a new molecular and pathologic classification of HCA. They divided HCA into four different subgroups according to genotypic and phenotypic characteristics and clinical features (7–9). The first group, comprising 35%–40% of the HCA cases, was defined by the presence of mutations in the T-cell factor 1 gene that inactivate the hepatocyte nuclear factor 1α. Hepatocyte nuclear factor 1α-inactivated HCAs lack expression of liver-fatty acid binding protein (L-FABP) in the tumor. As a result, the majority of these tumors are highly steatotic (10). The second group, 10%–15% of cases, showed the presence of β-catenin-activating mutations. β-Catenin-activated lesions seem to have a higher risk of malignant transformation in patients with an HCA larger than 4–5 cm (7,8). The third group, 50% of cases, showed inflammatory HCAs with serum amyloid A (SAA) and C-reactive protein (CRP) expression. Finally, less than 10% of HCAs were unclassified (8,10). Glutamine synthetase (GS) is another useful marker in pathologic analysis of liver tumors. Strong, diffuse, and homogeneous GS staining has been shown in β-catenin-mutated HCA. This is in contrast to focal nodular hyperplasia (FNH), in which GS staining forms large hepatocyte areas that are organized in a characteristic map-like pattern, defined as positive GS staining in hepatocytes forming anastomosing areas, often surrounding venous structures (11). As previously described by Laumonier et al. (12), magnetic resonance (MR) imaging seems to be a useful tool for identifying the two major subtypes of HCA (ie, L-FABP-negative HCA and inflammatory HCA). The purpose of our study was to investigate the correlation between MR imaging findings and pathologic subtype classification of HCA.

METHODS

Patients

This retrospective study was approved by the institutional ethical review board, and informed consent was waived. Between January 2000 and February 2010, a cohort of 58 patients (71 lesions) who were radiologically diagnosed with an HCA were treated with surgical resection. The lesions were previously reviewed and classified on the basis of pathologic and immunohistochemical analysis (13). Among these 58 patients, we identified 50 patients in whom liver MR imaging had been performed. Two patients

were excluded from the study owing to a lack of adequate MR imaging pulse sequences to allow evaluation. A total of 48 patients (median age, 36 years) were included in the study. Among this group, a total of 61 lesions were surgically excised.

Histopathologic and immunohistochemical analysis

Immunohistochemical staining was performed on paraffin sections representative of the tumor and included L-FABP (polyclonal antibody, 1:100 dilution; Bio-Connect, Huissen, the Netherlands), SAA (monoclonal mouse antibody, 1:200 dilution; Dako, Heverlee, Belgium), CRP (mouse monoclonal antibody, 1:1600 dilution; Bio-Connect), GS (monoclonal mouse antibody, 1:3200 dilution; BD Biosciences, Breda, the Netherlands), and β-catenin (monoclonal mouse antibody, 1:50 dilution; BD Biosciences), as previously described (13). For each immunohistochemical stain, positive and negative controls were used for quality control. The immunohistochemical analysis allowed us to classify the adenomas into four subgroups, and subtype classification was straightforward in more than 90% of HCA cases. A lack of L-FABP expression, compatible with hepatocyte nuclear factor 1α mutation, was present in nine HCA lesions. Four lesions were positive for β-catenin without expression of CRP and SAA. Nuclear staining of β-catenin with a concomitant diffuse and homogeneous staining pattern for GS was observed in one of these four β-catenin-positive HCAs. All lesions in this subgroup showed cytologic atypia. The largest group consisted of 30 inflammatory HCAs with expression of both CRP and SAA. Additional β-catenin activation with a concomitant diffuse and homogeneous staining pattern for GS was demonstrated in three inflammatory HCAs. One inflammatory HCA demonstrated a heterogeneous staining pattern of GS without nuclear β-catenin staining positivity. Five HCAs remained unclassified because they were negative for CRP, SAA, β-catenin, and GS, with a normal L-FABP staining pattern. Thirteen lesions that were morphologically compatible with FNH showed a characteristic map-like pattern of GS immunostaining; were negative for CRP, SAA, and β-catenin; and had normal L-FABP staining.

MR imaging technique and analysis

Forty-one patients were imaged at our institution. All these patients underwent MR imaging on one of two 1.5-T units (Philips Medical Systems, Best, the Netherlands; or Signa, GE, Milwaukee, Wisconsin, USA) with the same protocol. A fourchannel phased-array body coil was used. In each patient, a single-shot fast spin-echo sequence (repetition time msec/echo time msec, 832/80–120; flip angle, 90°) with varying echo times (short and long echo times of 80 and 120 msec, respectively), a fat-suppressed T2-weighted fast spinecho sequence (3000/80; flip angle, 90°), and T1-weighted in- and opposed-phase gradient-echo sequences (echo times, 4.6 and 2.3 msec, respectively; flip angle, 80°) were used. In addition, fat-suppressed dynamic gadolinium-enhanced T1-weighted

imaging was performed in at least four phases precontrast, arterial, portal, and delayed) after administration of an intravenous bolus of 30 mL of non-liver-specific gadolinium chelate (gadopentetate dimeglumine, Magnevist; Schering, Berlin, Germany). The optimal arterial phase was based on bolus tracking. The portal and delayed phases were acquired at 45 and 120 seconds, respectively, after the acquisition of the arterial phase. Delayed-phase three-dimensional T1-weighted gradient-echo imaging was also performed at least 4 minutes after contrast material injection. A section thickness of 5-7 mm was used in all sequences. Seven patients were imaged at collaborating hospitals, and their studies were reviewed at our institution. Minimal prerequisites for inclusion of these studies were the availability of T1- and T2-weighted images of the whole liver. T1- and T2-weighted images were available for all seven MR imaging studies performed at collaborative hospitals. In six of the seven studies, in- and opposed-phase images and dynamic contrast material-enhanced images were available. In one MR imaging study obtained at a collaborating hospital, only uniphase contrast-enhanced images in the venous phase were available. T1- and T2-weighted, in- and opposed-phase, and dynamic contrast-enhanced images were available for all MR imaging studies performed at our hospital. Two readers (M.G.J.T. and R.S.D., both with 7 years experience in abdominal imaging) reviewed the MR images independently while blinded to the clinical history and pathologic diagnosis. Thereafter, consensus on all imaging features was obtained. For all lesions, the following image features were noted by the radiologist: number of nodules, presence of steatosis in the nontumoral liver (absence, mild, moderate, or severe), location of resected lesion according to the Couinaud numbering system (14), maximum size of resected lesion, contour (regular or lobulated), overall aspect on T2-weighted images (homogeneous or heterogeneous), presence of macroscopic hemorrhagic component (defined as focal T1-weighted hyperintense area), presence of necrotic or cystic component (defined as pronounced hyperintense signal on T2-weighted images), presence of central scar (defined as T2-hyperintense lines enhancing in the late venous phase), presence and percentage of region of steatosis within the lesion (absence [0%], mild [<33%], moderate [33%–66%], or severe [>66%]) (empirically), presence of tumor capsule (low signal intensity on T2-weighted images and delayed phase enhancement) or pseudocapsule (high signal intensity on T2-weighted images and delayed phase enhancement) (15), signal intensity on T1- and T2-weighted images (slightly hypointense, markedly hypointense, isointense, slightly hyperintense, or markedly hyperintense), predominant phase of enhancement (arterial, portal, or venous; homogeneous, heterogeneous, or two phases), and intensity of enhancement (slight, moderate, or marked). Finally, on the basis of the images evaluated, each radiologist was asked to make a diagnosis for each lesion detected. Differentiation between HCA and FNH was based on typical features for both lesions, as previously published (16–19).

Statistical analysis

Categorical variables were summarized as frequency and percentages. Categorized variables were compared with each other by using the χ^2 or Fisher exact test. All reported *P* values were based on two-sided tests of significance. A Bonferroni correction was applied to correct for multiple testing (15 categorical variables). A *P* value of less than .0033 was considered to indicate a significant difference. Because the β-catenin-activated and unclassifiable groups were quite small, the statistical analysis was mainly focused on the inflammatory and L-FABP-negative groups. Interobserver agreement was calculated by using Cohen κ statistics (≤0.20, poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61-0.80, good agreement; and 0.81–1.00, very good agreement) (20).

RESULTS

Clinical and general pathologic and imaging features

We identified HCA in 38 patients (48 lesions) and FNH in 10 patients (13 lesions) on the basis of morphologic criteria and immunohistochemical analysis (Figure 1). Forty-six (96%) of forty-eight patients were women (median age, 36 years; range, 15–64 years). The two male patients were both diagnosed with HCA (median age, 35 years; range, 31–39 years). The median age at diagnosis for all individuals was 36 years (range, 15–64 years). Oral contraceptive use was documented in 40 women. The duration of oral contraceptive use was known in 27 women: 24 women (89%) had been taking

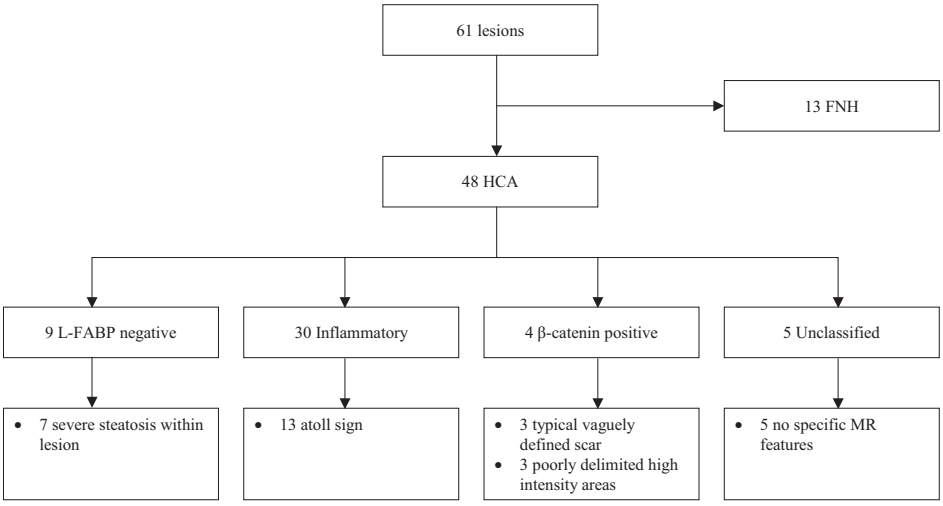

Figure 1. Flowchart shows specific MR imaging features according to pathologic subtype classification of HCA.

oral contraceptives for at least 5 years. Acute abdominal pain was the main reason for diagnostic imaging in 25 patients (52%), including bleeding of the lesion in six patients. Nonspecific symptoms were the reason for diagnostic imaging in seven cases, and the remaining cases were discovered as an incidental finding during radiologic examination of the abdomen for unrelated reasons. At MR imaging, 18 patients with HCA were considered to have a single lesion in the liver. Multiple adenomas (2-9 nodules) were found in 15 patients, and adenomatosis (≥10 nodules) was present in five patients. In three patients, multiple resected HCAs were of the same subtype (one patient with three L-FABP-negative HCAs; two patients with inflammatory HCAs [two or three lesions]). Two patients had one unclassified and one inflammatory HCA, and another patient had two β-catenin–positive HCAs and one unclassified HCA. At MR imaging (Table 1), 40 (85%) of 47 HCAs (one was not interpretable) were isointense to slightly hyperintense on T1-weighted images. On T2-weighted images, most HCAs were slightly hyperintense (37 of 48, 77%). No FNH lesions were hyperintense on T1-weighted images or contained intratumoral fat. On T2-weighted images, the signal was slightly hyperintense in eight (62%) of 13 FNH lesions. A central scar was seen in 10 (77%) of 13 FNH lesions, compared with 10 (21%) of 47 HCAs (one was doubtful) ($P = .001$). Markedly intense homogeneous enhancement in the arterial phase was seen in eight (62%) of 13 FNH lesions, compared

Table 1. MR imaging characteristics of HCA and FNH

Characteristics	HCA ($n = 48$)	FNH ($n = 13$)
Contour		
Regular	27 (56)	2 (15)
Lobulated	21 (44)	11 (85)
Aspect		
Homogeneous	17 (35)	6 (46)
Heterogeneous	31 (65)	7 (54)
Hemorrhagic component	10 (21)	0
Necrotic or cystic component		
Present	7 (15)	0
Doubtful	1	0
Central scar		
Present	10 (21)*	10 (77)*
Doubtful	1	0
Lesion Steatosis†		
Absent	35 (74)	13 (100)
Mild	4 (9)	0
Moderate	1 (2)	0
Severe	7 (15)	0

Table 1. (*continued*)

Characteristics	HCA (*n* = 48)	FNH (*n* = 13)
Not interpretable	1	0
Capsule	0	0
Pseudocapsule	14 (29)	5 (38)
T1-weighted signal intensity		
Slightly hypointense	5 (11)	8 (62)
Markedly hypointense	1 (2)	5 (38)
Isointense	29 (62)	0
Slightly hyperintense	11 (23)	0
Markedly hyperintense	1 (2)	0
Not interpretable	1	0
T2-weighted signal intensity		
Slightly hypointense	3 (6)	2 (15)
Markedly hypointense	0	0
Isointense	7 (15)	3 (23)
Slightly hyperintense	37 (77)	8 (62)
Markedly hyperintense	1 (2)	0
Not interpretable	0	0
Enhancement phase		
Arterial	47 (100)	13 (100)
Portal	0	0
Venous	0	0
Not interpretable	1	0
Enhancement		
Homogeneous	26 (57)	8 (62)
Heterogeneous	14 (30)	5 (38)
Two phases	6 (13)	0
Not interpretable	2	0
Intensity of enhancement		
Slightly	5 (11)	0
Moderate	24 (51)	2 (15)
Markedly	18 (38)	11 (85)
Not interpretable	1	0
Atoll sign		
Present	13 (27)	0
Doubtful	6 (13)	1 (8)

Note – Data are numbers of lesions, with percentages of lesions with interpretable results for that characteristic in parentheses.

* $P = .001$ for difference between HCA and FNH.

† Absent = 0%, mild = <33%, moderate = 33%-66%, severe = >66%

with 12 (26%) of 46 HCAs (two were not interpretable). On T2-weighted images, a characteristic hyperintense rim-like band in the periphery of the lesion (like an atoll) that was isointense to surrounding liver in the center of the lesion (like the surrounding sea) was seen in 13 (27%) of 42 (doubtful in six) of HCAs and in no FNH lesions. We termed this the *atoll sign* (Figures 2, 3). Interobserver agreement for the final diagnosis of each lesion was moderate (κ= 0.484).

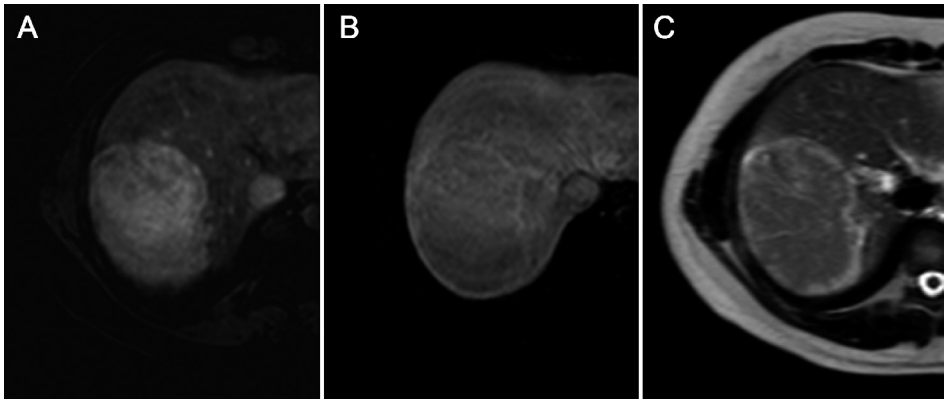

Figure 2. (a) Arterial- and **(b)** late vascular–phase dynamic contrast-enhanced T1-weighted transverse MR images. **(c)** T2-weighted MR image shows characteristic atoll sign of an inflammatory HCA in segment 6/7, which includes a T2-hyperintense signal band in the periphery of the lesion (like an atoll) with a center that is isointense to surrounding liver (like the surrounding sea). T2-hyperintense region typically enhances in the **(b)** late vascular phase, possibly corresponding to dilated sinusoids within inflammatory HCA.

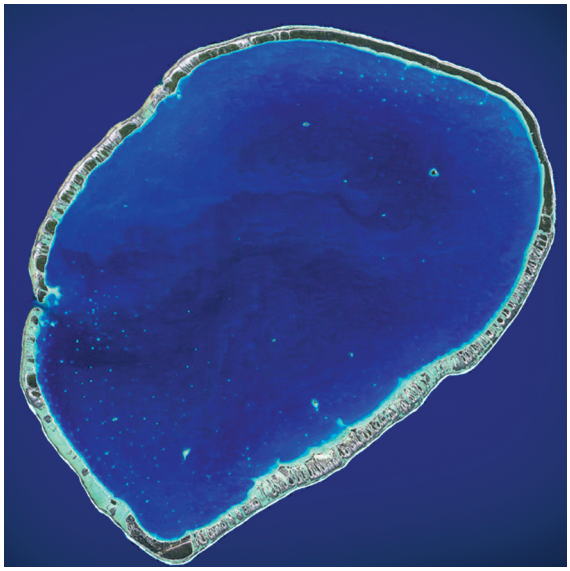

Figure 3. Satellite image of southern part of Tikehau Atoll. (Image courtesy of National Aeronautics and Space Administration Earth Observatory; http://earthobservatory.nasa.gov/IOTD/view.php?id=39329.)

MR image analysis by subgroup

L-FABP-negative HCAs

Decreased signal intensity on T1-weighted opposed-phase images owing to intratumoral fat deposition was present in seven (78%) of nine L-FABP-negative HCAs, measured as a region of severe and diffuse steatosis within the lesion (Table 2) (Figure 4). None of the other subtypes had diffuse steatosis within the lesion. Five (17%) of 29 inflammatory HCAs (one was not interpretable) showed only focal steatosis within the lesion ($P = .001$). All L-FABP-negative HCAs were slightly hyperintense on T2-weighted images.

Table 2. MR imaging characteristics of HCA by subtype

Characteristics	L-FABP-negative (*n* = 9)	Inflammatory (*n* = 30)	B-catenin-positive (*n* = 4)	Unclassified (*n* = 5)
Size (mm)*	75 (28-124)	77 (15-184)	51 (25-80)	51 (42-110)
Nontumoral liver steatosis				
Absent	9 (100)	18 (62)	4 (100)	3 (60)
Mild	0	2 (7)	0	1 (20)
Moderate	0	2 (7)	0	0
Severe	0	7 (24)	0	1 (20)
Not interpretable	0	1	0	0
Contour				
Regular	4 (44)	18 (60)	3 (75)	2 (40)
Lobulated	5 (56)	12 (40)	1 (25)	3 (60)
Aspect				
Homogeneous	4 (44)	10 (33)	2 (50)	1 (20)
Heterogeneous	5 (56)	20 (67)	2 (50)	4 (80)
Hemorrhagic component	2 (22)	4 (13)	1 (25)	3 (60)
Necrotic or cystic component				
Present	2 (22)	2 (7)	2 (50)	1 (20)
Doubtful	0	1	0	0
Central scar				
Present	1 (11)	5 (17)	3 (75)	1 (20)
Doubtful	0	1	0	0
Lesion Steatosis†				
Absent	2 (22)	24 (83)	4 (100)	5 (100)
Mild	0	4 (14)	0	0
Moderate	0	1 (3)	0	0
Severe	7 (78)	0	0	0
Not interpretable	0	1	0	0

Table 2. (*continued*)

Characteristics	L-FABP-negative (*n* = 9)	Inflammatory (*n* = 30)	B-catenin-positive (*n* = 4)	Unclassified (*n* = 5)
Capsule	0	0	0	0
Pseudocapsule	2 (22)	7 (23)	3 (75)	2 (40)
T1-weighted signal intensity				
Slightly hypointense	1 (13)	4 (13)	0	0
Markedly hypointense	0	1 (13)	0	0
Isointense	6 (75)	16 (53)	4 (100)	3 (60)
Slightly hyperintense	1 (13)	8 (27)	0	2 (40)
Markedly hyperintense	0	1 (3)	0	0
Not interpretable	1	0	0	0
T2-weighted signal intensity				
Slightly hypointense	0	2 (7)	0	1 (20)
Markedly hypointense	0	0	0	0
Isointense	0	3 (10)	2 (50)	2 (40)
Slightly hyperintense	9 (100)	24 (80)	2 (50)	2 (40)
Markedly hyperintense	0	1 (3)	0	0
Not interpretable	0	0	0	0
Enhancement phase				
Arterial	9 (100)	29 (100)	4 (100)	5 (100)
Portal	0	0	0	0
Venous	0	0	0	0
Not interpretable	0	1	0	0
Enhancement				
Homogeneous	6 (67)	16 (57)	2 (50)	2 (40)
Heterogeneous	3 (33)	8 (29)	2 (50)	1 (20)
Two phases	0	4 (14)	0	2 (40)
Not interpretable	0	2	0	0
Intensity of enhancement				
Slightly	3 (33)	1 (3)	1 (25)	4 (80)
Moderate	3 (33)	14 (48)	3 (75)	0
Markedly	3 (33)	14 (48)	0	1 (20)
Not interpretable	0	1	0	0
Atoll sign				
Present	0	13 (43)	0	0
Doubtful	2 (22)	4 (13)	0	0

Note – Unless otherwise specified, data are numbers of lesions, with percentages of lesions with interpretable results for that characteristic in parentheses.

* Data are medians, with ranges in parentheses.

† Absent = 0%, mild = <33%, moderate = 33%-66%, severe = >66%.

P = .001 for L-FABP-negative vs inflammatory HCAs.

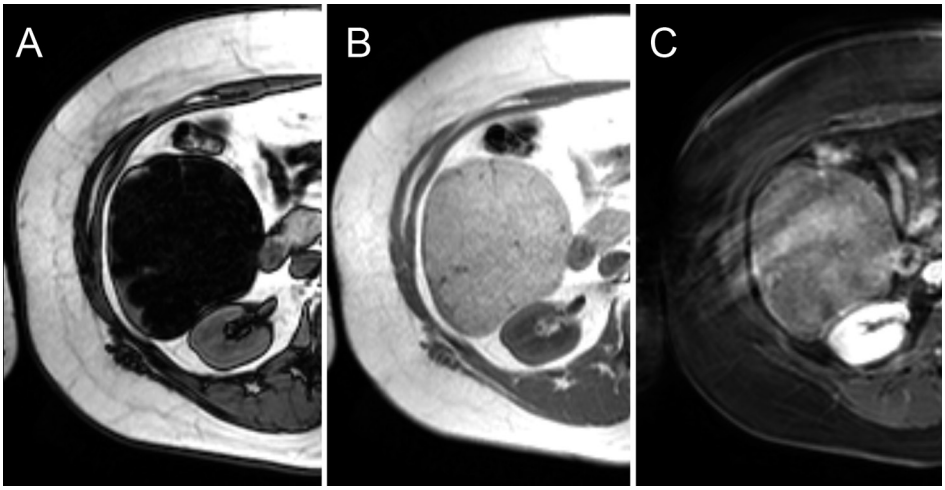

Figure 4. Transverse **(a)** opposed-phase, **(b)** in-phase, and **(c)** contrast-enhanced venous-phase T1-weighted MR images show an L-FABP-negative HCA in segment 5/6, which shows a strong homogeneous drop in signal intensity on a and slight enhancement on **c**.

β-catenin–positive HCAs

Nuclear staining of β-catenin (without expression of CRP and SAA) was observed in four HCAs. On MR images, three (75%) of these nodules demonstrated a scar and poorly delimited high-signal-intensity areas (Figure 5). A pseudocapsule was present in three (75%) of the four β-catenin-positive HCAs, whereas none of these had a fibrous tumor capsule. One lesion had a hemorrhagic component.

Inflammatory HCAs

Twenty-four (80%) of 30 inflammatory HCAs appeared isointense to slightly hyperintense to the surrounding liver on T1-weighted images and appeared slightly hyperintense on T2-weighted images. Steatosis within the nontumoral liver was present in 11 (38%) of 29 inflammatory HCAs (one was not interpretable), whereas none of the L-FABP-negative HCAs showed steatosis within the nontumoral liver ($P = .038$). The characteristic atoll sign was seen in 13 (43%) of 26 inflammatory HCAs, and a doubtful atoll sign was noted in four lesions. No clear cases with an atoll sign were seen in the L-FABP-negative group ($P = .027$) or other subgroups. Focal positivity for β-catenin with a concomitant diffuse and homogeneous staining pattern of GS was seen in three inflammatory HCAs. None of these β-catenin-positive inflammatory HCAs showed steatosis within the nontumoral liver, and only one lesion showed mild steatosis within the lesion. These lesions appeared heterogeneous on images obtained with each sequence. These lesions appeared isointense to slightly hyperintense to the surrounding liver on T1-weighted images and appeared slightly hyperintense on T2-weighted images. In accordance with β-catenin-positive HCAs without expression of CRP and SAA (see above), two β-catenin-positive

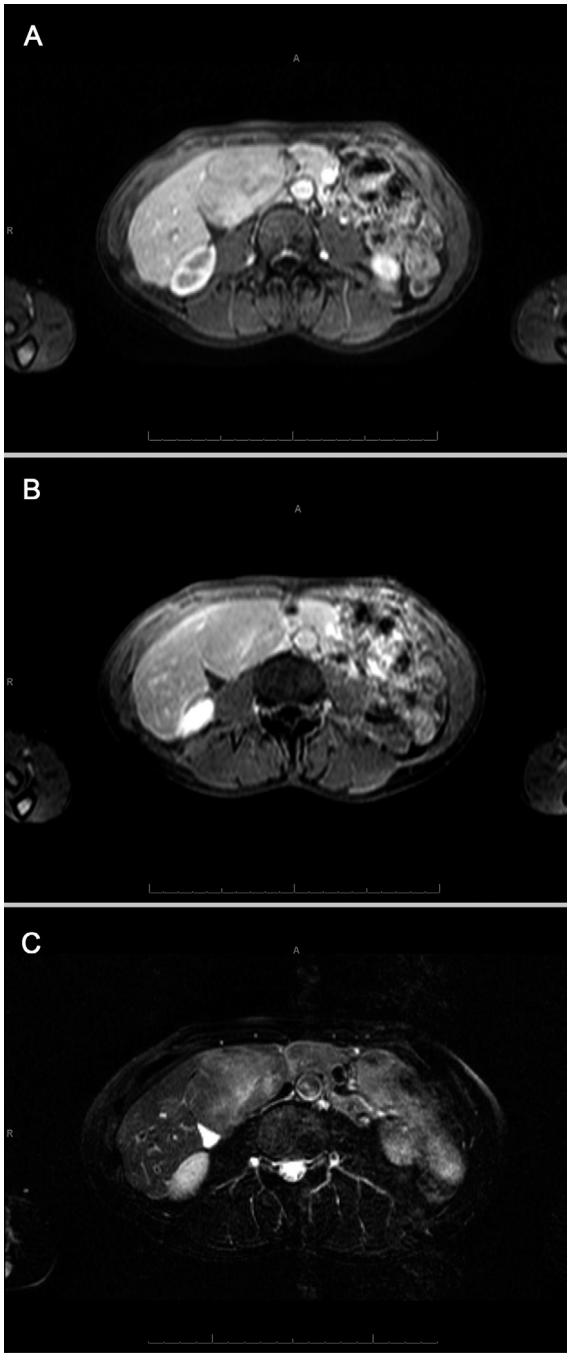

Figure 5. Transverse **(a)** arterial- and **(b)** late vascular–phase T1-weighted dynamic contrast-enhanced and **(c)** T2-weighted fat-saturated MR images show a β-catenin-positive HCA located in segment 4, with poorly delineated areas of increased signal intensity and a hyperintense scar on **c**. Lesion enhances irregularly on **b**.

inflammatory HCAs showed a central scar. None of the β-catenin-positive inflammatory HCAs had a hemorrhagic component. One inflammatory HCA demonstrated a heterogeneous staining pattern of GS without nuclear β-catenin staining. This lesion was heterogeneous on all MR images. On T1- and T2-weighted images, this lesion appeared slightly hyperintense to the surrounding liver. This lesion also had a central scar.

Unclassified HCAs

A small group of five HCAs remained unclassified with immunohistochemical analysis. In this group, no characteristic features were seen on MR images. None of these lesions showed steatosis within the lesion. Hemorrhagic components were seen in three (60%) of the five unclassifiable lesions.

Central scar in β -catenin- and GS-positive lesions

Ten (77%) of 13 FNH lesions had a typical scar revealing hyperintense lines on T2-weighted images, which enhanced in the portovenous phase. Ten (21%) of 47 HCAs had a central scar, and one HCA had a central scar that both readers interpreted as doubtful. Three of four β-catenin-positive HCAs (without expression of CRP and SAA) showed poorly delimited high-signal-intensity areas on T2-weighted images as hyperintense scar regions, which enhanced late during the porto-venous phase. These regions were revealed as a spotty less-demarcated pattern of enhancement (Figure 5). Three inflammatory HCAs showed a central scar, which was revealed as hypointense thin lines on T2-weighted images. Two inflammatory HCAs with nuclear positivity for β-catenin and a homogeneous GS staining pattern also showed a scar. Signs of a scar were present in one L-FABP-negative HCA and in one unclassified HCA. β-Catenin positivity in HCA and GS positivity in HCA and FNH were significantly associated with the presence of a central scar. Presence of a central scar was seen in five (71%) of seven β-catenin-positive HCAs compared with five (13%) of 40 β-catenin-negative HCAs ($P = .003$) (one was doubtful). HCA and FNH showed the presence of a central scar in 14 (78%) of 18 GS-positive lesions compared with six (14%) of 42 GS-negative lesions (one was doubtful) ($P < .001$). The final diagnosis of the pathologist was compared with the final consensus interpretation of the two abdominal radiologists. In six cases, the diagnosis differed: Two of 48 HCAs were mistaken for FNH, and four of 13 FNH lesions were mistaken for HCA. Both false-negative HCAs showed presence of scar regions.

Two of the four missed FNH lesions showed no scar, and one missed FNH was wrongly diagnosed owing to multiple smaller liver lesions reminiscent of multiple adenomas. All false-negative FNH lesions showed a homogeneous isointense or slightly hyperintense signal on T2-weighted images.

DISCUSSION

The main goal of our study was to investigate the correlation between MR imaging findings and pathologic subtype classification since state-of-the-art MR imaging provides the most comprehensive and noninvasive imaging work-up of patients suspected of having HCAs (15). We were able to confirm specific MR imaging features that can be used to identify different subgroups of HCA, especially inflammatory and L-FABP-negative HCAs, as previously described by Laumonier et al. (12). L-FABP-negative HCA can be recognized with high reliability and is seen as a diffuse decrease in signal intensity on opposed-phase images because of the presence of intratumoral fat in the lesion. MR imaging was used to detect L-FABP-negative HCA in 78% of L-FABP-negative adenomas in which marked intratumoral steatosis was present. Only 17% of inflammatory HCAs showed steatosis within the lesion ($P = .001$); however, this subgroup showed only mild to moderate steatosis, which was distributed focally. All L-FABP-negative HCAs showed slightly hyperintense signal on T2-weighted images, possibly owing to the intratumoral T2 effect of fat (J-coupling effect) (21). In almost half of the inflammatory HCAs, we found a typical atoll sign on MR images, which is characterized by a hyperintense signal band in the periphery of the lesion (like an atoll) and isointensity of the center of the lesion with respect to the surrounding liver (like the surrounding sea) on T2-weighted images. No clear cases with an atoll sign were seen in the L-FABP-negative or other subgroups; however, the difference did not reach significance since a Bonferroni correction was applied to correct for multiple testing. In 10 (77%) of 13 inflammatory HCAs with a characteristic atoll sign, T2-hyperintense islands were visible in the center portion of the lesion. The T2-hyperintense regions (signal band and center islands) typically enhance in the late vascular phase. This characteristic atoll sign is possibly due to sinusoidal dilatation within inflammatory HCA. These areas of sinusoidal dilatation enhance in the venous phase, whereas the rest of the tumor enhances in the arterial phase. Those areas are hyperintense on T2-weighted images, which is probably reflective of the high water content in these bloodfilled regions.

The presence of a vaguely demarcated scar in HCA was significantly associated with nuclear staining of β-catenin ($P = .003$). At microscopic examination of the available slides from the tumor, two of five β-catenin-positive HCAs with presence of a vaguely demarcated scar showed pathologic areas and septa of fibrosis. The remaining β-catenin-positive HCAs with presence of a scar did not show areas of fibrosis, which may be owing to sampling error because of the large size (29, 70, and 100 mm) and limited sampling of these lesions. Presence of a scar in HCA and FNH was significantly associated with a diffuse and homogeneous GS staining pattern ($P < .001$). However, three lesions presented a central scar without positive β-catenin and GS findings. All β-catenin-positive HCAs showed features of slight to moderate enhancement compared with FNH, which showed

marked enhancement in most cases. We did not observe β-catenin or GS positivity in L-FABP-negative lesions. Therefore, by combining the atoll sign with the presence of a scar, we may be able to differentiate between β-catenin-positive inflammatory HCA and β-catenin-negative inflammatory HCA. Typical poorly delimited high-signal-intensity areas on T2-weighted images may be another characteristic MR imaging feature observed in β-catenin-positive HCAs, since this was also described by Laumonier et al. (12). No specific MR imaging features were identified for the unclassified group of HCA.

In most cases in our study, a clear diagnosis of HCA or FNH could be made. However, two (4%) of 48 HCAs were mistaken for FNH, and four (31%) of 13 FNH lesions were mistaken for HCA. The high percentage of FNH lesions that were mistaken for HCAs may be owing to a verification bias since the FNH lesions included were diagnosed as HCAs at the time of resection. It is likely that more atypical FNH lesions were included in our study. The verification bias may also be a reason for the low percentage (62%) of FNH lesions showing intense homogeneous enhancement. The moderate interobserver agreement, mainly owing to the verification bias of atypical FNH lesions, may suggest that the identification of imaging features of benign hepatic lesions such as HCA and FNH may be quite challenging at times.

The question is: How can we differentiate HCA from FNH with more certainty? It is probably that accurate differentiation requires the combination of different features. Hyperintensity on both in- and opposed-phase T1-weighted images (owing to intratumoral blood degradation products) is often seen in HCA and has rarely been noted in FNH lesions (22). Intratumoral fat deposition is a typical feature in HCA and is seldom seen in FNH. While slight enhancement in the arterial phase can be seen in HCA, typical FNH lesions have more pronounced enhancement. Moreover, the presence of a scar in the lesion is not solely found in FNH lesions but may also be seen in HCAs. In all HCA cases in our study where there was a misdiagnosis (probably owing to the internal scar), the slight degree of enhancement of the lesion should have alerted us that the lesion could be HCA instead of FNH.

We suggest classifying HCA by using state-of-the-art MR imaging and following the Bordeaux criteria. Specific subgroups of patients with HCA could be counseled appropriately. In women with a clear diagnosis of HCA lesions at least 5 cm in diameter that do not show adequate regression after discontinuation of oral contraceptives, we recommend surgical resection. Steatotic HCAs smaller than 5 cm may be observed, and follow-up may be stopped when the lesion remains stable or shows reduction in size after 6 months of follow-up, since we did not observe β-catenin positivity in L-FABP-negative HCAs. HCAs that present with a central scar and without other signs of FNH require a more aggressive approach because of the risk of malignant transformation. Close follow-up or resection may be advised in these cases (Figure 6). No published data are available on the success rate of using immunohistochemical markers to classify

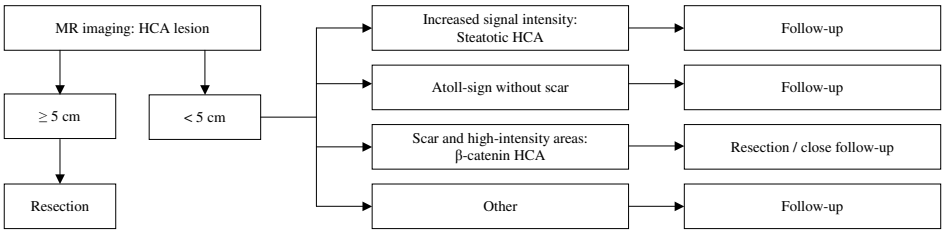

Figure 6. Flowchart shows suggested surgical management of HCA on the basis of MR imaging findings.

subgroups at biopsy. The interpretation of β-catenin staining on biopsies may be difficult because of the heterogeneous and sometimes focal nuclear staining pattern, and our previous experience suggests that sampling error will remain a problem in this situation (13).

The major limitation of our study was the small number of β-catenin-positive HCAs (four lesions of the β-catenin subtype and three β-catenin-positive inflammatory lesions) we were able to include. The identification of inflammatory β-catenin-positive HCA remains a crucial issue owing to the risk of malignant transformation. Therefore, the poorly delimited high-signal-intensity areas observed in β-catenin-positive HCAs deserve additional investigation. Multicenter studies will be required to improve the identification of HCA subgroups and to investigate the consequences for clinical management.

MR imaging may improve the subtype classification of HCA, especially in cases of inflammatory and L-FABP-negative HCAs. MR imaging findings of a vaguely demarcated scar and poorly delimited high-signal-intensity areas on T2-weighted images in HCA seem to be related to β-catenin positivity. Since β-catenin-positive lesions seem to have a higher risk of malignant transformation, surgical resection or close follow-up is advocated in patients presenting with these lesions.

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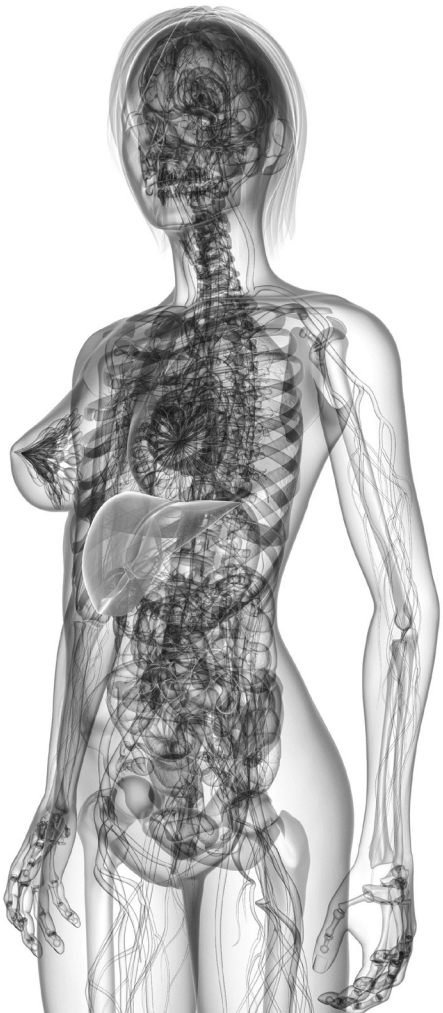
Chapter 4.1

Management of hepatocellular adenoma during pregnancy



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ABSTRACT

Background & Aims: Hepatocellular adenoma in pregnant women requires special considerations because of the risk of hormone induced growth and rupture. To prevent these potential lethal complications, pregnancy is either often discouraged or the surgical resection of large adenomas is recommended. It may be questioned whether it is justified to deny a young woman a pregnancy, as the biological behaviour of hepatocellular adenoma may be less threatening than presumed. In this study we establish the management of hepatocellular adenoma during pregnancy based on our own experience and literature.

Methods: Twelve women with documented hepatocellular adenoma were closely monitored during a total of 17 pregnancies between 2000 and 2009. Their files were reviewed.

Results: In four cases, hepatocellular adenomas grew during pregnancy, requiring a Caesarean section in one patient (two pregnancies) at 36 and 34 weeks because of an assumed high risk of rupture. In one case radiofrequency ablation therapy was applied in the first trimester to treat a hormone sensitive hepatocellular adenoma, thereby excluding potential growth later in pregnancy. No intervention was performed in the other 14 cases and all pregnancies had an uneventful course with a successful maternal and fetal outcome.

Conclusions: A "wait and see" management may be advocated in pregnant women presenting with a hepatocellular adenoma. In women with large tumours or in whom hepatocellular adenoma had complicated previous pregnancies, surgical resection may be recommended. In women with smaller adenomas it may no longer be necessary to discourage pregnancy.

INTRODUCTION

Hepatocellular adenoma (HCA) is an uncommon benign tumour of the liver that occurs particularly in women during their reproductive years. The annual incidence rate of HCA is approximately 1-1.3 per 1,000,000 in women who have never used oral contraceptives (OC), compared to 30-40 per million in long-term users [1,2]. Thus, most HCAs are associated with the use of OC [3–5], an association which was first described in 1973 [3]. Other conditions associated with the presence of HCA have been described, including anabolic steroids, glycogen storage disease I and III and pregnancy [6–13]. Most likely the association of HCA and pregnancy is due to the increased levels of steroid hormones [14,15]. The presence of HCA can be complicated by hormone induced growth and subsequently, spontaneous haemorrhagic rupture that may threaten the life of both mother and child. A growing or bleeding adenoma may present with persistent or acute severe pain localized in the upper right quadrant and in the epigastric region. Its presentation can be difficult to differentiate from more common aetiologies of abdominal pain in pregnancy, like preeclampsia, Haemolysis Elevated Liver enzymes and Low Platelets (HELLP) syndrome or non-obstetric pathology like appendicitis, gallbladder disease, biliary pancreatitis, or pulmonary embolism [16]. This differential diagnosis may lead to a diagnostic delay. Early detection of HCA and a correct management of these patients are highly important, since several manuscripts documented high maternal and fetal risks in case of a ruptured HCA during pregnancy with a reported maternal and fetal mortality rate of 44% and 38%, espectively [17]. In the last decennium, the introduction and widespread use of highly advanced image modalities have probably decreased the doctors' delay in the diagnosis of HCA and the associated maternal and fetal mortality risk might be reduced significantly. No ruptures associated with gestation were reported in tumours less than 6.5 cm in size [17]. In non pregnant women haemorrhage has been documented in a tumour of 4.5 cm in size but is most commonly seen in tumours greater than 10 cm [17]. The risk of rupture is highest during the third trimester, most likely due to the accumulating level of estrogens and an increase in hyperdynamic circulation combined with an increase in vascularity of the liver with growth of the adenoma [17]. In the postpartum period, the risk of bleeding seems to be high as well; this can be explained by the sudden withdrawal of estrogens after delivery that may cause a sudden massive regression of the tumour leading to haemorrhage [17]. Because of the unpredictable behaviour of HCA and high maternal and fetal mortality of a ruptured HCA during pregnancy women with a large HCA or a growing and hormone sensitive HCA are advised to avoid pregnancy by most experts (either incidental findings previous to a pregnancy or women who experienced complications of an adenoma during pregnancy) [2,15]. In addition, pregnancy itself limits the diagnostic modalities and interventions may be associated with greater risks in case of large adenomas [17]. At our centre, HCAs with a

diameter of 5 cm or larger that do not show adequate regression after discontinuation of the use of OC are considered for invasive treatment before pregnancy [15]. We were able to study 12 patients from a prospectively acquired database who sustained HCAs of different sizes during a total number of 17 pregnancies.

PATIENTS AND METHODS

The Erasmus Medical Centre is a tertiary referral centre for focal liver lesions with an area of adherence of approximately 4 million people. From 2000 to 2009 all data of patients with HCA were recorded prospectively in a weekly multidisciplinary meeting attended by a radiologist, hepatologist, pathologist, and surgeon specialized in solid liver tumours. At the time of diagnosis every HCA patient was advised to discontinue the use of OC and to prevent pregnancy. If pregnancy would nevertheless occur, patients were strongly advised to contact our centre to evaluate growth of the tumour by the surgeon or hepatologist. Follow-up of the fetus was carried out by the gynaecologist on a regular basis. A gynaecologist was consulted only in those cases where a significant growth of the adenoma was observed and its management could influence pregnancy. The patients described (12 of 183 patients with HCA) were diagnosed by contrast enhanced CT or MR imaging between January 2000 and December 2009. Until 2008 Gadolinium was the contrast agent of choice for MR imaging. In some cases, Gadolinium was followed by Resovist contrast for increased diagnostic certainty. After 2008, MultiHance was the contrast agent of choice for MR imaging. During their pregnancy they were closely monitored by means of repetitive ultrasound and/or MR imaging. The frequencies of the measurements had no fixed time schedule and depend on the size and changes in the characteristics of the lesion. Their files were reviewed to evaluate presentation and time of presentation, use of OC, size and growth before and during pregnancy and postpartum, complications and management during pregnancy, gestation time and way of delivery, maternal and fetal outcome, and complications and management after delivery.

RESULTS

Nearly all women (11 of 12) were diagnosed with HCA prior to their pregnancy. In one patient, HCA was diagnosed during pregnancy (Table 1). Eleven patients were using OC at the time of diagnosis, or had used OC in the past. In four patients there had been a regression of HCAs after discontinuation of OC. One patient became pregnant before it was possible to evaluate her hormone sensitivity for the HCA. Another two patients

Table 1. Patient characteristics, diagnosis and management

Case no.	Age	Presentation before pregnancy	OC	Diagnosis	Management before pregnancy	Course of HCA after discontinuation OC
1	29	Symptomatic (bleeding, haemodynamically stable)	Yes	3 HCAs, all < 5,0 cm	Elective surgery; laparoscopic segment 2/3 resection. Discontinuation OC	No regression or growth of lesions
2	37	No complaints; incidental finding on US	Yes	1 HCA, < 5,0 cm	Conservative. Discontinuation OC	Regression of lesion
3	30	Symptomatic (bleeding, haemodynamically stable)	Yes	Multiple HCAs, one > 5,0 cm	Conservative. Discontinuation OC	Unknown; stopped OC before HCA was diagnosed
4	28	Unspecific complaints; incidental finding on US	Yes	Multiple HCAs, all < 5,0 cm	Conservative. Discontinuation OC. Weight reduction	Regression of lesions
5	25	Unspecific complaints; incidental finding on US	Yes	3 lesions, atypical FNH/ adenoma, all < 5,0 cm	Conservative. Discontinuation OC	Unknown
6	41	No complaints; incidental finding on US	Yes	3 HCAs, one > 5,0 cm	Elective surgery, segment 4 resection	No regression or growth of lesions
7	33	Presentation during pregnancy; symptomatic (pain right flank)	Yes	1 HCA, < 5,0 cm	Before 2nd pregnancy RFA; segment 4a. Discontinuation OC	Unknown; stop of OC before HCA was diagnosed
8	23	Unspecific complaints (abdominal pain); diagnosis elsewhere	Yes	2 HCAs, one > 5,0 cm	Elective embolisation. Discontinuation OC	Growth of lesions
9	31	Unspecific complaints; incidental findings on US	No	Multiple HCAs, one > 5,0 cm	Conservative.	-
10	35	Symptomatic (bleeding, haemodynamically stable)	Yes	Multiple HCAs, all < 5,0 cm	Elective surgery; segment 3/6 resection. Discontinuation OC	No regression or growth of lesions
11	36	Unspecific complaints; incidental findings on CT	Yes	1 HCA, < 5,0 cm	Conservative. Discontinuation OC	Regression of lesion
12	28	Unspecific complaints; incidental findings on US	Yes	2 HCAs, one > 5,0 cm	Conservative. Discontinuation OC	Regression of lesions

US = ultrasound

stopped OC before HCA was diagnosed. In one patient there was growth of the HCA two and a half years after discontinuation of OC. No regression or growth of the HCA was noticed in three patients. Ten patients presented in the first trimester of pregnancy for monitoring of the HCA (Table 2). In one patient with multiple HCAs (case No. 3) there was serious concern about the risk of rupture of these lesions. One year before pregnancy she presented with an acute sensation of upper right quadrant pain, based on an

Table 2. Details of HCA with concern to pregnancy and follow-up after delivery

Case no.	Pregnancy no.	Growth	Interventions during pregnancy	Follow-up after delivery	Course of HCAs during follow-up
1	1	No	None	Follow-up elsewhere	
2	1	No	None	10 months	Regression, HCA hardly visible on last US
	2	No	None	8 months	Regression of lesion
3	1	Yes: > 5cm	C-section and administration on IC-unit after delivery.	17 months	Some regression of 3 HCAs, remaining HCAs status quo. No evidence of rupture.
	2	Yes: > 5cm, in two tumours	C-section	Ongoing	Some regression of HCAs on CT, No evidence of rupture
4	1	No	None	None	Unknown
5	1	Yes, but < 5cm	None	24 months	Regression of lesion
	2	No	None	Ongoing	Unknown
6	1	No	None	3 months	On US no evidence of focal liver lesions
7	1	Yes: > 5 cm	None	Follow up elsewhere	Regression of lesion
	2	No: no tumour after RFA	None	5 months	On US no evidence of focal liver lesion
8	1	No	None	10 months	1 HCA regression, 1 HCA status quo ante
	2	No	None	Ongoing	Unknown
9	1	No	RFA 1st trimester; segment 6	48 months	1 HCA regression after RFA, remaining HCAs status quo ante
10	1	2nd trimester minimal regression	C-section	16 months	Regression, HCA hardly visible on last MRI
11 *	1	Unknown	None	8 months	Regression of lesion
12	1	No	None	Ongoing	Unknown

US = ultrasound

* In case no. 11 there was no monitoring of HCA in our hospital.

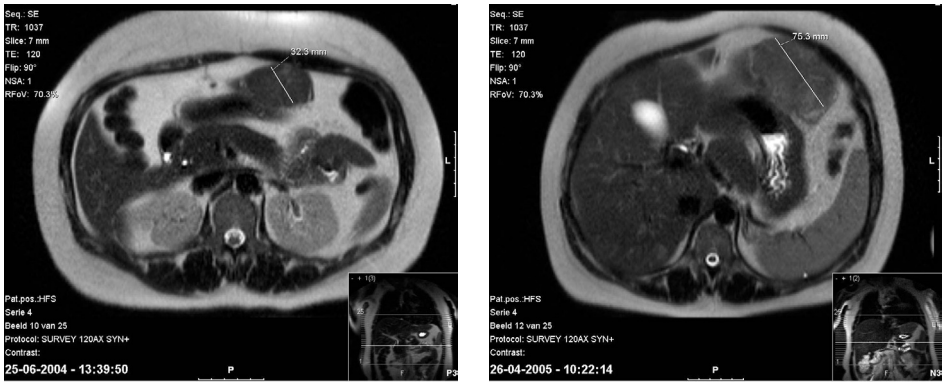

Figure 1. MR-images of one of the adenomas (segment 2/3) of patient no. 3, nine months after diagnosis and discontinuation of OC's and in the 34th week of pregnancy. Due to pregnancy and the volume of the abdomen, the tumour was displaced in segment 2 and 3 cranially. The tumour shows significant growth.

intracapsular haemorrhage of an HCA. She withdrew from medical attention during the first trimester of her first pregnancy, but presented at the gynaecologist at 33 weeks gestation because of diabetes gravidarum. Until then, the patient was under surveillance at her general practitioner. At 33 weeks gestation, MR imaging, after ultrasound was performed, revealed a significant growth of the largest lesion from 32 to 75 mm (Figure 1). Another lesion showed signs of haemorrhage that had been noticed 2 years ago. At that time the lesion was measured 60 mm. This lesion measured 40 mm during her 33 weeks of gestation. To exclude any further risks, it was decided to deliver the child by means of a Caesarean section (C-section) at 36 weeks with close postpartum monitoring of the mother at the Intensive Care Unit for several days because of an increased risk of haemorrhage. Despite our advice to prevent further pregnancies, this patient became pregnant a second time. In between her first and second pregnancy, there was a regression of the lesion from 75 to 40 mm demonstrated by MR imaging. During her second pregnancy, marked growth of the HCAs was noticed again, resulting in a C-section at 33 weeks. Both children were born healthy. Two patients (case Nos. 5 and 7) showed growth in association with pregnancy and regression of the tumour postpartum (Figures 2 and 3). In one patient (case No. 9), who wanted to keep her pregnancy, the tumour was treated with radiofrequency ablation (RFA) during the first trimester of her second pregnancy. The HCA showed regression during her pregnancy from 43 x 35 mm to 27 x 19 mm. Maternal and fetal outcomes were excellent in all cases and none of the HCAs resulted in complications during pregnancy or after delivery.

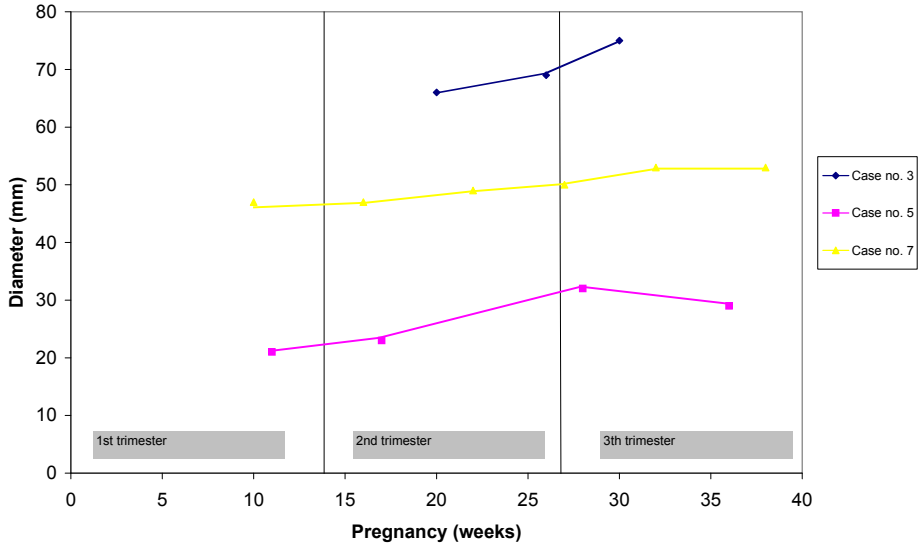

Figure 2. Growth of the largest adenoma during pregnancy.

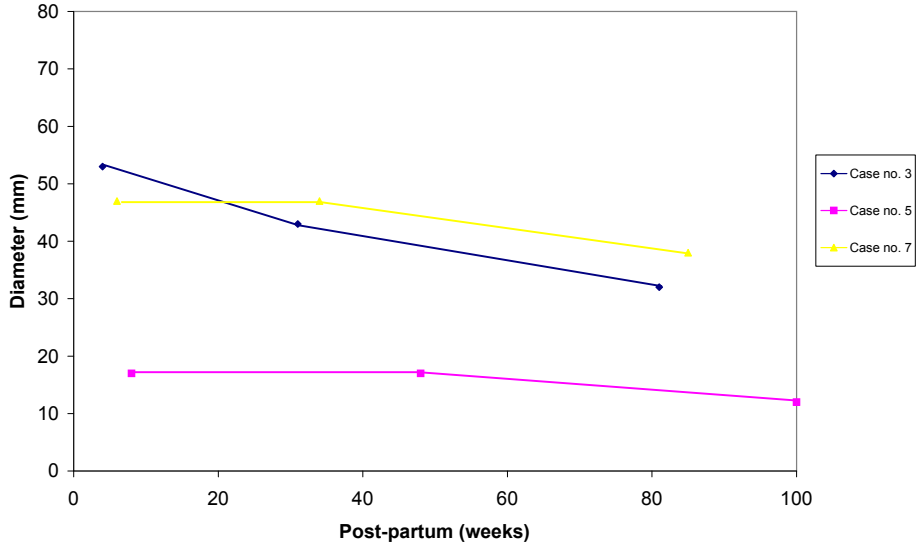

Figure 3. Regression of the largest adenoma postpartum.

DISCUSSION

The diagnosis of HCA may severely impact the life of a young fertile woman, in particular because of the overall agreed advice to avoid pregnancy. Literature on the course of HCA during pregnancy and recommended management is scarce. Some authors advocate that women with HCA should not get pregnant [2,15]. As to date we cannot identify pre-

cisely those at risk of complications. It is likely that only a small subgroup of patients may experience complications. We provide a small but unique series of women who were monitored meticulously during pregnancy. Most cases of HCA related to pregnancy described in the literature were presented during pregnancy or shortly postpartum. From the international literature between 1966 and 2003, Cobey et al. retrieved 26 cases of women presenting with HCA during pregnancy or early postpartum and proposed an algorithm for their diagnosis and management [17]. Presentation was acute and often dramatic with rupture of the adenoma in 16 women, and frequently with a delay in establishing the correct diagnosis, with high maternal and fetal mortality. An aggressive approach towards resection of HCA was advocated, especially for those greater than 5 cm, based upon the high maternal and fetal mortality (44% and 38%, respectively) for women presenting with HCA during pregnancy. Small adenomas were supposed to be managed by observation [17]. We have previously reported that more than half of the HCAs are discovered after the patient has sustained at least one pregnancy [18]. None of these patients have reported problems during their pregnancies. In the current small series, just one patient presented with a tumour growth of real concern and that demanded an invasive intervention during pregnancy. In addition, rupture or other complications of solitary or multiple HCAs did not occur during intensive follow-up. Based on these data we believe that a plea for a less aggressive surgical approach towards HCA in pregnant women may be justified. Especially in small tumours (<5 cm) we propose close monitoring and we believe it can be safe to allow pregnancy. However, in some women in whom the growth of the HCA is substantial there is reason for concern. Some authors suggest a C-section for HCA given the tendency to rupture at term [17]. In our study three C-sections (two patients) were performed, without complications. In one case (No. 3) the C-section was performed in consultation with the patient because of marked growth and an unknown risk of rupture of the HCAs. In the other patient (case No. 10) C-section was due to decelerations on the cardiotocography. All other patients had a normal delivery which was never complicated by the rupture of an HCA. Therefore, in our opinion, patients with HCA may deliver vaginally if there are no complicating factors, like perinatal problems. Prognostic factors on rupture and malignant degeneration during pregnancy remain unknown until this moment. Women with HCAs must be informed about the possible risks before pregnancy. The literature on the management of HCAs during pregnancy is scarce due to the low incidence of HCAs in general [2,15], and the low number of HCAs detected during pregnancy in particular. Growth of HCA in pregnant women requires special considerations for contemplating and timing possible interventions.

In the cases where an intervention is indicated, surgical resection as well as a minimal invasive approach may be considered, especially in smaller lesions. An intervention is safest in the 2nd trimester [14]. RFA is a minimally invasive technique, which is widely

used for the treatment of patients with primary and secondary malignant tumours especially when resection is not an option. RFA is believed to be a relatively safe procedure in experienced hands with low mortality and morbidity [19–22]. In 2006, Fujita et al. reported a pregnant patient with a HCA that was treated by RFA during her 18th gestational week [23]. In our centre RFA is occasionally used as an alternative treatment in women with HCA. A disadvantage of RFA is that after ablation of the tumour there is no material for pathological analysis. When there is any doubt about the diagnosis, especially about the benign character of the tumour, the diagnosis should be confirmed first. If malignancy cannot be excluded, surgical resection is preferred. Selective arterial embolization can be used both as an elective treatment to reduce the size of the HCA as well as the initial emergency treatment in case of active bleeding of the HCA [24–26]. It is a minimally invasive and safe procedure compared to laparotomy and complications are rare. There are no large patient series, and especially in pregnant women with HCA there is little experience with the use of arterial embolization, although some authors suggest that it is a safe and effective treatment for HCA [27,28]. Since the risk of radiation exposure [29,30] to the fetus is increased, especially before 26 weeks of gestation, we feel that selective arterial embolization should only be used as an emergency treatment when RFA or surgery are not a favourable option, for instance for more centrally located tumours that are hardly accessible by RFA.

In conclusion, based on our small but unique prospective series we propose to not discourage all women with HCAs from pregnancy. We hypothesize that pregnancy may be allowed in case of a known HCA under certain conditions such as size and after discussing the risk-benefit ratio with the patient. Women should be aware of the potential risks as an intervention may still be indicated during pregnancy, especially if the lesion is accessible for limited surgical resection or a percutaneous RFA. Close monitoring by liver ultrasound every 6 weeks may offer adequate information for surveillance of the hepatic lesion. In women who have large tumours or who have experienced complications of HCA in previous pregnancies, a negative advice against pregnancy is justified because of an increased risk of complications. In that case, surgical resection should be recommended before pregnancy. HCA in pregnant women implies special considerations, therefore, additional data from different centres for the risk of hormone induced growth and rupture of the adenoma during pregnancy are needed.

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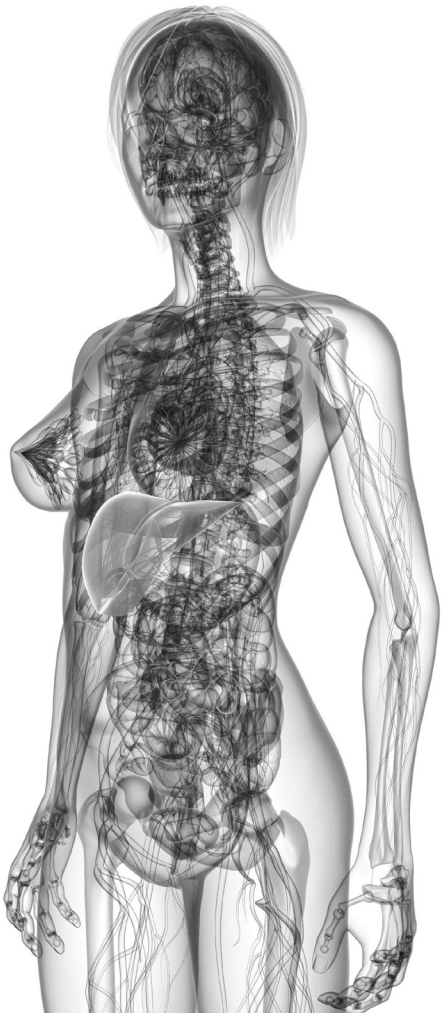
Chapter 4.2

Pregnancy And Liver adenoma Management – PALM study



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ABSTRACT

Background: Hepatocellular adenoma (HCA) in pregnant women requires special considerations because of the risk of hormone induced growth and spontaneous rupture, which may threaten the life of both mother and child. Due to scarcity of cases there is no evidence-based algorithm for the evaluation and management of HCA during pregnancy. Most experts advocate that women with HCA should not get pregnant or advise surgical resection before pregnancy. Whether it is justified to deny a young woman a pregnancy, as the biological behaviour may be less threatening than presumed depends on the incidence of HCA growth and the subsequent clinical events during pregnancy. We aim to investigate the management and outcome of HCA during pregnancy and labor based on a prospectively acquired online database in the Netherlands.

Methods & Design: The Pregnancy And Liver adenoma Management (PALM) - study is a multicentre prospective study in three cohorts of pregnant patients. In total 100 pregnant patients, ≥ 18 years of age with a radiologically and/or histologically proven diagnosis of HCA will be included in the study. Radiological diagnosis of HCA will be based on contrast enhanced MRI. Lesions at inclusion must not exceed 5 cm. The study group will be compared to a healthy control group of 63 pregnant patients and a group of 63 pregnant patients with diabetes mellitus without HCA. During their pregnancy HCA patients will be closely monitored by means of repetitive ultrasound (US) at 14, 20, 26, 32 and 38 weeks of gestation and 6 and 12 weeks postpartum. Both control groups will undergo US of the liver at 14 weeks of gestation to exclude HCA lesions in the liver. All groups will be asked to fill out quality of life related questionnaires.

Discussion: The study will obtain information about the behaviour of HCA during pregnancy, the clinical consequences for mother and child and the impact of having a HCA during pregnancy on the health related quality of life of these young women. As a result of this study we will propose a decision-making model for the management of HCA during pregnancy.

Trial registration: Dutch trial register: NTR3034

INTRODUCTION

Hepatocellular adenoma (HCA) is rare benign tumor of the liver that occurs particularly in women during their reproductive years. The incidence is not exactly known. Studies performed years ago show an estimate incidence of 1-1.3 per 1,000,000 in women who have never used oral contraceptives (OC), compared to 30-40 per 1,000,000 in long-term users [1-2]. The association of HCA with the use of OC was first described in 1973 [3]. In subsequent years many authors have supported the hypothesis of an association between OC and HCA [4-8]. The mechanism by which estrogen or other steroids contributes to the development of HCA is still not understood and studies are rare. Symptomatic patients with HCA present with right upper quadrant abdominal pain or discomfort secondary to bleeding within the HCA, elevated liver enzymes and symptoms of life treating hemorrhage into the peritoneal cavity. However, most patients with HCA are asymptomatic and present as an incidental finding during ultrasonographic examination of the abdomen for unrelated reasons or are noted during laparoscopic cholecystectomy. Despite its benign nature, the diagnosis of HCA has a great impact of the lives of these, mostly, young women because HCA can be complicated by hormone induces growth and rupture. Besides that malignant transformation of HCA into hepatocellular carcinoma has been reported with an overall frequency of 4.2% [9].

Regardless of the exact etiology and risk factors all female patients should be advised to stop OC's and other hormone medication such as hormone replacement therapy, since regression of HCA may occur when steroids are withdrawn [10-13] and observation should be the first choice of treatment for most patients with HCA. Because of the risk for spontaneous rupture most authors believe that surgical resection is required if the diameter exceeds 5 cm after 6 months of follow-up without OC use, if the lesion does not show adequate regression after discontinuation of OC or if rebleeding occurs [14-17]. Surgical resection is also indicated if there is diagnostic doubt e.g. whether a tumor is malignant [18-19].

HCA in pregnant women requires special considerations because of the risk of hormone induced growth and spontaneous rupture, due to increased levels of steroid hormones during pregnancy that may threaten the life of both mother and child. Most experts advocate that women with HCA should not get pregnant or advise surgical resection before pregnancy [2, 18]. Cobey et al. reported a maternal and fetal mortality risk of ruptured HCA during pregnancy of 44% and 38%, respectively [20]. However, all these cases were published in the 1970s and 1980s and nowadays the introduction and widespread use of highly advantage imaging modalities have probably decreased the doctors' delay in the diagnosis of HCA. We recently proposed not to discourage all women with HCA from pregnancy, based on a study in which we monitored twelve women with documented HCA during a total of 17 pregnancies. In 4 cases HCA's grew during pregnancy, requiring

a Caesarean section in 1 patient (2 pregnancies) and radiofrequency ablation (RFA) in 1 case during the first trimester of pregnancy. All pregnancies had an uneventful course with a successful maternal and fetal outcome [21]. However, there is no evidence-based algorithm for the evaluation and management of HCA during pregnancy and labor, due to scarcity of cases. The conclusion not to discourage all women with HCA from pregnancy has, however, to be proven in a large multicentre study in which we will closely monitor pregnant patient with a HCA in a prospectively acquired database to give more insight in the behaviour of HCA during pregnancy.

METHODS & DESIGN

Study objective

In this study we will investigate the management and outcome of HCA during pregnancy and labor based on a prospectively acquired online database in the Netherlands.

Main objective of the PALM-study

- To investigate the incidence of HCA growth during pregnancy and labor.

Secondary objectives of the PALM-study

- To investigate in which trimester of pregnancy growth of HCA occurs;
- To investigate the degree of growth of HCA during pregnancy;
- To investigate whether there is regression of HCA postpartum;
- To investigate the HCA-related interventions during pregnancy and labor;
- To investigate the incidence of bleeding of HCA during pregnancy and labor;
- To investigate liver-related clinical signs during pregnancy;
- To investigate elevated liver enzymes during pregnancy;
- To evaluate the health related quality of life of pregnant patients with HCA;
- To investigate whether there is a difference between health related quality of life of pregnant patients with HCA and pregnant patients with other co-morbidity that have an indication for pregnancy care at the obstetrician in secondary care and healthy pregnant patients.

Study design

The PALM-study is a multi-centre prospective study in three cohorts of pregnant women. The study starts on November 1 2011 and inclusion of patients will be a period of minimal 3 to maximal 5 years. In total 100 pregnant patients with HCA < 5 cm will be included in the study. These patients will be compared to a healthy control group consisting of 63 pregnant patients without HCA and a group consisting of 63 pregnant

patients with diabetes mellitus (DM). The exact sample size will be 226 patients. Approval of the medical ethical committee was obtained.

Patient selection

Study group

Properly Dutch speaking, pregnant patients, 18 years of age or older with a radiologically and/or histologically proven diagnosis of HCA can be included in the study. Radiological diagnosis of HCA will be based on contrast enhanced magnetic resonance imaging (MRI) and if available in combination with (contrast enhanced) ultrasonography (US). Lesions must not exceed 5 cm. In the first weeks of pregnancy patients will be referred to the obstetrician for pregnancy care. Baseline starts at 14 (+/- 3) weeks of gestation. At this day and every 6 weeks patients will undergo US of the HCA lesion at the radiologist. Before US of the HCA lesions patients will be asked to fill out generic health related quality of life questionnaires (12-item Short Form SF 12 and EuroQol questionnaire EQ-5d), a generic anxiety questionnaire (State-Trait Anxiety Inventory STAI-6) and the Impact of Event Scale (IES) questionnaire for thoughts and feelings about HCA around the US. One week afterwards the study group will be asked to fill out the STAI-6 en IES again. At 14 and 32 weeks of pregnancy patients will undergo venapunction.

Control group 1 (healthy pregnant patients without HCA)

Properly Dutch speaking, healthy pregnant patients, 18 years of age or older without HCA. In the Netherlands, pregnant women will start pregnancy care with an independently practicing midwife early in pregnancy at the primary care level [22]. The midwife is responsible for the pregnant women as long as the pregnancy, labor or postpartum period is normal [23]. In case of complication, the midwife will refer the women to the obstetrician in secondary care [22-23]. Women with a high risk profile based on their medical or obstetric history will be cared for the obstetrician from the start of pregnancy [22-23]. Patients presenting at the practicing midwife will be asked to participate in the study. Thereafter, the patients will be included in the study by the study investigator. Patients will undergo US of the liver at 14 (+/-3) weeks of gestation to exclude HCA lesions in the liver. At this day and every other 6 weeks patients will be asked to fill out the SF-12 and EQ-5d questionnaire. At 14 and 32 weeks of pregnancy patients will undergo venapunction. In case of an uncomplicated pregnancy, the patient remains under the care of her practicing midwife during her pregnancy and postpartum.

Control group 2 (pregnant patients with Diabetes Mellitus)

Properly Dutch speaking, pregnant patients, 18 years of age or older with Diabetes Mellitus, can be included in the study. These patients have an indication for pregnancy care

at the obstetrician in secondary care. Patients will undergo US of the liver at 14 (+/-3) weeks of gestation to exclude HCA lesions in the liver. At this day and every other 6 weeks patients will be asked to fill out the SF-12 and EQ-5d questionnaire. At 14 and 32 weeks of pregnancy patients will undergo venapunction.

For all groups informed consent is mandatory. A patient can always withdraw her consent at anytime during the study where after she is referred for the present standard of care.

Hypothesis

Pregnancy may be allowed in case of one or more known HCA < 5 cm (without previous intervention), because a HCA < 5 cm will not disturb the course of pregnancy.

Disrupted course of pregnancy:

- Interventions during pregnancy (radiological and/or surgical intervention).
- Decreased quality of life and/or anxiety in patients during pregnancy related to the presence of HCA in the liver and possible growth during pregnancy.

Retrospective cohort study

We have previously reported that more than half of the HCA are discovered after the patient has sustained at least one pregnancy and none of these patients have reported problems during their pregnancies [19]. As mentioned above, recently we described a small but unique series of 12 women with documented HCA who were closely monitored during a total of 17 pregnancies between 2000 and 2009. In 4 cases HCA's grew during pregnancy, requiring a Caesarean section in 1 patient (2 pregnancies) and RFA in 1 case during the first trimester of pregnancy to treat a hormone sensitive HCA, thereby excluding potential growth later on in pregnancy. No intervention was performed in the other 14 cases. All pregnancies had an uneventful course with a successful maternal and fetal outcome and we concluded that a "wait and see" management may be advocated in pregnant women presenting with HCA. In women with large tumours or in whom HCA had complicated previous pregnancies, surgical resection may be recommend [21]. However, additional data from different centres for the risk of hormone induces growth and rupture of HCA during pregnancy is needed.

Interventions

During their pregnancy HCA patients will be closely monitored by means of repetitive US (and MRI in case of growth of the lesion) at 14 (+/- 3) and 20 and 26 and 32 and 38 weeks of gestation and 6 and 12 weeks postpartum. At the same days both control groups will be asked to fill out the SF-12 and EQ-5d questionnaire at 14 (+/- 3) and 20

and 26 and 32 and 38 weeks of gestation and at 6 and 12 weeks postpartum. (Figure 1) The study group will be asked to fill out the SF-12, EQ-5d, STAI-6 and IES questionnaires before and one week after US of the HCA lesion(s). Both control groups will undergo US of the liver at 14 (+/- 3) weeks of gestation to exclude HCA lesions in the liver. At 14 and 32 weeks of pregnancy all patient groups will undergo venapunction.

Pregnancy			
Weeks	**Ultrasonography**	**Venapunction**	**Questionnaires**
14	S, C1, C2	S, C1, C2	S, C1, C2 *
20	S		S, C1, C2 *
26	S		S, C1, C2 *
32	S	S, C1, C2	S, C1, C2 *
38	S		S, C1, C2 *
Post-partum			
Weeks	**Ultrasonography**	**Venapunction**	**Questionnaires**
6	S		S, C1, C2 *
12	S		S, C1, C2 *

S, study group; C1, control group 1 (healthy pregnant patients without HCA); C2, control group 2 (pregnant patients with Diabetes Mellitus).

* The study group will be asked to fill out the SF-12, EQ-5d, STAI-6 and IES questionnaires before and one week after US of the HCA lesion(s). Both control groups will be asked to fill out the SF-12 and EQ-5d questionnaire.

Figure 1. Study protocol.

Online database

We established a website which allows hepatologists, surgeons and gyneacologists to submit clinical data in an online database. Each centre will have a code to log in and patients will be consecutively assessed a unique number. Registration of a new patient includes entry of the following data: date of birth, weight, height, date of hospital admission, symptoms at presentation, known risk factors for HCA such as glycogenosis and familial polyposis, [24] previous pregnancies, previous use of OC or other hormone medication including hormone replacement therapy, course of HCA after discontinuation of OC, size of HCA before pregnancy, size of HCA during pregnancy (14 (+/– 3) and 20 and 26 and 32 and 38 weeks), course of HCA postpartum (6 and 12 weeks postpartum), complications and management during pregnancy, gestation time, way of delivery (vaginally, Caesarean section), maternal and fetal outcome, complications and management after delivery. Only authorized users can gain action to the online database of his or her patients. The database offers excess to the registered data on anytime and anywhere. The coordinating investigator will monitor whether all required fields are completed.

Follow-up

Follow-up of patients takes place at 6 and 12 weeks postpartum postpartum by means of US (and MRI in case of growth) to document the size of HCA postpartum. Both control groups will be asked to fill out the SF-12 and EQ-5d questionnaires at these days. The study group will be asked to fill out the SF-12, EQ-5d, STAI-6 and IES questionnaires before and one week after US of the HCA lesion(s).

Outcome measures

Primary outcome: Biological behaviour and clinical consequences of HCA < 5 cm during pregnancy. Growth is measured by repetitive US (and MRI in case of growth) at 14 (+/- 3) and 20 and 26 and 32 and 38 weeks of gestation. Secondary outcome: General health and pain scales as a measure for quality of life and anxiety related questionnaires for thoughts and feelings of adenomas around US. Other secondary outcomes are complications due to growth of the HCA during pregnancy possibly followed by interventions during pregnancy, incidence of hemorrhage and rupture of the HCA, incidence of liver-related clinical signs during pregnancy (itch, icterus), incidence of elevated liver enzymes during pregnancy.

Power calculation

In our previous study we measured growth of HCA in 4 out of 17 pregnancies (24%) or in 3 out of 12 women (25%). On a yearly basis approximately 50 new patients with HCA are seen at the outpatient clinic of the Erasmus University Medical Centre. The expectation is that 10% (5) of these women get pregnant. The expectation is that a total of 100 pregnant HCA patients from different tertiary referral centres in the Netherlands can be included in the study during a period of 3 to maximum 5 years. For an expected incidence of 25% of HCA growth during pregnancy we calculated a 95% confidence interval of +/– 8.5% [16.5 - 33.5%], which we consider sufficiently small.

A difference of 0.5 Cohen's D in health-related quality of life is a relevant difference [25]. We calculated that for this purpose 63 patients in both control groups have to be enrolled. A two-sample t test was performed with a two-sided significant level of 0.05 and a power of 0.80.

Access to personal data

Medical data with which the identity of a patient could be traced will be replaced by a code number. The coordinating investigator is the only one who has the key to the code numbers and knows which code number stands for which patient. The principal investigator has only access to the coding system of his or her patients and will never be able to open the database from other centres. Only members of the investigating team and members of the medical ethical committee of the participating centres will

have access to the medical data. All data will be collected in a prospectively acquired database by the principal investigators and managed by the coordinating investigator.

DISCUSSION

Once the diagnosis of HCA has been established, patients will be advised to discontinue OC. Expert opinions are very variable regarding treatment and follow up in complex situations were multiple factors play a role in determining the management strategy, like pregnancy [18]. As to date there are limited data about the behavior of HCA during pregnancy and labor and therefore we cannot identify precisely those at risk for complications. However, in 2006 we reported a series of 48 patients of which in 44% HCA were discovered after the patient had sustained at least one pregnancy [19]. None of these patients have reported problems during their pregnancies. Likely, only a small subgroup of patients may experience complications and to date pregnancy might be discouraged in too many patients caused by unnecessary intervention before pregnancy. We hypothesize that pregnancy may be allowed in case of one or more known HCA < 5 cm (without previous intervention), because HCA < 5 cm will not disturb the course of pregnancy. Close monitoring during pregnancy by means of repetitive US (and MRI in case of growth) should be carried out to rule out rapid growth of the lesion. The risk of rupture seems the highest during the third trimester of pregnancy [20]. Most likely due to the cumulating level of estrogens and an increase in hyperdynamic circulation combined with an increase in vascularity of the liver with growth of the adenoma [20]. Symptoms and the level of liver enzymes will be registered to find out if there is a relation between symptoms, elevated liver enzymes and growth of the HCA during pregnancy. Patients will be followed-up postpartum to investigate if there is a risk of HCA complications after delivery.

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) provided guidelines for diagnosis, treatment, and use of laparoscopy for surgical problems during pregnancy [26]. However, these guidelines are mostly based on case reports and retrospective studies and therefore graded at a low level of evidence. The SAGES suggest that MRI without the use of intraveneous gadolinium, and US is considered safe and can be used at any stage of pregnancy (Level IIIB and Level IIA respectively) [26]. Data regarding safety of CEUS during pregnancy is scare and yet uncertain. However, Hua et al. reported an animal study in which SonoVue may affect the placenta [27]. Therefore, we will not use CEUS for patient follow-up during pregnancy.

One should be aware of the potential risks as an intervention may still be indicated during pregnancy. In approximately one in 635 pregnancies a non-obstetric operation during pregnancy is required, especially appendectomy, cholecystectomy and adnexal procedures [28]. However, it is conceivable that more non-obstetric operations might be

required due to the risk of hormone induced growth and spontaneous rupture of HCA during pregnancy. Despite maternal and fetal outcomes following abdominal disease and surgery in pregnancy improved over the past years, the exact risk of HCA-related interventions during pregnancy to both mother and fetus is unknown [29]. We do know that changes in physiology and abdominal anatomy characteristics of pregnancy make abdominal surgery more difficult [29]. The least risk of general anaesthesia is in the 2nd trimester of pregnancy [30].

Based on a systematic review of the literature, Wilson et al. suggested angio-embolisation and formal resection in case of haemorrhage of HCA during pregnancy and suggested this strategy to be safe for both the mother and the fetus with good clinical outcomes [31]. The role of RFA during pregnancy is not well studied. In our previous study we described a RFA procedure during the first trimester of pregnancy [21] and Fujita et al. reported a pregnant patient with a HCA that was treated by RFA during her second trimester of pregnancy (18th week of gestation) [32].

The influence on the course of pregnancy, since a woman is aware of having a HCA, is also unknown. Patients can get horrified when confronted with the new diagnosis of a hepatic mass [20] and it is conceivable that women can be anxiety during pregnancy due to the presence of HCA in the liver and the possible growth during pregnancy. Therefore, quality of life will be an important measurement for future management of HCA during pregnancy. It is conceivable that frequent monitoring by means of US may comfort the patients or can be frightening. All patient groups will be asked to fill out the SF-12 and EQ-5d questionnaires every 6 weeks. HCA patients will be asked to fill out the STAI-6 and IES questionnaires before the US of the liver lesions and one week after US to investigate anxiety related to HCA and US during pregnancy.

Our main point of interest is whether it is justified to deny a young woman with a HCA < 5 cm a pregnancy. With this study we hope to obtain information about the behaviour of HCA during pregnancy and the impact of HCA during pregnancy on the life of these young women. Furthermore we hope to propose a decision-making model for the management of HCA during pregnancy.

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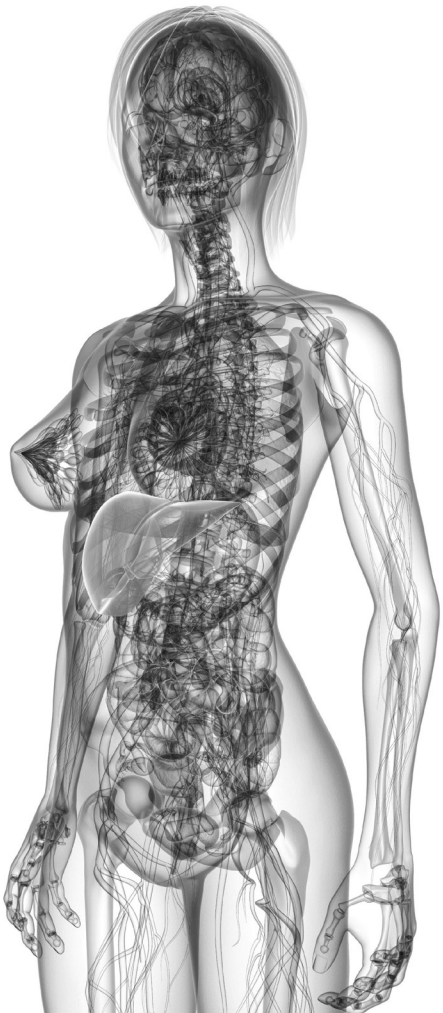
Chapter 5.1

Safety and efficacy of radiofrequency ablation for hepatocellular adenoma



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ABSTRACT

Purpose: To investigate the safety and efficacy of radiofrequency (RF) ablation for the treatment of hepatocellular adenoma (HCA).

Materials and Methods: From 2000 to 2009, 170 patients with HCA were referred to a single tertiary hepatobiliary center. Medical records of 18 patients treated with RF ablation were retrospectively analyzed.

Results: All patients were female, and the majority had a history of hormonal contraceptive use. Ten patients (56%) had multiple HCAs, with a median number of two lesions (range, one to 12) per patient. Median size of HCA at the time of RF ablation was 3.0 cm (range, 0.8 -7.3 cm). A total of 45 HCAs were ablated in 32 sessions (open, n = 4; percutaneous, n = 28). RF ablation was complete after the first session in 26 HCAs (57.8%), and the majority of patients underwent multiple RF ablation sessions to fully ablate all HCAs. Major complications developed in two patients.

Conclusions: RF ablation can be used effectively in the treatment of HCA. However, multiple sessions are often required, and signs of residual adenoma might persist in some patients despite repetitive treatment. RF ablation might be especially beneficial in cases not amenable to surgery or in patients who would require major hepatic resection otherwise.

INTRODUCTION

Hepatocellular adenoma (HCA) is an uncommon benign tumor of the liver that is most often diagnosed in young women in the second or third decade of life (1). Although the development of HCA has traditionally been associated with long-term use of hormonal oral contraceptive agents, an association with pregnancy has also been reported (2) in which existing or newfound HCA tumors tend to grow under the influence of increased serum estrogen levels. Although benign itself, HCA has a potential for malignant degeneration or spontaneous rupture, with potentially life-threatening hemorrhage. Therefore treatment is indicated in selected patients (3,4). Historically, surgical resection has been the treatment of choice for the management of HCA, but in some cases, these young and otherwise healthy patients would require large hepatic resections for centrally located or bilaterally distributed HCA, with associated morbidity and costs (5–7). Several authors have, therefore, described the successful application of minimally invasive strategies such as transarterial embolization and radiofrequency (RF) ablation, although we are aware of no published series larger than 10 patients (8–13). Here we describe our experience with RF ablation for the treatment of HCA in 18 patients. Institutional review board approval is not required at our institution for retrospective studies such as this one.

MATERIALS AND METHODS

Between 2000 and 2009, a total of 170 consecutive patients with the diagnosis of HCA were referred to Erasmus Medical Center in Rotterdam, The Netherlands. Sixty-two patients (36%) underwent invasive treatment, and in 18 patients (11%), this treatment involved open or percutaneous RF ablation of one or more HCAs. In addition, in 39 patients (23%), surgical resection of one or more HCAs was the treatment of choice. Another five patients (3%) underwent transarterial embolization of their HCA. The medical records of 18 patients treated with RF ablation were retrospectively analyzed.

Patient characteristics

The median age of the 18 patients who underwent RF ablation for one or more HCAs was 29.5 years (range, 21-37 y), and all patients were female. The median body mass index was 26 kg/m^2 (range, 18-44 kg/m^2), and all but one patient had a history of hormonal oral contraceptive agent use. None of the patients had a history of viral hepatitis or liver cirrhosis. In the majority of patients, HCAs were asymptomatic and were detected incidentally on imaging studies obtained for other purposes. Two patients presented with acute bleeding from a previously unknown HCA (patients 6 and 10), one of whom required transarterial embolization to control bleeding 2 years before the final RF abla-

tion treatment. RF ablation treatment of the residual HCA tissue was initiated in these two patients because both had an active desire to become pregnant. Treatment of HCA was believed to be indicated because of an active pregnancy wish in 13 patients with proven hormone-sensitive HCA (72%), growth of HCA lesions in two patients (12%; one during pregnancy), HCA exceeding 5 cm in size in one patient (6%), and a lifelong dependence on hormone-substitution therapy in two patients (12%).

Diagnosis and workup

Initial treatment was usually conservative, consisting of discontinuation of oral contraceptive agents for at least 6 months and radiologic follow-up with computed tomography (CT) or magnetic resonance (MR) imaging every 3-6 months to monitor growth or regression of HCA. Patients were offered invasive treatment when (i) lesions remained larger than 5 cm or did not stop growing after cessation of oral contraceptive treatment, (ii) malignancy could not be excluded, or (iii) the patient expressed a desire for pregnancy in the presence of a hormone-sensitive HCA tumor larger than 3 cm. RF ablation was the treatment of choice for cases not amenable to surgery in view of the location or number of HCAs or if resection was considered potentially harmful as a result of insufficient volume of the future liver remnant (< 25% of total liver volume). If uncertainty existed regarding the diagnosis based on radiologic examinations, surgical resection was the treatment of choice and RF ablation was not considered. Diagnostic imaging included a triphasic CT scan in all patients and dynamic four-phase contrast-enhanced MR scan in 17 patients. Histologic specimens for biopsy were not obtained in any patient included in the study.

Procedures

RF ablation was performed by using a 480-kHz RF Cool-tip RF system (Radionics, Burlington, Massachusetts) with a single 3-cm needle (if HCA was < 3 cm) or three clustered 3-cm needles (for larger lesions) or a 250-W RITA RF generator with a Starburst RF ablator (AngioDynamics, Queensbury, New York). The procedures were carried out under general anesthesia by an experienced interventional radiologist (all > 50 cases). For the open approach, a right subcostal incision was made to gain access to the abdominal cavity, and the liver was mobilized for optimal exposure. In each case, RF electrodes were introduced into the lesion under contrast-enhanced CT or ultrasound (US) guidance. Lesions were ablated for 5-15 minutes after target temperatures were reached (100°C) until the ablation zone was believed to encompass the entire tumor based on US and CT images. Ablation of approximately 0.5 cm of healthy liver tissue surrounding the lesion was attempted in all cases. In the majority of cases, efficacy of treatment and the presence of complications (eg, pneumothorax) was estimated based on contrast-enhanced CT images obtained directly after ablation. Because of a lack of availability of intraoperative CT scanning, open ablations were performed under US guidance.

Assessment of response and follow-up

All patients underwent triphasic contrast-enhanced CT scanning at 4-6 weeks after the RF ablation procedures to asses any residual disease (Figure 1). When no signs of residual disease were found, follow-up scans were obtained every 3-6 months for the first year after RF ablation treatment.

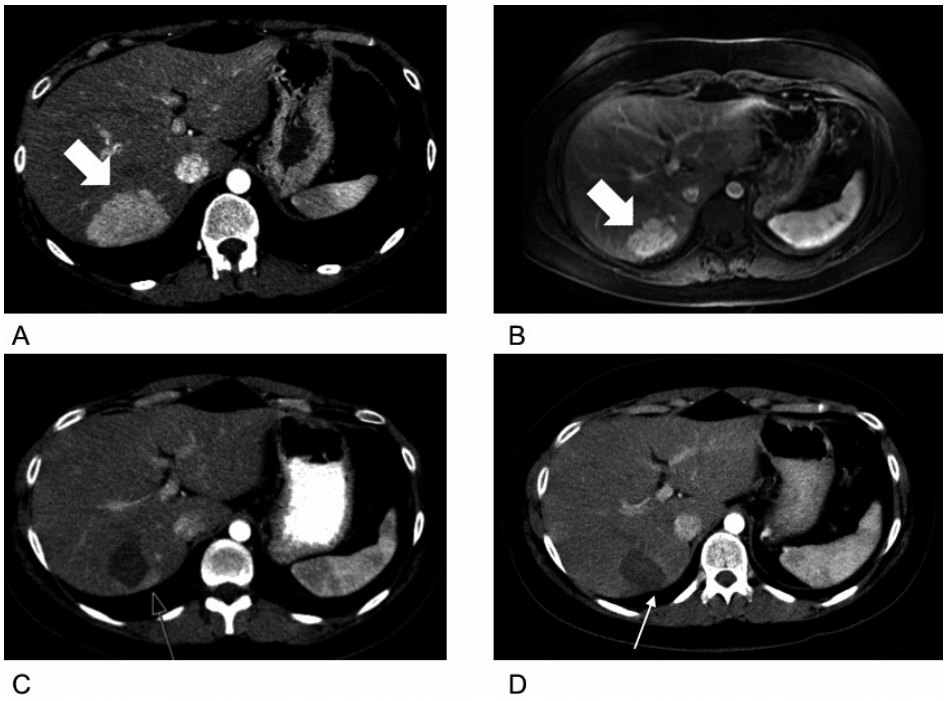

Figure 1. (a) Arterial-phase CT image of a large HCA (arrow) in the posterior segment of the liver in a 22-year-old woman. **(b)** Contrast-enhanced MR image of the same HCA (arrow) 8 months after cessation of oral contraceptive treatment. **(c)** Arterial-phase CT image of HCA after incomplete percutaneous RF ablation. Hyperattenuating residual HCA tissue (arrow) is observed at the posterior border of the hypoattenuating RF ablation zone. **(d)** Arterial-phase CT image of HCA after successful repeat percutaneous ablation. No residual HCA tissue is observed (arrow).

Statistical analysis

Data are expressed as medians and ranges or means ± SD for continuous variables and as proportions (in percent) for binary variables. Differences between groups were investigated by using the Student *t* test for continuous variables and the χ^2 test for binary variables. All statistical analysis were performed by using SPSS software (version 16.0; SPSS, Chicago, Illinois).

RESULTS

A total of 76 HCAs were diagnosed in the 18 patients included in the study, ranging in size from 1.0 cm to 14 cm at the time of diagnosis. The median number of HCAs per patient was two (range, one to 12). Multiple HCAs (two to nine nodules) were found in seven patients, and liver adenomatosis (ie, ≥ 10 nodules) was present in three cases. After various durations of conservative management, including cessation of oral contraceptive treatment and serial imaging, the median diameter of the largest HCA at the time of treatment was 3.8 cm (range, 1.5-7.3 cm; mean ± SD, 3.9 cm ±1.2).

Treatment

The Table shows the clinical and treatment-related characteristics of the 18 patients with HCAs treated with RF ablation. In these 18 patients, a total of 45 HCA lesions were ablated in 32 RF ablation sessions. The median number of HCAs ablated per patient was one (range, one to nine; mean ± SD, 2.8 ± 3.2), with a median size of 3 cm (range, 0.8 -7.3 cm; mean ± SD, 2.9 cm ± 1.2). The median number of RF ablation sessions per patient was two (range, one to four). Although the majority of patients were treated with only percutaneous RF ablation, an open approach was applied in three patients that combined RF ablation with resection of one or more HCAs (n = 5). One of these patients underwent additional percutaneous treatment of two HCAs after incomplete ablation of these lesions. In addition, in one patient with liver adenomatosis (ie, ≥ 10 nodules) located in both lobes of the liver, a staged procedure was attempted, with complete resection and ablation of all left-sided lesions during a first stage that also included right portal vein embolization to obtain adequate volume of the left lobe to allow for a later right hepatectomy. However, during the second stage of the operation, it was believed that the quality of the left lobe was insufficient to withstand a right hepatectomy and it was decided instead to ablate all HCAs in the right liver lobe 2 months after right portal vein embolization. In addition, in another patient with two HCAs, one lesion was treated with percutaneous RF ablation and another HCA was treated with percutaneous ethanol injection, as this lesion was not considered to be eligible for RF ablation because of its proximity to the gallbladder in segment 5. Finally, a total of 25 small HCAs were left untreated in six patients with multiple adenomas (all < 1.5 cm in diameter).

Outcome

Eight patients (44%) required one session of RF ablation each, seven (39%) required two sessions each, and two (11%) required more than two RF ablation sessions to obtain a satisfactory treatment of all HCAs (with no need for further treatment). In one patient (6%) with extensive adenomatosis (ie, ≥ 10 HCAs), four dominant lesions were successfully treated in two percutaneous RF ablation sessions, but one lesion (4.5 cm) in the left

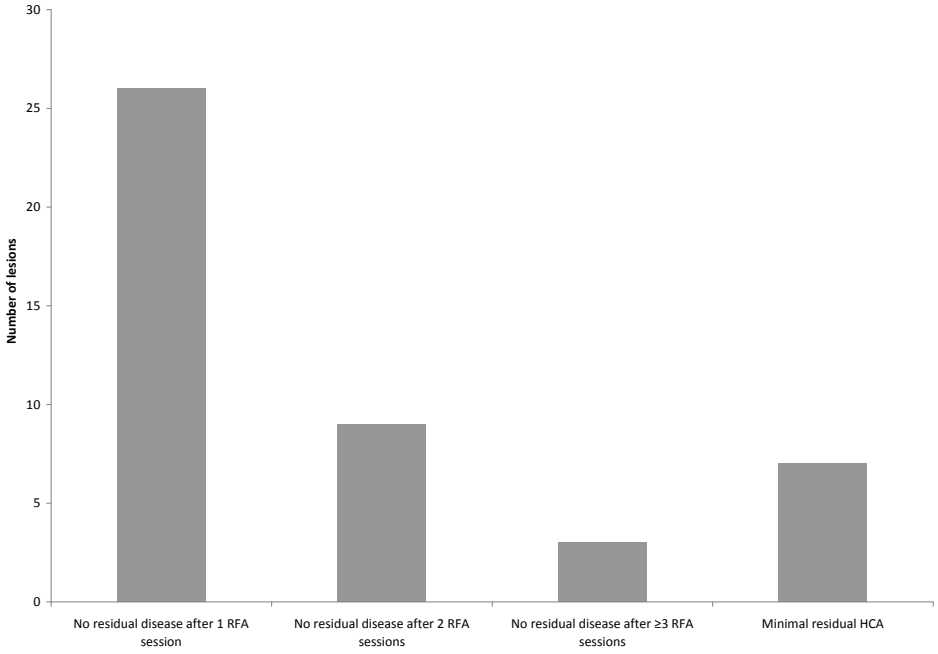

Figure 2. The rate of success after ablation of HCA per lesion. The y-axis shows the number of lesions that were ablated in one, two, three, or more sessions, respectively, as indicated on the x-axis.

lateral segment was situated superior to the stomach and could not be reached percutaneously during either session. Despite a clinically satisfactory result, minimal residual disease (< 1 cm) was observed around one ablated HCA after one or more subsequent sessions of RF ablation in five patients. However, no further treatment was offered in these cases, and it was decided to follow these patients radiologically. Three of these patients also had several small HCA lesions (< 1 cm) in the remainder of the liver that we chose not to treat.

When analyzed per lesion, 26 of 45 HCAs (58%) were successfully ablated at the first attempt, and nine HCAs (20%) were successfully ablated in a second session. Three HCAs required three (n = 2) or four (n = 1) RF ablation sessions to achieve complete ablation (Figure 2). Seven HCAs (in five patients) still show evidence of minimal residual HCA tissue adjacent to the ablation zone at the time of the present manuscript submission. No difference was observed in the mean size of HCAs with residual disease after one RF ablation session (2.9 cm) versus that of HCAs that showed a complete radiologic response after one session (3.1 cm; $P = .73$, Student t test). However, open RF ablation of HCA was successful on the first attempt significantly more often (15 of 19 HCAs; 79%) compared with percutaneous ablation (11 of 26 HCAs; 31%; $P = .013$). The median follow-up of all lesions was 440 days (range, 41-1,351 d).

Table 1. Clinical characteristics and treatment outcomes of the 18 patients with HCAs treated with RF ablation

Pt. no	Age (y)	BMI	Tumors		Largest (mm)	Segment	Course *	Indication	Treatment (no.)	Complications	Outcome
			Diagnosed	Ablated							
1	32	26	1	1	38	4	Unknown	Pregnancy wish	Percutaneous RF (1)	-	No evidence of disease
2	36	22	12	9	73	3, 5-8	Regression of lesions	Pregnancy wish	Open RF/resection (1); percutaneous RF	Hematoma in abdominal wall, no intervention	No evidence of disease
3	34	18	1	1	30	5	NA	Hormone dependency	Percutaneous RF (2)	-	Minimal residual HCA
4	31	23	1	1	44	4	Unknown	Pregnancy wish	Percutaneous RF (3)	-	No evidence of disease
5	32	27	10	9	61	1-4, 7, 8	Unknown	Size > 5 cm	Open RF/resection (1); percutaneous RF (3)	Bleeding (right hepatic artery), no intervention	Minimal residual HCA
6	23	24	1	1	38	5	Unknown	Pregnancy wish	Percutaneous RF (2)	-	Minimal residual HCA
7	23	29	1	1	42	7	Regression of lesion	Pregnancy wish	Percutaneous RF (2)	-	No evidence of disease
8	21	20	1	1	32	2	NA	Hormone Dependency	Percutaneous RF (2)	-	No evidence of disease
9	26	20	6	2	35	5, 6	Regression of lesions	Pregnancy wish	Percutaneous RF (2)	Bleeding (liver parenchyma), no intervention	No evidence of disease
10	22	23	1	1	15	6	Regression of lesion	Pregnancy wish	Percutaneous RF	-	No evidence of disease
11	30	32	2	2	40	2, 6	Regression of lesions	Pregnancy wish	Percutaneous RF (1)	-	No evidence of disease

Pt. no	Age (y)	BMI	Tumors		Largest (mm)	Segment	Course *	Indication	Treatment (no.)	Complications	Outcome
			Diagnosed	Ablated							
12	37	29	7	2	35	2, 4	Unknown	Pregnancy wish	Percutaneous RF (2)	-	Minimal residual HCA
13	27	41	1	1	36	4	Unknown	Pregnancy wish	Percutaneous RF	-	No evidence of disease
14	32	44	9	5	45	3-8	Regression of lesions	Pregnancy wish	Percutaneous RF (3)	-	One untreated HCA
15	33	26	4	3	36	5-8	Regression of lesions	Pregnancy wish	Percutaneous RF (1)	-	No evidence of disease
16	28	35	2	1	28	7	Growth of lesions	Pregnancy wish	Percutaneous RF (1)	Liver abcess, percutaneous drainage	No follow-up available
17	25	33	6	3	37	2, 3, 5	Unknown	Growth	Open RF/resection (1)	-	Minimal residual HCA
18	29	24	10	1	43	6	No OC use	Growth during pregnancy	Percutaneous RF (1)	CVA, no intervention	Minimal residual HCA

Note - BMI = body mass index; CVA = cerebrovascular accident; HCA = hepatocellular adenoma; OC = oral contraceptives; RF = radiofrequency.
Course of HCA after discontinuation of oral contraception.

COMPLICATIONS

There were two major procedure-related complications (Society of Interventional Radiology [SIR] class D [14]). One patient who underwent open RF ablation of two lesions and a right posterior segmentectomy for a third HCA developed cerebral ischemia with concomitant temporary paresis of the left arm caused by severe intraoperative bleeding. However, complete neurologic recovery was observed 3 months after surgery. Further cardiologic workup revealed a persistent foramen ovale, which likely contributed to the development of this serious complication. Another patient who underwent concomitant percutaneous ethanol injection of one HCA developed a hepatic abscess at the site of ethanol injection that required prolonged percutaneous drainage. Minor complications (SIR class A and B) included minor bleeding in three patients that required no further intervention (14).

DISCUSSION

The diagnosis of HCA in young women often raises dilemmas for the treating physician. A conservative approach consisting of discontinuation of oral contraceptive treatment, radiologic follow-up, and negative advice regarding pregnancy would be preferable for many patients. However, the risk of life-threatening hemorrhage or malignant degeneration as well as the need for lifelong radiologic follow-up or a desire to have children has often led to a preference for active treatment. In patients with centrally located HCA or multiple HCA tumors in both lobes of the liver, complete resection of all lesions would necessitate a large liver resection, which would rather be avoided in this young and otherwise healthy population. In addition, hepatic adenomatosis is frequently associated with moderate to severe steatosis, precluding major hepatic resection (15).

Previously, we reported on the cost effectiveness of various treatment strategies for HCA, showing that RF ablation was the least expensive treatment with the most gained quality-adjusted life years (16); however, no data were provided on the efficacy of RF ablation for HCA. Limited data from other centers (9–13) shows that, with the availability of minimally invasive techniques such as RF ablation, HCA can be treated with low morbidity and high satisfaction. However, these data were largely anecdotal. One larger series of 10 patients described the successful application of RF ablation for the management of one or two HCA tumors. All patients tolerated the procedure well and no cases of local failure were reported (13). The present data suggest that RF ablation of HCA can lead to complete the destruction of all viable HCA tissue with no signs of residual or recurrent HCA on follow-up imaging in some patients, thereby "saving" these patients from hepatic resection. Nonetheless, residual HCA tissue adjacent to the zone

of ablation was often observed on follow-up imaging, resulting in repeat RF ablation sessions in many patients. In selected patients, we chose not to treat this residual HCA tissue, especially when other small (< 1 cm) HCAs were also present. We hypothesize that a small amount of remaining HCA tissue will behave similarly to a small HCA tumor. Even though some growth might occur, the chance the HCA will reach dimensions that pose a risk for rupture remains unlikely (17). The fact that no residual lesions in the present study have shown growth or other changes visible on CT or MR imaging during follow-up supports this strategy. Clearly, the rate of local technical failure is relatively high in the present series, with many HCAs requiring multiple sessions of RF ablation treatment. This is somewhat surprising given the efficacy of RF ablation reported in the treatment of hepatocellular carcinoma, which is similar to HCA in many ways (18). However, the absence of liver cirrhosis and a capsule around the tumor might limit the efficacy of RF ablation when applied to HCA compared with HCC. Also, more than half of the treated HCAs in the present study were larger than 3 cm, which could have contributed to the failure of this technique. In addition, several other factors might have contributed to the failure of RF ablation in these patients, including difficulties with three-dimensional probe positioning and decreased target visualization as a result of steatosis and patients' central adiposity. The fact that open ablation resulted in a higher rate of complete ablations in the first attempt supports this, as targeting is often easier in an open setting. Also, the inability to accurately monitor the effect of thermal ablation in these lesions might have partly contributed to the high local failure rate (19). In all patients with residual HCA tissue on follow-up images, there was discordance between the immediate postprocedural CT scan (showing complete ablation) and the 4–6-week follow-up scan (showing residual HCA tissue). Also, in several cases, US showed hardly any tissue-specific changes resulting from ablation, making it particularly difficult to assess the success of this treatment in real time. Supposedly, these limitations can be addressed in the future with the availability of new ablation methods such as microwave ablation, more sophisticated image guidance platforms, and novel techniques to monitor thermal ablation such as MR thermography or US elasticity imaging (20,21). In the cohort of patients presented here, the diagnosis of HCA was made exclusively based on radiologic studies, including contrast-enhanced MR imaging and multiphasic CT imaging. On both modalities, HCAs typically show early homogeneous arterial enhancement without signs of washout or capsular enhancement and are usually well differentiated from hepatocellular carcinoma or focal nodular hyperplasia lesions (22). Tissue biopsy was not performed routinely given the high specificity of cross-sectional imaging and the associated risk of tumor seeding and sampling error. Rather, resection was the treatment of choice for lesions that raised concern for malignancy. Which patients should undergo surgical treatment for HCA and which patients should not remains a topic largely open for debate. Some data show that the risk of bleeding and

malignant degeneration is particularly increased in large or growing HCA tumors. A recent large retrospective multicenter study (4) in 124 patients showed that malignant degeneration and bleeding occurred only in patients with very large HCAs (> 8 cm and > 7 cm, respectively), and most would agree that HCAs of this size range require surgical intervention in most cases (4). Moreover, a recent systematic review (23) incorporating all known reports on malignant degeneration in HCA showed an overall risk of 4.2% of malignant degeneration in HCA, of which only 4% occurred in lesions smaller than 5 cm. However, a selection bias should be acknowledged based on the fact that these reports include only patients who underwent surgical intervention and do not include those patients who underwent conservative management. Taking these data into consideration, it might be controversial to treat lesions smaller than the threshold of 5 cm. However, in our opinion, young women with one or more HCAs smaller than 5 cm and an active pregnancy wish constitute a special patient group. When these HCAs have been shown to be hormone-sensitive (eg, shrank after cessation of oral contraceptive treatment), one might anticipate them to grow during pregnancy. Given the increased risk of bleeding and its associated morbidity and mortality in growing adenomas, as well as the possibility of these lesions reaching a size too large to treat with local ablative therapies and therefore requiring liver resection, we have often considered early treatment of these relatively small lesions (17).

The present study might offer some guidance to the clinician to define the position of RF ablation in the treatment of HCA. Satisfactory results were obtained in most patients, and the postprocedural course was mild in the majority of patients. We suggest that RF ablation could be applied selectively for the treatment of HCA, especially in patients who would require large liver resections otherwise or in whom resection is not possible in view of bilateral spread of HCA. However, even percutaneous RF ablation can be associated with severe complications (although both patients with major complications in the present study underwent other concomitant procedures), and many patients required multiple sessions of RF ablation, increasing the costs and use of resources significantly for these patients. Therefore, future research should focus on the comparison of different treatment modalities for the treatment of HCA, including laparoscopic liver resection, alternative ablative therapies, and transarterial embolization.

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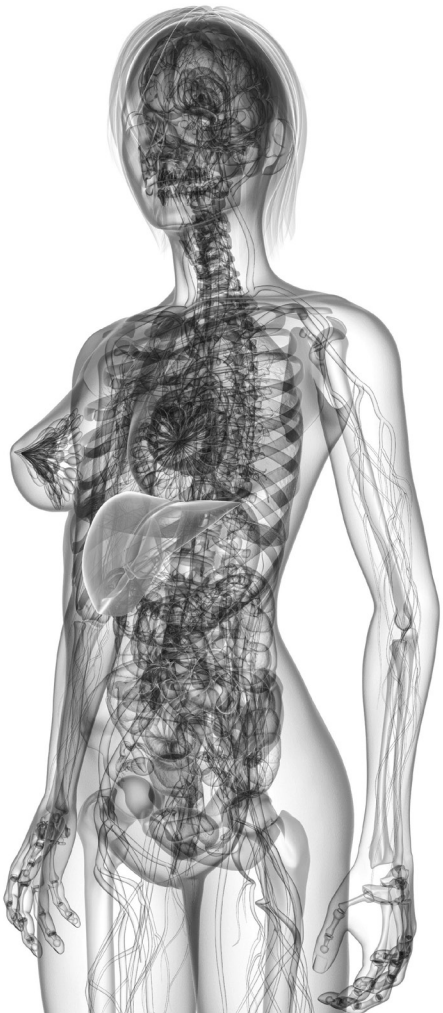
Chapter 5.2

Management of liver adenoma by radiofrequency ablation



Digestive Surgery, 2011; 28(3):173-7

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ABSTRACT

Traditionally, surgical resection has been the treatment of choice in many patients with hepatocellular adenoma because of the risk of rupture, hemorrhage and malignant transformation. However, some patients are not amenable for surgery due to the extensive involvement of the liver, as in patients with liver adenomatosis. We report 2 cases with liver adenomatosis in which we combined surgery with open and percutaneous radiofrequency ablation for lesions located in both lobes of the liver. Minimal invasive treatment including radiofrequency ablation may offer new perspectives in the treatment of patients with liver adenomatosis.

INTRODUCTION

Hepatocellular adenoma (HCA) is a rare benign tumor of the liver, occurring mostly in young women in their reproductive years and is associated with long-term exposure to estrogens, mostly oral contraceptives (OC). In the last decennium, the introduction and widespread use of highly advanced image modalities has increased the number of incidental HCA findings [1,2]. HCA can be complicated by life-threatening complications such as malignant transformation, rupture and hemorrhage [3,4]. There is an ongoing debate on the management of hepatic adenomas, regarding surveillance, surgical resection and other less invasive treatments, such as radiofrequency ablation (RFA) and transarterial embolization. In most cases the discussion is focused on the management of solitary adenomas. The management might even become more complex when patients present with multiple adenomas as is the case of liver adenomatosis (LA). Here, we report the treatment of 2 female patients with bilobar liver adenomatosis in whom we combined surgical resection with RFA.

CASE 1

A 35-year-old woman presented at a neurological outpatient clinic because of restless legs. Abnormal liver enzymes were discovered by routine laboratory work-up. The patient had no abdominal complaints and had used OC for 20 years. Her γ-glutamyltransferase level was 183 U/l (normal 0-34 U/l) and her alkaline phosphatase level was 286 U/l (normal: 0-119 U/l). Laboratory values of aspartate aminotransferase, alanine aminotransferase, total bilirubin and coagulation tests were within the normal range. Additional analysis by abdominal ultrasound showed a large hyperechoic lesion with a diameter of approximately 10 cm situated in the right lobe and multiple smaller hyperechoic lesions in both lobes of the liver. A magnetic resonance (MR) imaging scan of the abdomen revealed multiple lesions in both lobes of the liver and a well-defined lesion in segment VIII of the liver measuring 12.0 cm x 7.8 cm in size. On T1-weighted MR imaging, all tumors were isointense compared to the surrounding liver. T2-weighted imaging showed hyperintense lesions compared to the surrounding liver and diffuse homogeneous signal intensity after contrast administration. In the delayed phase, the lesions remained slightly hyperintense to the surrounding liver. The MR imaging findings were consistent with LA. A needle biopsy of the largest lesion, which was performed elsewhere, was revised in our clinic and confirmed the diagnosis. First, cessation of OC was advised and regression of most lesions was seen after 6 months (Table 1; Figure 1). However, no further regression was seen 8 months later. Because of the size of the adenomas, our multidisciplinary team decided to remove the adenomas in several steps. Three small

Table 1. Size of HCA lesions 6 months after discontinuation of OC

HCA segment	HCA size during OC use, cm	HCA size 5 months after discontinuation of OC, cm
VIII	12.0 x 8.7	6.7 x 7.7
VII	6.1 x 5.5	5.7 x 4.5
II	3.4 x 3.0	2.8 x 2.0
III	3.0	2.3
III	3.2	2.4
V/VI	5.2 x 3.8	3.8 x 3.0
V	3.4 x 2.2	3.1 x 1.8
VI	5.9 x 4.0	4.7 x 3.1
IVa/IVb/VI/VII/VIII	some small lesions < 2.6	no difference

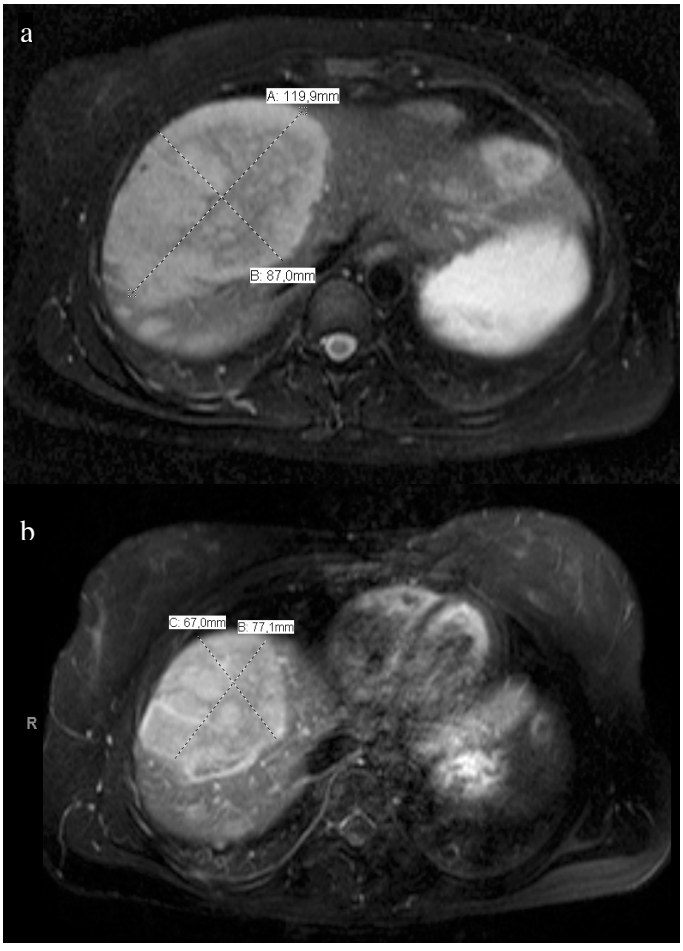

Figure 1. MR image of the biggest HCA in segment VIII of the liver at presentation **(a)** and after 6 months of OC cessation **(b)**.

superficial adenomas in the left lobe were resected and 5 adenomas in segment II, III and IVa of the liver were treated with open RFA during the same session. RFA was performed using a 480-kHz radiofrequency (RF) generator with a Cool-Tip RF System and Switching Controller (Valleylab, Covedien, Burlington, Mass., USA). The RFA procedure was carried out under general anesthesia by an experienced interventional radiologist. For the open approach, the patient was positioned in a supine position. The liver was mobilized for optimal exposure. After lesion identification, a RF electrode was placed in the lesion of interest under ultrasound guidance. Lesions were ablated for 5-15 min or until target temperatures were achieved in 1 or more sessions. Ablation of approximately 0.5 cm of healthy liver tissue surrounding the lesion was attempted. Histological examination of the resected lesions showed inflammatory adenomas, expressing serum amyloid A and C-reactive protein. Recent studies have shown that tumors with homogeneous glutamine synthetase staining and β-catenin positivity have a higher risk of malignant transformation of HCA into hepatocellular carcinoma [5,6] . However, in these lesions glutamine synthetase and β-catenin stainings were negative. In preparation of a right-sided extended hemihepatectomy, right portal embolization was performed 16 weeks later to induce an atrophy of the embolized lobe to be resected, with a compensatory hypertrophy of the counter lobe to be preserved. However, resection was considered potentially harmful for the patient as there was a lack of hypertrophy of the left lobe which would lead to not having enough residual liver volume after surgery. It was decided to perform open RFA of the 9 remaining lesions, including the largest one in segment VIII of the liver which measured 73.0 mm x 63.0 mm in size 10 weeks before right portal embolization. Follow-up multiphasic computed tomographic (CT) scans performed 2, 8 and 16 months later showed adequate ablation of all lesions (Figure 2). After follow-up of 34 months, there was no evidence of recurrent liver lesions.

CASE 2

A 32-year-old woman was referred to our hospital for evaluation of multiple liver lesions. Her complaints consisted of abdominal discomfort, feeling of cramps, bloated abdomen and irregular bowel movement. Physical examination revealed normal signs, except obesity with a BMI of 27.5. Laboratory values of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin and coagulation tests were within the normal range. Her γ-glutamyltransferase level was 75 U/l (normal 0-34 U/l). Work-up by her general practitioner involved an abdominal ultrasound, which showed multiple liver lesions. She had used OC up to half a year ago for a long period and after which she switched to an intrauterine device, NuvaRing, which locally releases a continuous low-dose of estrogen and progestin. She had a wish for pregnancy in the near future.

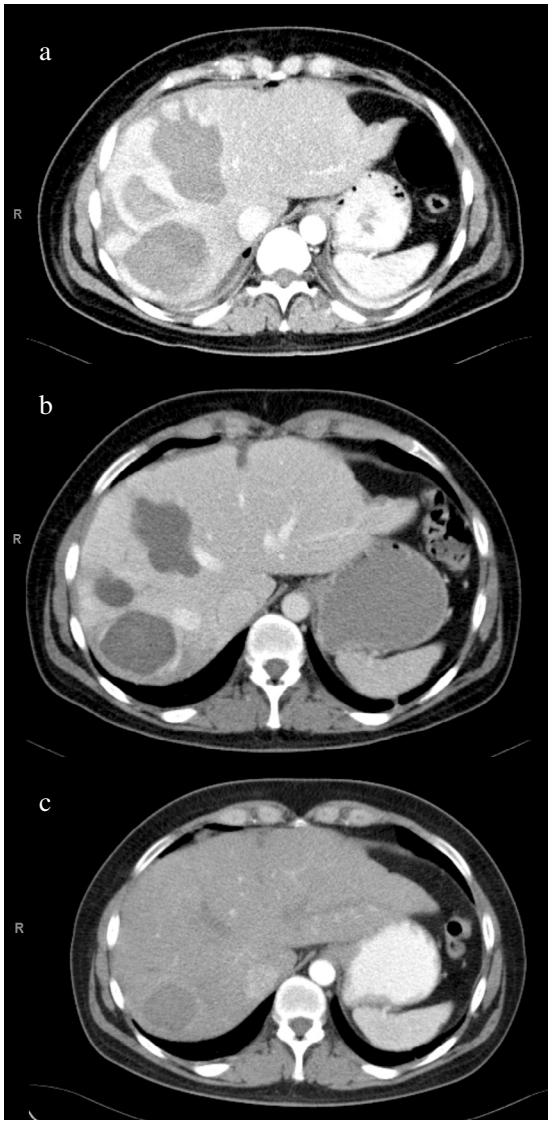

Figure 2. CT image 3 days **(a)**, 2 months **(b)** and 16 months **(c)** after RFA. There is no enhancing tissue observed around the zone of thermal ablation, indicating adequate treatment effect.

She denied a history of alcohol or intravenous drug abuse. The patient underwent a multiphasic CT scan that revealed a 5.9 cm x 6.2 cm lesion in segment V, 2 lesions of 3.0 cm and at least 10 multiple smaller lesions in each the right and left lobes of the liver, all compatible with the diagnosis of HCA. Radiological follow-up with a CT scan 3 months later did not show any regression of the lesions despite withdrawal of OC. The patient was discussed in our weekly multidisciplinary meeting and because of the size of the largest adenoma and a wish for pregnancy, surgery on the largest adenoma and an

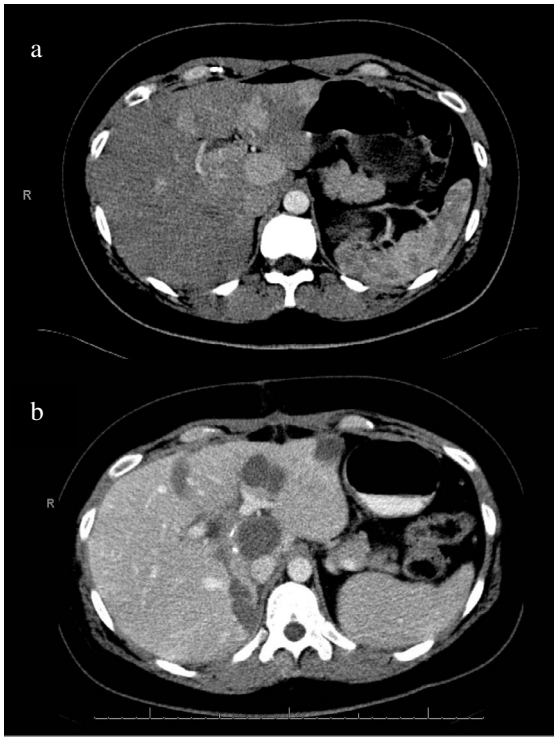

Figure 3. CT image of multiple HCA lesions 6 months before **(a)** and 2 weeks after **(b)** first RFA.

open RFA of the smaller lesions was advised (Figure 3). Histological examination [including glutamine synthetase as a useful immunohistochemical marker in the diagnosis of focal nodular hyperplasie (FNH)] of the resected lesion showed FNH [7]. Because of this unexpected finding of a FNH, a radiological re-evaluation of the residual lesions was performed and the residual lesions were still regarded to be adenomas. A CT scan was performed 3 months postoperatively, and showed 7 adenomas successfully ablated at the first attempt, 1 hypervascular zone adjacent to one of the ablation fields being suspicious for vital HCA tissue, incorrect placement of the RFA needle in 1 adenoma, and 2 vital adenomas not treated with RFA and not visible at first CT scan. Because this patient had a clear pregnancy wish, percutaneous RFA of the 4 remaining lesions was advised and again performed. The MR scan which was performed 6 weeks post-RFA showed 2 adenomas that were ablated successfully and again 2 zones suspicious for residual HCA tissue. Twelve and 31 weeks after the first percutaneous RFA session, a 3rd and 4th session of percutaneous RFA was performed for the remaining 2 residual HCA tissue zones. Again a CT scan was performed, which showed adequate ablation of all lesions.

DISCUSSION

In 1985, Flejou et al. [8] described a series of LA defined as the presence of ≥ 10 adenomas in an otherwise normal liver parenchyma. The diagnosis of HCA has a great impact on the lives of young women, especially if they have a wish for pregnancy. HCA in pregnant women requires special considerations because of the risk of hormone-induced growth and rupture due to the increased levels of steroid hormones during pregnancy that may threaten the life of both mother and child [9]. Historically, surgical resection of HCAs has been the treatment of choice if the tumor diameter exceeds 5 cm after 6 months of follow-up after cessation of OCs, because of the risk of hemorrhage or malignant degeneration [2,10–12]. Although tumor size is one of the main factors in deciding whether to manage HCA by observation or to perform a surgical resection, we advise a conservative policy if the tumor still shows adequate regression after 6 months of cessation of OC. We consider surgery in lesions ≥ 5 cm in size that show no more decrease in size after 6 months of cessation of OC. However, some patients are not amenable for surgery due to centrally located tumors or due to the extensive involvement of the liver in LA. In such cases, an alternative minimal invasive treatment like RFA may be the treatment of choice. RFA can be performed percutaneously or in an open setting [13]. Moreover, RFA procedures can be electively performed and carefully planned.

RFA destroys tissue by application of interstitial hyperthermia resulting in coagulative necrosis, and is a safe and successful treatment for adenomas, especially those with a diameter of < 4 cm. However, limited data are available on this topic [13–17]. The largest series was described by Rhim et al. [15], who performed percutaneous RFA in 10 patients with 12 pathologically proven HCAs. Adequate ablation was found in all adenomas and all patients tolerated the procedure well. Fujita et al. [13] reported a combined hepatic resection and open RFA for 3 patients with multiple HCAs, with a maximum of 3 ablated adenomas per case.

We report 2 cases with LA in which we combined surgery with open and percutaneous RFA for lesions in both the right and left liver lobe. Although multiple sessions were required, a follow-up CT scan showed adequate ablation of all the lesions at the end. There is still the question, however, as to which patients should be selected for RFA only and which patients should undergo surgical treatment followed by RFA. In patients with multiple bilateral or right-sided lesions warranting large resections, the choice for RFA seems apparent. Patients with smaller lesions or left-sided lesions, which can be easily resected using a small laparotomy or even using laparoscopic techniques, might pose a larger dilemma. This choice is not as clear given the fact that multiple RFA sessions might be needed for the treatment of 1 lesion, which could be resected in a single surgical session. In these cases the anatomical location of the lesion within the liver parenchyma may influence the preferred treatment.

Although HCA is a benign disease, malignant transformation of HCA to hepatocellular carcinoma has been described in the literature, especially in large lesions. Moreover, a recent systematic review incorporating all reports on malignant degeneration in HCA showed an overall risk of 4.2% of malignant transformation of HCA into hepatocellular carcinoma, of which only 4.4% occurred in lesions smaller than 5 cm [18]. Therefore in patients with multiple HCAs or LA, one should strictly consider a surgical resection of adenomas ≥ 5 cm in diameter or adenomas with radiological signs of malignancy. The surgical procedure may be combined with open RFA for the remaining smaller lesions, and can be considered a safe and effective treatment option because of the low mortality and morbidity rates of this procedure [17]. Furthermore, in small tumors RFA is the preferred treatment because of the short hospital stay, low cost and the best gain in quality-adjusted life years [17]. The low costs are due to low procedural costs, the relatively low complication rate and the absence of a long follow-up period for patients with no residual tumor [17]. Transcatheter arterial embolization followed by RFA could be an alternative and effective treatment strategy for LA to prevent rupture and hemorrhage in large tumors when it is difficult to perform a hepatectomy [19].

In case 2 there was a simultaneous occurrence of LA and FNH in the liver. Discrimination between HCA and FNH can be difficult on radiological imaging and alternation of these diagnoses may be harmful because HCA has an increased risk of hemorrhage, rupture and malignant transformation, while FNH does not. Little literature is available on the simultaneous occurrence of HCA and FNH and the simultaneous occurrence of multiple HCAs or LA and FNH [20]. Laurent et al. [20] described 5 out of 30 cases of multiple benign hepatic nodules in which HCA was found together with FNH. This association could be coincidental or secondary to shared causal mechanisms like angiogenic abnormalities induced by OC, tumor-induced growth factors or thrombosis, and local arteriovenous shunting [20]. Although the association of FNH and HCA could be coincidental, it seems that the presence of FNH is higher than expected in adenomatosis and multiple inflammatory HCAs [20]. In conclusion, minimal invasive treatment like RFA might be helpful in the treatment of patients with LA or multiple HCAs located in both lobes of the liver. Although LA can be regarded as a benign liver disease, proper control of multiple lesions may be indicated in selected patients.

A balanced approach using surgery and RFA is advocated in the management of this complex disease.

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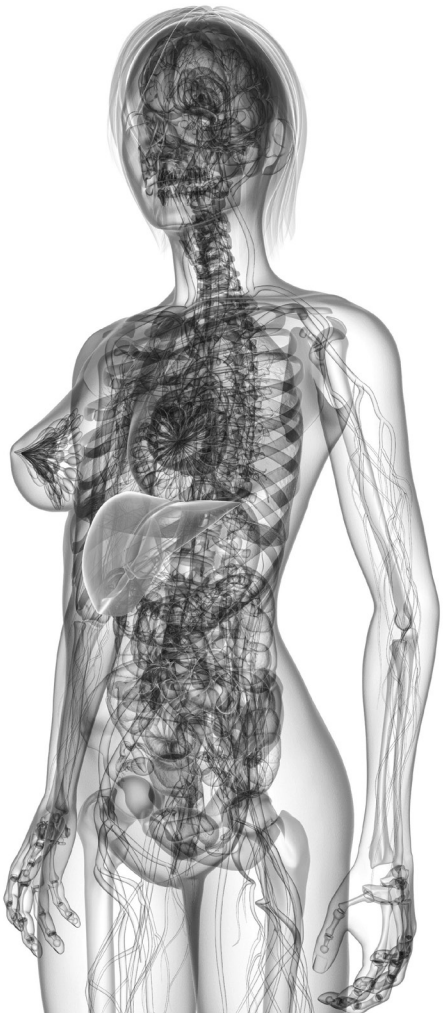
Chapter 6

Hemorrhage and rupture of hepatocellular adenomas: A systematic review



Submitted

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ABSTRACT

Background: Although benign in itself, hepatocellular adenoma (HCA) can be complicated by hormone induced growth and subsequently hemorrhage and rupture. However, the true risk of hemorrhage and rupture is not exactly known. A systematic review of literature was performed to make a risk estimate for hemorrhage and rupture in HCA.
Methods: A systematic literature search of the PubMed and Embase databases was performed for all articles published from 1969 till March 2011, relevant to hemorrhage and/or rupture of HCA.
Results: Twenty-eight articles were selected containing a total of 1 176 patients. Hemorrhage was reported with an overall frequency in 27.2% of cases, and in 15.8% of the total number of HCA lesions. Rupture and intraperitoneal bleeding were reported in 17.5% of cases. Acute symptoms of hemorrhage prior to the diagnosis HCA were present in 86.4% of patients. Six out of 13 articles in which the size of HCA lesions in which hemorrhage occurred was noted, reported hemorrhage in HCA < 5 cm.
Conclusion: Hemorrhage and rupture is a common complication in patients with HCA with an overall frequency of hemorrhage in 27.2% of cases. To identify those patients who require aggressive treatment prospective multicentre studies are warranted to establish the incidence of hemorrhage and rupture for small HCA.

INTRODUCTION

Hepatocellular adenoma (HCA) is a rare benign tumor of the liver that occurs particularly in women during their reproductive years[1]. Although benign in itself, the diagnosis of HCA has a great impact on the lives of these, mostly, young women. Malignant transformation of HCA into hepatocellular carcinoma has been reported in literature. Besides that, the presence of HCA can be complicated by hormone induced growth and subsequently, rupture and bleeding, which is usually the cause of right upper quadrant abdominal pain. HCA in pregnant women requires special considerations because of the risk of hormone-induced growth and rupture due to the increased levels of steroid hormones during pregnancy that may threaten the life of both mother and child[2]. Because of the risk of hemorrhage, rupture and malignant transformation surgical resection is the preferred treatment in patients with HCA > 5 cm[3-6]. A recent systematic review incorporating all reports on malignant degeneration showed an overall risk of 4.2% on malignant transformation of HCA into hepatocellular carcinoma, of which only 4.4% occurred in lesions smaller than 5 cm in diameter[7]. However, the true incidence of hemorrhage and rupture is not exactly known and the reported rate of hemorrhage and rupture in literature varies from 11% to 49%[3,8]. The aim of this systematic review is to make a risk estimate for hemorrhage and rupture in HCA as reported in the literature.

METHODS

Literature search strategy

A systematic literature search of the PubMed and Embase databases was performed for all articles published from 1969 till March 2011, relevant to rupture and/or hemorrhage

Database	Search terms
PubMed	(Adenoma, Liver Cell[Mesh] OR liver cell adenoma*[tiab] OR Liver adenoma*[tiab] OR Hepatocellular adenoma*[tiab] OR Benign Hepatoma*[tiab] OR Hepatic adenoma*[tiab]) AND (Rupture, Spontaneous[mesh] OR Rupture*[tiab] OR Hemorrhage[mesh] OR Hemorrhag*[tiab] OR Haemorrhag*[tiab] OR Bleeding[tiab] OR blood[tiab]) NOT (animals[mesh] NOT humans[mesh]) AND (english[lang] OR dutch[lang])
Embase	((liver OR hepatocellular OR hepatic) NEAR/2 adenoma*):ab,ti,de OR (benign NEAR/2 hepatoma*):ab,ti AND ('rupture'/de OR 'blood vessel rupture'/de OR rupture*:ab,ti OR 'bleeding'/exp OR hemorrhag*:ab,ti OR haemorrhag*:ab,ti OR bleeding:ab,ti OR blood:ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND (English:la OR dutch:la)

Figure 1. Search terms used in PubMed and Embase databases.

of HCA. There was no literature available prior to 1969 in either databases. Search terms used in different databases are shown in Figure 1. All titles and abstracts were screened and relevant articles were selected.

Literature screening

Studies were evaluated for inclusion by two independent researchers (SMA, TT) for relevance to the subject. A random check was performed by a supervisor (JNMIJ). Study selection was accomplished through three levels of study screening (Figure 2). Articles were included if they described a series of patients with HCA seen in a particular time period. Studies which described only patients with liver adenomatosis were excluded. At level 1, duplicate articles found in both databases were excluded. At level 2, titles and abstracts of all articles were screened for relevance. Irrelevant articles, case reports, review articles and abstracts presented at scientific meetings were excluded. At level 3, a full text review was conducted for final inclusion. In case of overlapping series, only the most recent publication was included to avoid double counting of patients with HCA. Irrelevant articles were those articles that did not describe a series of patients in a particular time period, articles that gave only a summary of current knowledge of HCA, articles focusing on focal nodular hyperplasia or articles that did not answer the research question.

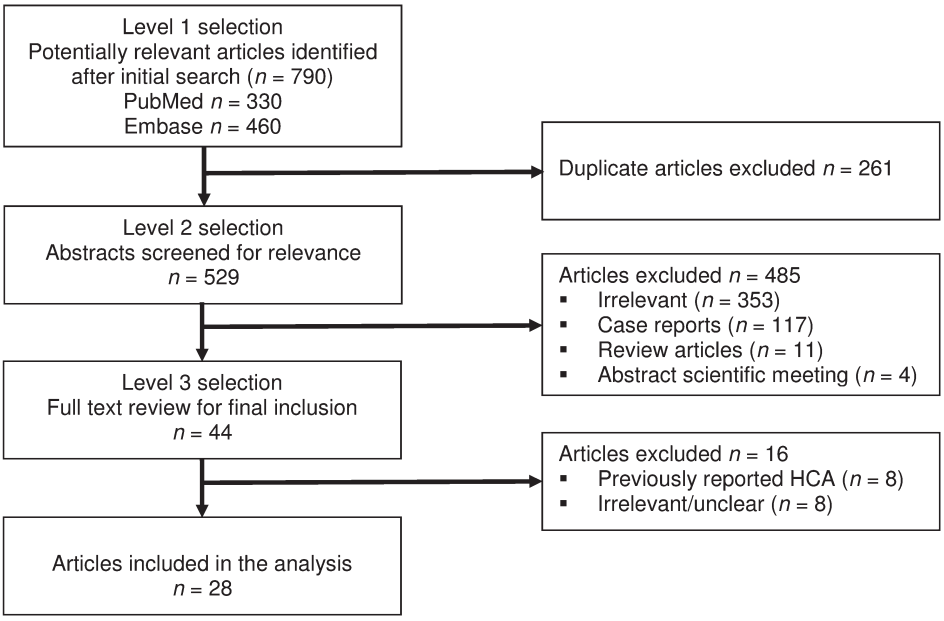

Figure 2. Flow diagram showing selection of articles. HCA: hepatocellular adenoma.

Data extraction

For all articles data regarding the number of cases with HCA, the total number of HCA lesions, the number of cases who underwent surgical resection for HCA, the number of female cases, mean age at presentation, OC use, number of HCA lesions with hemorrhage, number of cases in which hemorrhage and intraperitoneal rupture occurred and the diameter of HCA lesions in case of hemorrhage were assessed. Hemorrhage was defined as macroscopic signs of hemorrhage at pathological examination and/or hemorrhage identified by radiologic imaging.

Statistical analysis

Data were presented in a table and were presented as mean and percentages. Numerator and denominator were noted for number of hemorrhage and rupture.

RESULTS

At level 1 selection, a total of 790 articles were identified by the initial search through PubMed (n = 330) and Embase (n = 460) databases. A total of 261 duplicate articles were excluded. At level 2 selection 485 articles were excluded of which 353 irrelevant articles, 117 case reports, 11 review articles and 4 abstracts presented at scientific meetings. Forty-five articles were selected for full text review (level 3 selection). Because of overlapping data 9 articles were excluded as well as another 8 irrelevant articles which did not answer the research question. In total 28 articles describing a series of patients with HCA seen in a particular time period and reporting the total number of HCA (cases) in which hemorrhage and rupture occurred were included in the analysis[3-6,8-31].

General analysis

27 out of 28 articles included in the study contained a total of 1176 patients with one or more HCA (Table 1). One series described by Mathieu et al. did not indicate the total number of patients. In this study only the total number of HCA diagnosed by magnetic resonance imaging, all of which were histologically proven, were noted. 1073 out of 1176 (91.2%) patients with HCA underwent surgical resection of HCA. In 24 articles (972 patients) the male/female ratio was available, included were 880 women (91.0%) and 92 (9%) men.

Analysis of hemorrhage and rupture

As shown in table 1, information about the total number of HCA lesions with hemorrhage was available in 748 lesions. 118 out of 748 HCA lesions (15.8%) presented with hemorrhage. Information about the total number of cases showing hemorrhage was available in 1160 cases, with hemorrhage noted in 315 cases (27.2%). When studies were excluded

Table 1. Overview of patient series with hepatocellular adenomas with or without hemorrhage and/or rupture reported in literature

Reference	Year	Patients *(n)*	HCA *(n)* [a]	Resected *(n cases)*	Female sex *(n)*	Mean age (range) *(y)*	OC use *(%)* [b]	Hemorrhage *(n HCA)*	Hemorrhage *(n cases)*	Rupture intra-peritoneal *(n cases)*	Diameter (cm) [c]
Edmondson et al. [9]	1976	42	-	41	42	-	85	-	10/42	10/42	> 5
Rooks et al. [8]	1979	85	-	84	85	16-61	92	-	42/85	29/85	-
Vana et al. [10]	1979	96	-	70	-	-	87	-	11/96	-	-
Nime et al. [11]	1979	37	37	37	-	-	100	10/37	10/37	10/37	-
Barrows et al. [12]	1983	71	71	71	-	30,2 (14-55)	85	22/71	22/71	22/71	-
Thompson et al. [13]	1983	5	5	5	5	32 (22-44)	60	2/5	2/5	1/5	-
Gonzalez et al. [14]	1985	12	14	12	10	28,1 (21-57)	90	3/14	3/12	3/12	-
Mathieu et al. [15]	1986	27	27	27	27	34 (24-50)	90	4/27	4/27	-	-
Leese et al. [16]	1988	24	-	21	16	4-45	81	-	11/24	2/24	5
Paulson et al. [17]	1994	14	66	7	11	32 (17-55)	75	10/66	9/14	-	6.4 ± 3,3
Chung et al. [18]	1995	16	31	15	14	34.6 (19-60)	36	10/31	-	-	≥ 5
Ault et al. [19]	1996	12	-	5	10 [d]	37.6 (25-57)	90	-	4/12	-	6
Mathieu et al. [20]	1997	-	14	-	-	-	-	3/14	-	-	-
Ribeiro et al. [21]	1998	27	-	27	25	27-79	88	-	10/27	2/27	-
Closset et al. [22]	2000	16	18	16	16	35 (16-50)	63	-	7/16	3/16	7
Ichikawa et al. [23]	2000	25	44	14	21	-	57	11/44	10/25	2/25	-
Ji et al. [24]	2000	4	4	4	1	37 (31-47)	0	3/4	3/4	-	-
Weimann et al. [25]	2000	77	-	77	64	34.9 (15-78)	92	-	12/77	7/77	-
Reddy et al. [26]	2001	25	-	25	25	33	96	-	3/25	-	4
Hung et al. [27]	2001	12	12	12	6	46.8 (26-69	33	4/12	4/12	1/12	4.2
Terkivatan et al. [5]	2001	33	-	19	29	34 (15-49)	93	-	12/33	-	

Reference	Year	Patients *(n)*	HCA *(n)* [a]	Resected *(n cases)*	Female sex *(n)*	Mean age (range) *(y)*	OC use *(%)* [b]	Hemorrhage *(n HCA)*	Hemorrhage *(n cases)*	Rupture intra-peritoneal *(n cases)*	Diameter (cm) [c]
Toso et al. [28]	2005	25	58	25	23	19-55	-	10/58	10/25	2/25	1.7
van der Windt et al. [6]	2006	48	-	16	48 [e]	19-53	94	-	21/48	-	
Chaib et al. [29]	2007	28	-	28	24	36.6 (22-51)	92	-	3/28	1/28	1 (n=1)
Cho et al. [3]	2008	41	-	41	38	19-65	58	-	12/41	3/41	> 5 (n=11)
Bioulac-Sage et al. [30]	2009	128	220	128	116	-	91	-	23/128	-	< 5
Deneve et al. [31]	2009	124	-	124	116	39	-	-	31/124	16/124	> 5
Dokmak et al. [4]	2009	122	365	122	108	-	88	26/365	26/122	-	< 5 (n=3) ≥ 5 (n=23)
Total		**1176** [f]		**1073** [f]				**118/748 (15.8%)**	**315/1160 (27.2%)**	**114/651 (17.5%)**	

HCA: hepatocellular adenoma; OC: oral contraceptive; -: no data available or no data reported

[a] Number of HCA described in study; [b] OC use (inclusive other hormone replacement therapy), % of patients in which OAC use is known ; [c] Smallest size of HCA in which hemorrhage occurred; [d] 10 female adult patients and 1 female; [e] Exclusion of male patients (n = 3); [f] Missing data from Mathieu et al.

that describe patient series before the introduction of second and third generation OC, which contained much lower hormone levels, a comparable risk of hemorrhage in 192 out of 755 cases (25.4%) was found[3-4,6,9,11-15,18-20,22-23,25-27,29,31-32].

Table 2. Overview of patients presented acutely with symptoms of hemorrhage prior to the diagnosis hepatocellular adenoma(s)

Reference	Year	Patients *(n)*	Resected cases *(n)*	Initial presentation with hemorrhage *(n cases)*
Edmondson et al. [9]	1976	42	41	10/10
Rooks et al. [8]	1979	85	84	3/42
Vana et al. [10]	1979	96	70	11/11
Nime et al. [11]	1979	37	37	-
Barrows et al. [12]	1983	71	71	-
Thompson et al. [13]	1983	5	5	2/2
Gonzalez et al. [14]	1985	12	12	2/3 [a]
Mathieu et al. [15]	1986	27	27	4/4
Leese et al. [16]	1988	24	21	11/11 [b]
Paulson et al. [17]	1994	14	7	-
Chung et al. [18]	1995	16	15	-
Ault et al. [19]	1996	12	5	4/4
Mathieu et al. [20]	1997	-	-	3/3
Ribeiro et al. [21]	1998	27	27	10/10
Closset et al. [22]	2000	16	16	5/7 [c]
Ichikawa et al. [23]	2000	25	14	-
Ji et al. [24]	2000	4	4	-
Weimann et al. [25]	2000	77	77	7/12 [d]
Reddy et al. [26]	2001	25	25	3/3
Hung et al. [27]	2001	12	12	1/4
Terkivatan et al. [5]	2001	33	19	12/12
Toso et al. [28]	2005	25	25	10/10
van der Windt et al. [6]	2006	48	16	13/21
Chaib et al. [29]	2007	28	28	3/3
Cho et al. [3]	2008	41	41	12/12
Bioulac-Sage et al. [30]	2009	128	128	-
Deneve et al. [31]	2009	124	124	-
Dokmak et al. [4]	2009	122	122	-
Total		**1176**	**1073**	**159/184 (86.4%)**

-: no data available or no data reported

[a] one of which had sustained abdominal trauma; [b] one of which had sustained abdominal trauma; [c] five patients presented acutely and two patients presented with chronic pain and had evidence of rupture; [d] two patients presented with a ruptured adenoma during pregnancy and one patient revealed intratumoural hemorrhage one week after caesarean section.

A total of 114 out of 652 cases (17.5%) presented with rupture and intraperitoneal bleeding. In 12 out of 28 articles the size of HCA after hemorrhage was noted. HCA in which hemorrhage occurred with a diameter of < 5 cm was shown in 6 articles (number of HCA unknown). The smallest reported HCA in this systematic review in which hemorrhage occurred was in a lesion of 1 cm. 159 out of 184 (86.4%) patients presented acutely with symptoms of hemorrhage prior to the diagnosis HCA. Hemorrhage and rupture due to abdominal trauma was described in 2 series[17,21]. (Table 2) Pregnancy related complications were described in one study and noted in three patients; two patients presented with a ruptured HCA during pregnancy and one patient revealed intratumoral hemorrhage one week after caesarean section[31].

DISCUSSION

Hemorrhage can be explained by the histological characteristics of HCA being a highly vascular tumour with multiple thin-walled sinusoids, feeding arteries, and poor connective tissue support[21,33-34]. Hemorrhage can easily spread into the liver or abdominal cavity, because HCA commonly lack a true, fibrous tumour capsule[35]. This systematic review shows that hemorrhage and rupture as described in literature is a common complication in patients with HCA with an overall frequency of hemorrhage in 27.2% of cases. Rooks et al. described a mortality rate of 21% (6 out of 29 patients) after rupture and intraperitoneal bleeding[8]. However, none of the other articles described mortality asscociated with the tumour and important is that the article described by Rooks et al. was published in the end seventies, a period in which experts were less familiar with the disease entity. Moreover, highly advanced image modalities were introduced in the last decennium and were not available in the end seventies.

The incidence and pathogenesis of HCA are not exactly known. The association of HCA with the widespread use of OC since the commercial introduction in the 1960s was first described by Baum et al. in 1973[36]. It should be noted that data regarding the incidence of HCA refer to studies performed decades ago. Nowadays benign liver tumours are detected more frequently as an incidental finding due to the increased routine use of abdominal imaging as part of a screening in case of a known extrahepatic malignancy or medical check-up. On the other hand, the incidence of HCA is reported to be lower by the introduction of new second and third generation OC during the mid seventies and eighties, respectively, which contain much lower hormone levels[37-38]. However, when studies were analysed which described patient series from the eighties and beyond, a comparable risk of hemorrhage in 25.4% of cases was found.

Many authors advocate surgical resection if the diameter of the lesion exceeds 5 cm because of the increased risk of hemorrhage and malignant transformation. Six out of

13 manuscripts that are included in this review and that do describe the size of the lesions in which hemorrhage occurred, reported hemorrhage in HCA smaller than 5 cm. Cho et al. reported hemorrhage in one lesion of 1 cm^3. It may be difficult to measure the size of HCA after hemorrhage, related to the hematoma around the lesion[39]. While on the one hand, the size of the lesion may be overestimated, on the other hand lesions may be estimated smaller because of the difficulty to distinguish vital HCA tissue from destructed parts of the lesion. Although hemorrhage is noted in very small tumours, the risk of hemorrhage and rupture seems to be very small. Three studies investigated the association between number of tumours and the risk of hemorrhage and rupture and showed that the risk of hemorrhage and rupture did not differ between patients with single or multiple HCA[4,15,29].

Recently the Bordeaux group established a molecular and pathological subtype classification of HCA. They divided HCA in four different subgroups based on morphological criteria, molecular characteristics and by the use of an immunohistochemical panel of markers; Hepatocyte nuclear factor 1α-inactivated HCA (H-HCA) which have a lack of liver-fatty acid binding protein expression in the tumour; β-catenin mutated HCA; inflammatory HCA with serum amyloid A and C-reactive protein expression; less that 10% remain unclassified[40-41]. Despite the expectation that the inflammatory subgroup has a higher risk of hemorrhage and rupture, due to the histomorphological characteristics of thick walled arteries, sinusoidal dilatation, inflammatory infiltrates and ductular reaction, there is no difference in the risk of bleeding for inflammatory HCA and the H-HCA subgroup of HCA[11,41]. Inflammatory HCA and H-HCA are the two major subgroups of HCA, however the numbers described in literature are small. A prospective multicentre study is warranted to establish the incidence of hemorrhage and rupture for small HCA and to establish the actual risk of hemorrhage and rupture for each subgroup to identify those patients who require aggressive treatment.

One of the limitations of this systematic review is that most articles reported their data on resected HCA, which could have led to an overestimation of the true risk of hemorrhage and rupture because small lesions were not detected, not reported or were treated conservatively and discharged from follow-up. In addition, in most articles published in the 70s, 80s and 90s most patients were advised to undergo resection of HCA to prevent a later presentation of malignant transformation and hemorrhage and rupture of the lesion.

The current systematic review reports on 1176 patients with HCA and shows that hemorrhage and rupture is a common complication in patients with HCA with an overall frequency of 27.2% of cases and in 15.8% of the total number of HCA lesions. Rupture and intraperitoneal bleeding were reported in 17.5% of cases. However, the risk of hemorrhage and rupture in HCA < 5 cm seems small. To identify those patients who require aggressive treatment multicentre studies are warranted to establish the actual risk of

hemorrhage and rupture for each subgroup of HCA following the Bordeaux criteria. So far, surgical resection of HCA ≥ 5 cm seems justified. The decisions on the management of smaller HCA should be based on symptoms, patient characteristics, a wish for pregnancy and the available expertise.

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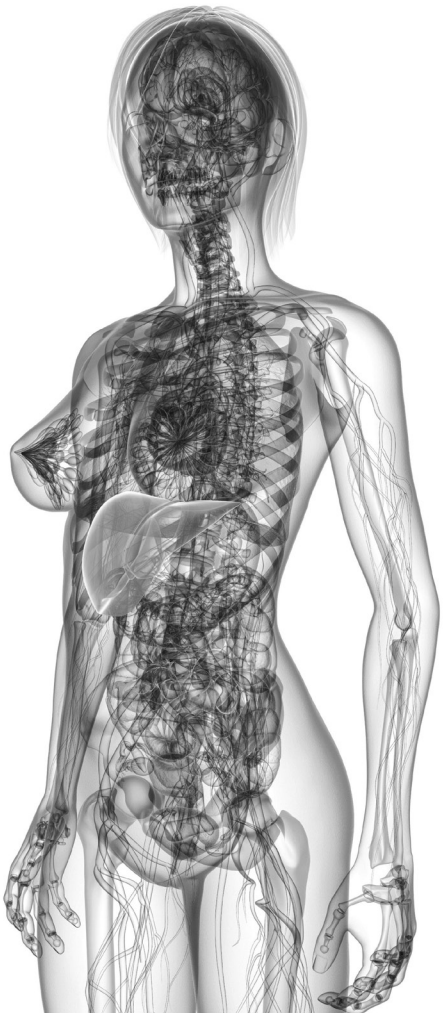
Chapter 7

Can a decision-making model be justified in the management of hepatocellular adenoma?



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ABSTRACT

During recent years, there was a great development in the area of hepatocellular adenomas (HCA), especially regarding the pathological subtype classification, radiological imaging and management during pregnancy. This review discusses the current knowledge about diagnosis and treatment modalities of HCA and proposes a decision-making model for HCA. A Medline search of studies relevant to epidemiology, histopathology, complications, imaging and management of HCA lesions was undertaken. References from identified articles were hand-searched for further relevant articles.

INTRODUCTION

Radiological, as well as histological differentiation of hepatocellular adenoma (HCA) from other benign or malignant liver tumours, such as focal nodular hyperplasia (FNH) or hepatocellular carcinoma (HCC) might be difficult. However, once the diagnosis of HCA has been established, defining the right management strategy may be challenging as well. There are no randomized controlled studies available that depict a clear decision-making for the treatment of HCA in various conditions, and the management of individual patients depends mainly on the physicians or surgeons insight. The need for a clear decision-making is obvious as, for example, in case of young women in her childbearing age with multiple, bilateral or centrally located lesions and a need for pregnancy. As new imaging and treatment modalities have been developed during the last years, management of HCA has also developed sufficiently to warrant an update. In this manuscript, we review the current knowledge about diagnosis and treatment modalities of HCA, based on our own experience and literature reports, and we define evidence-based management. A Medline search of studies relevant to epidemiology, histopathology, complications, imaging and management of HCA lesions was undertaken. References from identified articles were hand-searched for further relevant articles.

EPIDEMIOLOGY

HCA is a rare benign tumour of the liver that occurs more frequently in women within their reproductive years. The estimated incidence is about 1-1.3 per 1,000,000 in women, who have never used oral contraceptives (OC) compared to a substantial higher risk of 30-40 per 1,000,000 in long-term users (1, 2). It should be noted that these data refer to studies performed decades ago. Although the incidence of HCA is reported to be probably lower by introduction of new generation OC with much lower hormonal levels (3), nowadays benign liver tumours are detected more frequently as an incidental finding as a result of the increased routine use of abdominal imaging as part of a screening in case of a known extrahepatic malignancy or medical check-up.

HISTOPATHOLOGY

Macroscopy and microscopy

Macroscopically, an HCA lesion is smooth and soft on palpation and occurs as a solitary tumour, as well as multiple lesions. We reviewed our series of 221 patients with a clear diagnosis of HCA referred to our hospital between 2000 and 2009 and report HCA to

be solitary in 32% of the patients. Ninety-nine patients (45%) presented with multiple adenomas (2-9 HCA lesions) and 23% presented with hepatic adenomatosis, defined as the presence of ≥ 10 HCA (4). Microscopic examination shows cords of hepatocytes having a glycogen and lipid content and abnormal parenchymal architecture with absence of portal tracts and hepatic veins is seen. The hepatic plate can be two or more cells thick, separated by dilated sinusoids. Bile ducts are absent, a key histological feature that helps to distinguish it from FNH (5, 6). The cut surface of the adenoma has a characteristic yellow appearance, which comes from the lipid accumulation.

Classification

Recently, the Bordeaux group established a new molecular and pathological classification system for HCA (7). The classification described by Bioulac-Sage et al. is of great clinical importance. They divided HCAs in four different subgroups using an immunohistochemical panel of markers. These markers were defined by the presence of mutations in TCF1 gene, inactivating the hepatocyte nuclear factor 1 (HNF-1α) in 35-50% of the HCA patients; presence of β-catenin activating mutations was observed in 15-18% of patients; serum amyloid A (SAA) and C-reactive protein (CRP) expression in inflammatory HCA was found in 40–55% of patients, histomorphologically characterised by inflammatory infiltrates, thick walled arteries, sinusoidal dilatation and ductular reaction; less than 10% of HCA could not be classified (8, 9). There are several interesting findings from this study. The HNF-1α-mutated HCAs were most of the time highly steatotic, with a lack of expression of liver-fatty acid binding protein (L-FABP) in immunohistochemistry analysis (9). Liver adenomatosis (LA; HCA ≥ 10) was most often found in L-FABP-negative HCA (8) and germline HNF-1α mutations cause LA in addition to diabetes (MODY3) (10). Patients with a high body mass index and excessive alcohol consumption were more frequently observed in the inflammatory group (7, 11), whereas β-catenin-activated lesions seem to have a higher risk of malignant transformation in HCC in patients with HCA larger than 4-5 cm (7, 12). As previously described, it might be very difficult to distinguish HCA from a well-differentiated HCC. Identifying β-catenin-positive HCA is therefore of major interest. However, the risk of HCC in patients without β-catenin mutation is an unanswered question (9). Results of our series of 58 surgically resected HCA lesions were in accordance with data reported by Bioulac-Sage et al., confirming that inflammatory HCA and steatotic-type L-FABP-negative HCA to be the two main subgroups. They differ on clinical and pathological grounds showing the features as mentioned above (13). Morphology and immunohistochemistry allow subtyping of more than 90% of HCA (13) (Figures 1-3). Interpretation of immunohistochemistry needs adequate techniques and training, particularly for the interpretation of β-catenin and glutamine synthetase (GS). The identification of nuclear staining for β-catenin can be very difficult, because the number of β-catenin-positive cells may be limited. Moreover, interpretation of β-catenin

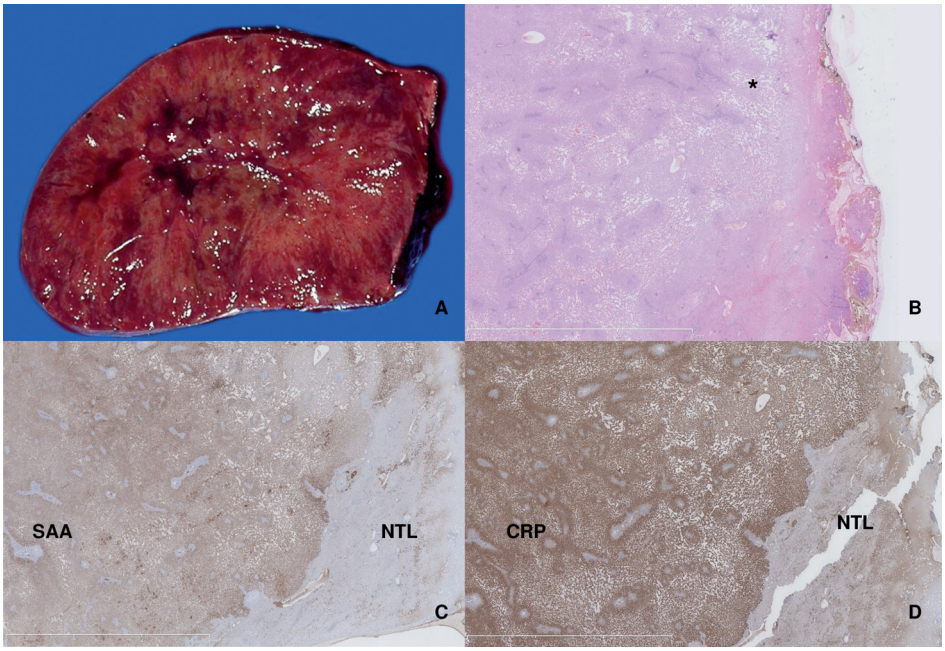

Figure 1. Inflammatory hepatocellular adenoma (HCA). **(a)** Macroscopic view of an inflammatory HCA of 9 cm in largest diameter. At cut section, the lesion has a red-brown aspect with areas of intratumoural fat and sinusoidal dilatation (*). **(b)** Paraffin section, haematoxylin and eosin stain. Sinusoidal dilatation (*), mild ductular reaction and inflammatory reaction. **(c,d)** Serum amyloid A (SAA) immunostaining expression and C-reactive protein (CRP) immunostaining expression in HCA in contrast with non-tumoural liver (NTL).

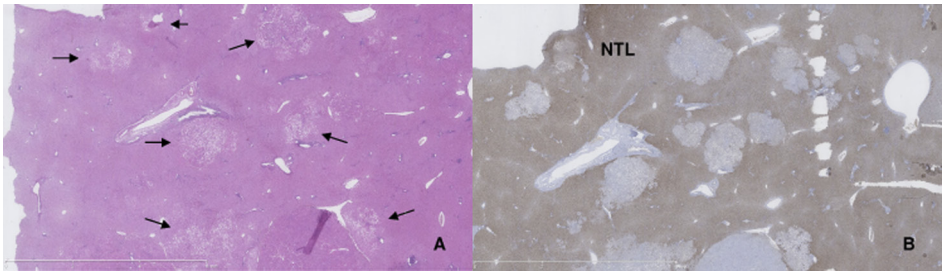

Figure 2. 'Steatotic' hepatocellular adenoma (HCA). **(a)** Paraffin section, haematoxylin and eosin stain. Marked steatosis in adenomatosis (arrows). **(b)** Liver-fatty acid binding protein immunostaining (L-FABP) in multiple steatotic HCA: lack of L-FABP in HCA in contrast with normal expression in non-tumoural liver (NTL).

may be difficult because of the heterogeneous and sometimes, focal nuclear staining pattern. Subtyping the lesion as β-catenin-positive HCA is straightforward when there is a strong and homogeneous GS staining pattern, and accompanied by nuclear β-catenin expression. However, if the GS over expression is heterogeneous, the interpretation becomes more difficult (13, 14). Paradis et al. described a variant of FNH, the so called telangiectatic FNH, which has a molecular pattern closer to HCA than to FNH. These

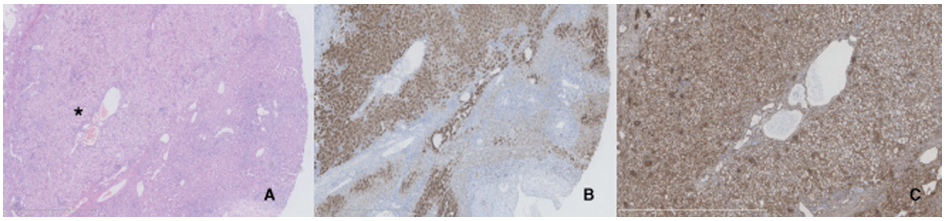

Figure 3. β-catenin activate hepatocellular adenoma (HCA). **(a)** Paraffin section, haematoxylin and eosin stain. Formation of pseudoglands (*) **(b)** Homogeneous glutamine synthetase immunostaining (GS) of HCA in contrast with non-tumoural liver (NTL). **(c)** Nuclear positivity of β-catenin immunostaining.

lesions would be more accurately referred to as 'telangiectatic hepatocellular adenomas' (15, 16). The Bordeaux group delivers more evidence that these telangiectatic lesions are defined by specific morphological characteristics, i.e. partially preserved lobulation, presence of portal tract-like structures with dystrophic arteries and ductular reaction (15). These lesions are frequently subject to bleeding because of the areas of sinusoidal dilatation and peliosis (17). The Bordeaux group demonstrated a common molecular link between telangiectatic FNH and inflammatory HCA and established that the so called telangiectatic FNH is part of the inflammatory subtype of HCA with telangiectatic features (7).

COMPLICATIONS

Haemorrhage

The presence of HCA can be complicated by hormone-induced growth and subsequently, rupture and bleeding, which is usually the cause of right upper quadrant abdominal pain in symptomatic patients. Haemorrhage can be explained by the histological characteristics of HCA being a highly vascular tumour with multiple thin-walled sinusoids, feeding arteries and poor connective tissue support (5, 6, 18). Haemorrhage will spread into the liver or abdominal cavity, because HCA commonly lack a true, fibrous tumour capsule (19). Deneve et al. analysed data from five academic medical centres and searched for factors that were associated with rupture of HCA. One hundred and nineteen patients were included in this study; a total of 31 patients (25%) had evidence of rupture. They concluded that patients with ruptured HCAs were more likely to have a history of recent use of OC compared to patients with a non-ruptured HCA (58% vs. 25%) (20). Whether rupture and bleeding will occur seems also be correlated with the size of the HCA. Deneve et al. reported that no tumour < 5 cm in largest diameter had evidence of rupture (20). Dokmak et al. described that a risk of haemorrhage was almost exclusively observed in HCA > 5 cm in diameter, and less than 1% of HCA < 5 cm had macroscopic haemorrhagic stigmata (21). In addition, the risk of rupture is believed to

increase during pregnancy because of the increased hormone levels (22). Haemorrhage of HCA is seldom caused by external trauma (23). Risk of rupture seems not to be associated with tumour number (20, 21). In our experience, in a series of 221 patients, 45 HCA patients (20%) presented with radiological evidence of haemorrhage. All patients in whom haemorrhage occurred were female with a median age of 38 years (range 21–66). Thirty-nine patients (87%) were using OC at the time of diagnosis, with data missing from five patients. Nine of 45 patients presented with an active bleeding during diagnosis. The initial management in four of them included haemodynamic support with suppletion of blood products and coagulants. In two of these patients, selective transcatheter arterial embolization (TAE) followed. In total, six of nine patients presented with an active bleeding were treated with TAE to stop the bleeding. The remaining 36 patients were stable. All patients are still alive. In four patients, haemorrhage of the HCA occurred after biopsy of the lesion. After rupture, the size of the HCA and the rate of regression of its diameter during follow-up may be difficult to measure as lesions tend to be estimated larger after rupture, related to the haematoma around the lesion (24). In our series, all lesions showed tumour regression or even disappearance of the lesion after rupture. This might be caused by devascularisation and shrinkage of the adenoma as a result of the bleeding, or regression of the lesion is due to withdrawn of OC use. The risk of rupture of other HCA lesions in the liver remains unknown.

Malignant transformation

Malignant transformation of HCA into HCC has been reported, although it is considered to occur rarely (25, 26). The reported proportion of malignant degeneration in HCAs vary from 4 to 18% (20, 25-27). Recently, Stoot et al. reported an overall frequency of malignant transformation of HCA of 4.2% (28). The HCA nodules with aberrant nuclear β-catenin expression (β-catenin-mutated adenomas) are of high risk of developing HCC out of HCA (see phenotype classification). The β-catenin-mutated subgroup seems overrepresented in male patients and specific risk factors, such as male hormone administration, are associated with their development (9). Some authors suggest the association of HCC with the simultaneous occurrence of HCA and glycogen storage disease type Ia (GSD Ia) (29–32). Kishnani et al. described the possibility that HCA associated with GSD Ia is to be related to HCC transformation because it is likely that cooperative activation of multiple oncogenes on 6p and inactivation of multiple tumour suppressor genes on 6q contribute to the development of HCAs in GSD Ia patients. Gain of 6p and loss of 6q are frequently indentified in HCC (31). However, the exact pathogenesis of malignant transformation of HCA remains unknown. Little literature is available about size as risk factor for malignant transformation of HCA. Micchelli et al. reported malignant transformation in HCA greater than 4 cm (25). It should be kept in mind that multiple HCA of different subtypes can occur in the same patients (33). Therefore, resection of an HCA

without malignant characteristics in a patient with multiple adenomas does not exclude possible malignant transformation of the remaining liver lesions.

BIOPSY

Liver biopsy can be used if imaging cannot firmly establish the diagnosis of a liver nodule. Whether the immunohistochemistry markers, as mentioned above, will also be accurate on biopsies of liver lesions suspected of being HCA needs to be questioned. Using the genotype/phenotype classification might allow the identification of patients at risk of rupture or malignant transformation. This information could, theoretically, be used to direct management. However, needle biopsies may lead to sampling error, and moreover, it may be associated with haemorrhage or needle-track tumour seeding in case of a malignant lesion (34). In addition, the amount of material obtained by biopsy is often insufficient to achieve a reliable diagnosis. In most cases, the identification of L-FABP-negative and inflammatory-type HCA with positive CRP and SAA staining should be feasible on a biopsy, because of more or less homogeneous staining pattern (33). However, the interpretation of β-catenin staining may be difficult because of the heterogeneous and sometimes focal nuclear staining pattern, and additional molecular biology may be required, as close relationships were found between genetic data and immunohistochemical data (33, 35–37). A concomitant staining with GS is warranted to increase sensitivity to detect a β-catenin mutation, especially in the case of a biopsy (33). Recent immunohistochemical data obtained on biopsies are very encouraging allowing the identification of subtypes in more than 80% of cases [abstract 1710 AASLD 2010, (38)] The role of needle biopsy or aspiration of focal liver lesions remains much debated. Although histological examination is still considered to be the gold standard in the diagnosis of benign and malignant liver tumours, the availability of highly advanced radiological techniques provides a noninvasive diagnostic tool that is being used frequently. Besides, radiological examination, especially magnetic resonance imaging (MRI), has a high accuracy rate for HCA (6, 8). This may have consequences for the role of histology during work-up of a focal liver lesion, which has its own diagnostic pitfalls.

IMAGING

On unenhanced computed tomography (CT) scans, HCAs are usually well-described lesions and become visible in the arterial phase with a subtle homogeneous blush of contrast enhancement and fade to isodensity in the portal or delayed phase (19, 39). Contrast-enhanced CT scans may show peripheral enhancement which reflects the pres-

ence of a large subcapsular feeding vessel, with a centripetal pattern of enhancement (5). Homogeneous enhancement in the arterial phase shown on CT scans obtained after i.v. injection of contrast plays an important role in diagnosis. The broad availability of CT, as well as, the recent development of the faster multirow detector machine does allow multiphasic dynamic contrast-enhanced imaging in relatively shorter scanning times. The shorter scanning times allow the capture of distinct phases, i.e. unenhanced phase, arterial phase, portal phase and venous phase that provide important information for characterisation of a focal liver lesion. In clinical practice, however, the number of phases is limited and often kept to a minimum, mainly because of the radiation hazard. At the same time, helical scanning and thinner collimation are used, more often. As a consequence, smaller hepatic lesions are detected that cannot be characterised with CT scanning after monophasic injection of contrast material.

State-of-the-art MRI provides the most comprehensive and non-invasive imaging work-up of patients with suspected HCA (19). Grazioli et al. reported a sensitivity and specificity in differentiating FNH from HCA and LA of 96.9 and 100% respectively. However, histological confirmation was not available in all lesions. Most HCA are almost isointense or slightly hyperintense to the surrounding liver on in-phase, gradient echo, T1-weighted images, showing decreased signal intensity in the opposed-phase T1-weighted images because of their fat content (19). On T2-weighted images, 47-74% of HCA are predominantly hyperintense to the surrounding liver (5) depending on fat or fibrosis within the lesion or because HCA is surrounded by fatty liver (19). The superiority of MRI is because of the differences in techniques of data acquisition, the absence of radiation and the possibility of using liver-specific contrast agents which lacks the hazards of ionising radiation, in addition to inherently greater tissue contrast with MRI (19). Superparamagnetic iron oxide (SPIO) and ultrasmall SPIO uptake is expected, as the lesions contains Kupffer cells which lead to a loss of signal intensity on ferumoxides-enhanced T2-weighted images (40, 41). However, differentiation between HCA and FNH with the use of SPIO is often difficult because of overlapping uptake of SPIO in HCA and FNH (42, 43). Gadobenate dimeglumine (Gd-BOPTA, Multihance; Bracco imaging, Milan, Italy) and gadoxetic acid (Gd-EOB-DTPA, Primovist; Schering, Berlin, Germany) are both gadolinium-based MR imaging contrast agents that are taken up by hepatocytes and their compound is excreted in the bile (6, 44). The HCA lack bile ducts which may result in the absence of Gd-BOPTA and Gd-EOB-DTPA uptake and transport compared to other benign hepatic lesions (6, 45). Dynamic gadolinium-enhanced imaging demonstrates homogeneous enhancement in the arterial phase after gadolinium and isointensity in the delayed phase without washout or capsular enhancement (19, 46). Grazioli et al. described a hypointense signal on delayed phase images (47). Although it is described by a few studies, including a small number of patients, accurate differentiation of HCA from FNH is achievable on delayed MRI after Gd-BOPTA administration (6). Another de-

velopment in imaging techniques, helpful in differential diagnosis of HCA is the clinical introduction of contrast-enhanced ultrasonography (CEUS). This technique allows the identification of the early enhancement in the periphery of the tumour, reflecting the presence of subcapsular feeding arteries with a mixed or centripetal filling (48, 49). In CEUS, microbubble contrast (second generation contrast agent, e.g. Sonovue; Bracco Imaging) is being used which delivers a pronounced enhancement in the arterial phase in HCA and FNH, but washes out rapidly in the portal venous and delayed phase in HCA (50–52). An important benefit of CEUS is the safety aspect, because of lack of radiation exposure and nearly absent of contrast-related complications and sensitivity reactions when compared to other contrast agents. In addition, the examination is short, less expensive than CT or MRI, and could reduce patient waiting time (51, 53, 54). Kim et al. reported a sensitivity and specificity in differentiating HCA from FNH ranging from 86 to 95% and from 74 to 79% respectively (49). Furthermore, a recent pilot study by Van den Esschert et al. showed that PET/CT with ^{18}F-fluorocholine can differentiate between HCA and FNH (55). However, because of a small number of lesions (10 HCA and 11 FNH), the diagnostic accuracy of PET/CT with ^{18}F-fluorocholine in differentiation of HCA from FNH needs to be confirmed in large number of patients. However, needle biopsy used to be accepted as the gold standard for diagnosing tumours, at present radiology, especially contrast-enhanced MRI, has equalled or even exceeded the value of needle biopsy as the gold standard. Moreover, MRI seems to be a useful tool for identifying the two major subtypes of HCA (L-FABP-negative HCA and inflammatory HCA) (56). Results of our series of 48 surgically resected HCA lesions who underwent MRI before resection showed that L-FABP-negative HCA, inflammatory HCA and β-catenin-positive HCA to be associated with specific MRI patterns. Intratumoural fat deposition and presence of an 'atoll' sign and/or central scar can be helpful to distinguish between these subtypes (57). Based on our own experience, we advocate contrast MRI and CEUS to diagnose HCA. In case, contrast MRI and CEUS are not in accordance with the diagnosis of HCA or in case of doubt on the diagnosis of HCA, a biopsy is needed (Figure 4).

MANAGEMENT

Overall management

Regardless the aetiology and risk factors, all female patients should be advised to stop OC and other hormone medication, such as hormone replacement therapy, as regression of HCA may occur when steroids are withdrawn (58). We reviewed our series of 221 patients with a clear diagnosis of HCA referred to our hospital between 2000 and 2009. We reported 104 of 221 HCA patients in which the course of HCA is noted. The course of HCA was unknown in case of lack of radiological imaging after discontinuation of OC,

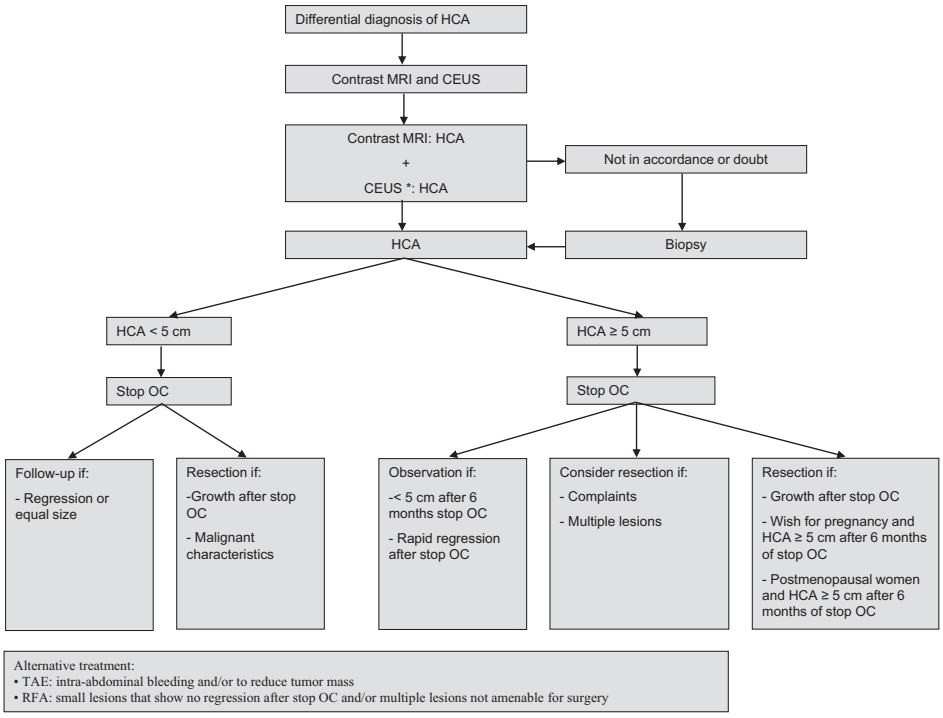

Figure 4. Management decision tree for hepatocellular adenoma.

or due to intervention, or due to haemorrhage or in case the data of discontinuation of OC was unknown. In 8 of 104 HCA patients, the use of OC was absent. Seventy-six of 96 (79%) HCA patients in whom the course of HCA after discontinuation of OC is noted showed regression of HCA. The HCA lesion showed regression from some millimetres to 8.5 centimetres. Some HCA lesions showed total regression of the tumour. Although several strategies for managing HCA were described in literature, the best treatment of HCA still remains controversial. Expert opinions are very variable regarding treatment and follow-up in complex situations, where multiple factors play a role in determining the management strategy, like multiple HCA and pregnancy (59). In case of a solitary adenoma, most authors advocate surgical resection only if the diameter exceeds 5 cm after 6 months of follow-up without OC use, if the lesion does not show adequate regression after discontinuation of OC or if rebleeding occurs (21, 34, 60, 61). Surgical resection is also indicated, if there is any doubt on malignancy or malignant transformation (59, 62). Observation should be the first treatment choice for lesions smaller than 5 cm or lesions showing regression during radiological follow-up (Figure 4). Based on our own experience, we advocate a first follow-up interval of 6 months for repeated MRI to compare adequate diameter and shrinkage. The length of follow-up should be determined on a custom-made base. Resection should be considered in case of a young

female patient with a wish for pregnancy with HCA ≥ 5 cm after 6 months of follow-up. Resection should also be considered in case of post-menopausal women with HCA ≥ 5 cm after 6 months of follow-up or in case of male patients, as these patients have a high risk on β-catenin-positive HCA (63).

New and less invasive treatments, such as radiofrequent ablation (RFA) and TAE, have been proposed as an alternative treatment. The RFA may be useful in selected cases in which radical resection is not possible because of centrally located lesions, multiple HCA in both lobes of the liver, those who refuse surgery or in patients with a wish for pregnancy (64-66). For small tumours that do not show regression after withdrawal of steroids, RFA might be the most favourable treatment because of the least expensiveness and most gained quality-adjusted life years (QALY's) (67). A limited available number of studies regarding this topic reported RFA to be a safe and successful application especially in HCA < 4 cm (64-66, 68, 69). Although used in emergency setting with or without intra-abdominal bleeding, TAE may also be used electively to reduce the tumour mass of a large HCA (70). The TAE is thought to be a less invasive therapy compared to hepatic resection. However, only limited studies are available about TAE as elective treatment for unruptured HCA (70, 71).

Rupture and bleeding

Management of a ruptured HCA is of major concern because initial bleeding may be severe enough to produce haemorrhagic shock. Haemodynamically unstable patients, despite adequate resuscitation, require immediate intervention to control haemorrhage (24). Intervention should consist of emergency laparotomy or laparoscopic resection. However, one should take into account the surgical procedure related to mortality and morbidity (67). The TAE as an initial treatment in patients with spontaneous bleeding of HCA with or without intra-abdominal rupture may reduce the need for urgent laparotomy to control bleeding (18, 60, 70, 72). However, no data are available regarding the long-term effects of TAE and complication risks (67). There are no data about RFA therapy for ruptured adenomas. If there is no regression or even growth of the lesion after haemorrhage, a surgical resection should be considered to prevent rebleeding (61).

Pregnancy

Hepatocellular adenoma in pregnant women requires special considerations because of the risk of hormone-induced growth and spontaneous haemorrhagic rupture, because of increased levels of steroid hormones during pregnancy that may threaten the life of both mother and child. The risk of rupture is the highest during the third trimester of pregnancy, most probably because of the cumulating level of oestrogens and an increase in hyperdynamic circulation combined with an increase in vascularity of the liver with growth of the adenoma (22). In literature, the maternal and fetal mortality

risks of ruptured HCA during pregnancy are reported to be 44 and 38% respectively (22). However, all of these cases were published in the 1970s or 1980s period, in which there might have been a delay in diagnosis as the entity of ruptured HCA was not well known yet, consequently leading to confusion with other pregnancy-related diseases, like pre-eclampsia, pulmonary embolism or gallbladder disease. In the last decennium, the introduction and widespread use of highly advanced imaging modalities has probably decreased the doctors' delay in the diagnosis of HCA. Intervention during pregnancy may be associated with greater risk for both mother and child. Little literature is available on the course and management of HCA during pregnancy. We monitored 12 women with documented HCA during a total of 17 pregnancies. In four cases, HCAs grew during pregnancy, requiring a Caesarean section in one patient (two pregnancies) and RFA in one patient during the first trimester of pregnancy. All pregnancies had an uneventful course with a successful maternal and fetal outcome. We concluded not to discourage all women with HCA from pregnancy. Negative advice against pregnancy is justified in women who have large tumours or who have experienced complications of HCA in previous pregnancies. In that case, surgical resection should be recommended before pregnancy (73). Moreover, a series of 48 patients showed that about half of women carried at least one pregnancy before HCA was discovered (62).

Multiple hepatocellular adenoma and liver adenomatosis

In 1985, Flejou et al. defined LA as the presence of ≥ 10 adenomas in an otherwise normal liver parenchyma. They reported that LA affects men and women equally without relation to the use of OC or GSD (4). Recent studies reported a gender distribution in favour of female patients (74, 75) and an association with OC use, glycogenosis, diabetes, high BMI, germline mutations of HNF-1α (L-FABP-negative HCA, a subgroup that seems to be associated with steatotis), non-alcoholic fatty liver disease and patients who undergo a Fontan procedure (8, 10, 35, 74, 76, 77). Eighteen per cent of patients with LA showed steatosis in non-tumoural tissue which affects the management of patients with LA as liver steatosis has an impact on the outcome of liver surgery (75, 78). Several other authors reported or suggested an increased incidence of multiple adenomas (≥ 2) in the setting of liver steatosis (11, 62, 77, 78). Chiche et al. identified two forms of LA: the 'massive' form and the 'multifocal' form (74). In the massive form, the liver is enlarged, the liver contour is deformed and the parenchyma is tumoural and hypervascularized. The liver contains nodules measuring 2-10 cm and this form may be progressive. Liver surgery on the massive form can be a therapeutic challenge. In contradiction to massive form, in the multifocal form, one or two nodules may be larger and may produce complications. The liver is not enlarged or deformed. Liver surgery on the multifocal form is easier compared to the massive form (74). There is an ongoing debate on the management of multiple hepatic adenomas and LA, regarding surveillance, surgical

resection or other less invasive treatments, such as RFA and TAE. Proper control of multiple lesions may be indicated in selected patients, like in patients with a strong wish for pregnancy. However, one should still limit surgical resection of adenomas ≥ 5 cm in diameter, to prevent the risk of bleeding and malignant transformation or adenomas with radiological signs of malignancy. Although, some patients are not amenable for surgery because of centrally located tumours or because of the extensive involvement of both lobes of the liver in LA. In that case, an alternative minimal invasive treatment, like RFA, may be the treatment of choice. The RFA can be performed percutaneously or in an open setting (65). However, limited data are available on this topic (64-67, 69). The surgical procedure may also be combined with open RFA for the remaining smaller lesions as a safe and effective treatment option because of low mortality and morbidity rates of this procedure. Furthermore, in small tumours, RFA is the preferred treatment because of the short hospital stay, low cost and the best gain in QALY's as we mentioned earlier (67). A case report published in 2009 suggested elective treatment of multiple HCA with TAE to prevent rupture and bleeding (79). Regarding the risk of malignant degeneration (80), Barthelmes reviewed 17 patients of liver transplantation for LA. In these series, there is clearly a selection bias, because some of the adenomas were suspected of malignant transformation and the patients were listed for transplantation. Outcome and survival are known for only 10 patients (81). Three of these patients developed HCC in the transplanted liver or developed lung metastasis, one patient died immediately post-operatively (81). Although LA is a benign disease, in patients who are not amenable for other treatment strategies, such as TAE, RFA or surgical resection, a liver transplantation may be the best option, especially in case of degenerated adenomas. However, Dokmak et al. reported that there is no indication for liver transplantation in patients with unresectable multiple HCA, because of the low risk of progression or complications of residual HCA (21).

CONCLUSION

Despite the great development in the area of HCA, especially in case of radiology, to date a decision-making model for the management of HCA as proposed in Figure 4 might not be justified for all patients, and a more custom-made approach should be followed. There are still many unanswered questions:

- What is the risk of bleeding in HCA > 5 cm and does bleeding occur in small lesions?
- A 'wait and see' management may be advocated in pregnant women presenting with HCA, however, there is no evidence-based algorithm for the evaluation and management of HCA during pregnancy.

- What is the best treatment in case of multiple HCA?

The most important progress concerning HCA contains its subtype classification. Data from different centres are needed to correlate the classification system with legitimized clinical management and to investigate whether the immunohistochemical markers will also be useful on biopsies from liver tumours, suspected of being HCA.

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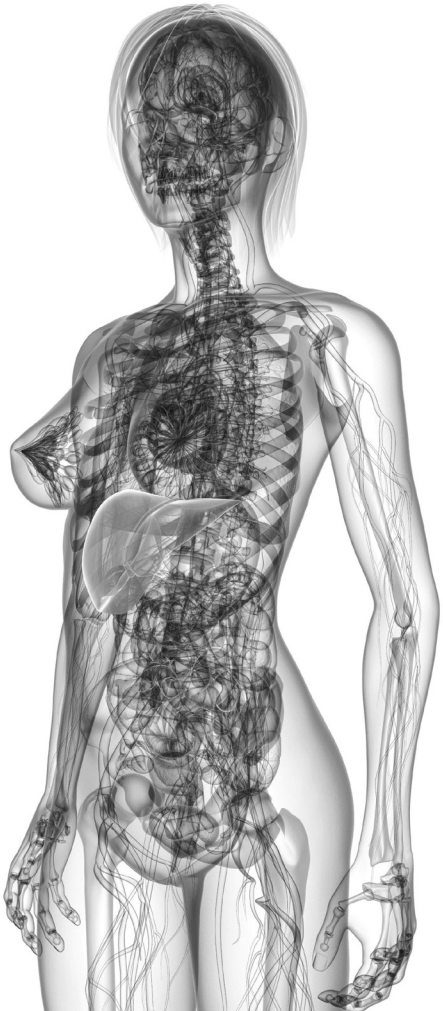
Chapter 8

General discussion



GENERAL DISCUSSION

Although hepatocellular adenoma (HCA) is a benign tumor of the liver, the diagnosis can have a great impact on the lives of these mostly young women because of the risk of bleeding complications and malignant transformation [1-2]. Female sex, oral contraceptives (OC) use and childbearing age are major factors for developing HCA. However, HCA can also occur in females without (previous) use of OC and occurs rarely in men. There is still much unknown about the etiology and epidemiology of HCA. Estimates of incidence and prevalence of HCA can hardly be made since there are a limited number of epidemiological studies as well as a diversity of imaging techniques with different imaging characteristics. Due to scarcity of cases there is still absence of an evidence-based approach for the management of HCA. Clinical dilemmas occur when multiple factors play a role for example in case of young women in her childbearing age with multiple, bilateral or centrally located lesions and a wish for pregnancy. Advice in the management of HCA is mainly based on retrospective studies, case series, incidental case reports and expert opinions. However, great progress has been made concerning HCA.

State-of-the-art magnetic resonance imaging (MRI) provides the most comprehensive and non-invasive imaging work-up of patients with suspected HCA [3]. The use of this highly advanced imaging modality reduces the number of biopsies and possible unnecessary surgery. Differentiation of HCA from other lesions in the liver is important but still can be difficult, especially differentiation of HCA from focal nodular hyperplasia (FNH). FNH generally does not require treatment and follow-up, whereas HCA does. When doubt remains on radiological imaging, immunohistochemical analysis can provide a solution. The morphological diagnosis of FNH is supported by a characteristic 'map-like' staining pattern of glutamine synthetase (GS) [4]. In cases where there is doubt about the diagnosis HCA there is a role for core needle biopsy.

The introduction of a molecular and pathological subtype classification system for HCA can be of great clinical importance. The main interest is the complication rate (hemorrhage and malignant transformation) related to each subgroup and subtype specific characteristics (e.g. number of tumors, body mass index). However, to investigate specific clinical and pathological features for each subgroup and related risks data from different centers need to be combined. To achieve this, widespread availability of standardized immunohistochemical techniques is needed.

Despite the great progress in the field of HCA, the debate whether to manage solitary HCA by conservative treatment or invasive treatment goes on. However, the rules for

now are as follows: we do believe and still advise all female patients to stop the use of OC and other hormone replacement therapies. Resection is indicated for HCA ≥ 5 cm in diameter after six months of first follow-up because of the risk of bleeding and malignant transformation. One should take into account that resection has an invasive nature with a risk of postoperative morbidity and mortality. Moreover resection of centrally located large lesions can be difficult and the risk of surgical resection should be weighted against the benefits. The idea to resect only large HCA is outdated. Resection is also advocated in smaller HCA which show signs of a typical vaguely defined scar on MRI, atypical characteristics, in case of growth after discontinuation of OC, HCA in men and HCA in context of chronic viral hepatitis. A homogeneous staining pattern of GS (which is a β-catenin target gene) and β-catenin positivity is a strong argument for resection of the lesion. However, more data are needed since we do not know the steps in the process of developing hepatocellular carcinoma out of HCA. New and less invasive treatments such as radiofrequent ablation (RFA) and transcatheter arterial embolization have been proposed as an alternative treatment. RFA may be useful in selected cases in which radical resection is not possible due to lesions located centrally, multiple HCA in both lobes of the liver, in those who refuse surgery or in patients with a wish for pregnancy [5-7]. However, since the biological behavior of HCA during pregnancy may be less threatening than presumed a wait and see management may be advocated in lesions < 5 cm in diameter. Livertransplantation might be used exceptionally in case of high risk patients with unresectable multiple HCA.

In conclusion, for an optimal care of patients with HCA the combined expertise of surgeons, hepatologists, radiologists, pathologists and gynecologists is needed. Treatment of solitary and multifocal liver tumors requires a multicenter approach.

There are still many unanswered questions:

- What is the complication risk for patients with multiple HCA of one or different subtypes?
- What is the exact incidence and prevalence of HCA worldwide and per region?
- What is the actual risk of hemorrhage and rupture for each subgroup of HCA and what is the risk in smaller HCA?
- What is the risk of malignant transformation in β-catenin positive HCA?
- What is the risk of malignant transformation in β-catenin and GS negative HCA?
- What is the mechanism of malignant transformation of HCA?
- Which subtype of HCA lesions will regress, what is the speed of regression and is there regression of HCA after menopause?
- What is the best way to follow-up patients with HCA: what is the length and interval of follow up?

- What is the biological behavior of HCA during pregnancy and what is the complication risk?

FUTURE PERSPECTIVES

For the near future it is necessary to confirm the promising results described in this thesis and to obtain answers on the questions mentioned above in a large multicenter study.

It would be of great benefit if we could provide a large multicenter prospective database to correlate data to perform a legitimized clinical management protocol. The consequence for treatment and follow-up of the subtype classification remains to be determined. Systematic registries are needed for better knowledge about the different subgroups and their behavior, to find surrogate markers and to improve the identification of HCA subgroups based on imaging. Moreover, risk factors for each individual subgroup need to be investigated. Therefore, a multicenter study is warranted to investigate specific clinical and pathological features for each subgroup and to propose guidelines for the management for each individual patient. It is warranted to establish the actual risk of hemorrhage and rupture for each subgroup of HCA and to identify those patients who require aggressive treatment. In the near future, international studies will be established to collect data from referral centers from different countries to answer questions related to diagnosis and treatment of HCA (and HCA subtypes).

The conclusion not to discourage all women with HCA from pregnancy will be investigated in a large multicenter study in the Netherlands in which pregnant patient with HCA will be closely monitored in a prospectively acquired database to give more insight in the behavior of HCA during pregnancy. We hypothesize that pregnancy may be allowed in case of one or more known HCA < 5 cm, because HCA < 5 cm will not disturb the course of pregnancy. Whether it is justified to deny a young woman a pregnancy, as the biological behavior may be less threatening than presumed will be investigated in the PALM-study.

Which patients should undergo surgical treatment and which patients should not remains a topic largely open for debate. Therefore, future research should focus on the comparison of different treatment modalities for the treatment of HCA, including laparoscopic liver resection, ablation therapies, transarterial embolization and conservative management.

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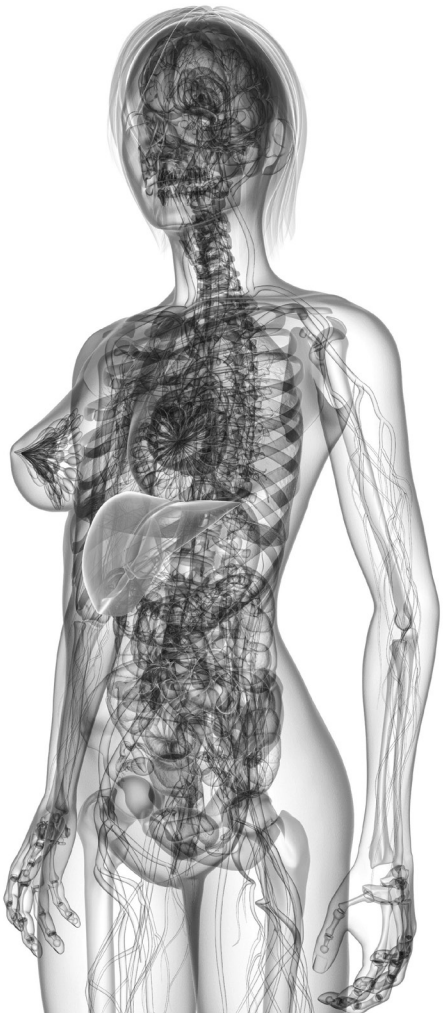
Chapter 9

Summary and conclusions

Nederlandse samenvatting en conclusies



Summary and conclusions

SUMMARY

In **chapter 2** we described the present day-to-day management of hepatocellular adenoma (HCA) in the Netherlands based on expert opinions on diagnosis and treatment of HCA. We concluded that the management of HCA is rather uniform, except in some cases in which multiple factors play a role such as bleeding, a wish for pregnancy or multiple lesions. In the majority of hospitals management of HCA was determined by a multidisciplinary approach. The diagnosis was based on contrast-enhanced, multiphase spiral CT or MRI series. All patients were advised to stop oral contraceptives (OC) use and outpatient control by MRI, CT or ultrasound was performed at least once. Conservative treatment was the initial treatment for HCA < 5 cm in diameter in all hospitals. A tumor size > 5 cm and abdominal complaints were major criteria for surgical resection. However, sometimes resection was performed if there was a wish for pregnancy, potential signs of malignancy on imaging, tumor growth or in case of diagnostic doubt. Pregnancy was not discouraged in most of the clinics, however most experts wanted to exclude the risk of hormone induced rupture and bleeding by resection before pregnancy. In our opinion it seems unjustified to discourage all women with HCA < 5 cm from pregnancy. There are no randomized controlled studies available that depict a clear decision making model for the treatment of hepatic adenomas in various conditions and the management of individual patients depends mainly on the physicians or surgeons insight. The need for a clear decision making model is obvious. Therefore, future research should be focused on the management of HCA in patients with multiple HCA, HCA > 5 cm, pregnancy and bleeding lesions.

In **chapter 3** we investigated the possibility to distinguish subgroups of HCA based on pathological findings and the possibility to correlate pathological findings with imaging characteristics on state-of-the-art MRI. Recently the Bordeaux group established a molecular and pathological classification system for HCA. HCA were divided into four different subgroups based on morphological criteria, molecular characteristics, and by the use of a panel of immunohistochemical markers [1-3]. We validated the classification system on 57 HCA lesions and concluded that morphology and additional imuunohistochemical markers can discriminate between different types of HCA in > 90% of cases. Multiple HCA of different subtypes can be found in patient. Focal nodular hyperplasia (FNH) can be found with high reliability by the use of glutamine synthetase (GS), which shows a characteristic 'map-like' staining pattern in case of FNH lesions. The identification of β-catenin positive lesions is of major interest since β-catenin positive

lesions seems to have a risk on malignant transformation [4-6]. However, interpretation of nuclear staining for β-catenin can be difficult due to uneven staining distribution or focal nuclear staining. In this situation additional molecular biology may be required.

We were able to confirm specific MRI features that can be used to identify different subgroups of HCA, especially for the inflammatory and L-FABP-negative HCA. L-FABP-negative HCA can be recognized with high reliability, and presents as a diffuse decrease in signal intensity on out-of-phase signal images because of the presence of intratumoral fat. In almost half of the inflammatory HCA lesions we found a typical 'atoll' sign on MRI, characterized by a hyperintense signal band on T2-weighted pulse sequences in the periphery of the lesion (i.e. like an atoll) and isointensity of the center of the lesion with respect of the surrounding liver (like the surrounding sea). The presence of a vaguely demarcated scar in HCA was significantly associated with nuclear staining of β-catenin. In these cases surgical resection or close follow-up is advocated. The clinical consequence for the treatment and follow-up based on the pathological subtype classification remains to be determined. A multicenter study is warranted to investigate specific clinical and pathological features for each subgroup and to propose guidelines for the management for each individual patient.

It is thought that HCA can be complicated by hormone induced growth and subsequently, spontaneous hemorrhagic rupture. In **chapter 4** we proposed not to discourage all women with HCA from pregnancy, based on a study in which we monitored twelve women with documented HCA during a total of 17 pregnancies. In 4 cases HCA grew during pregnancy, requiring a Caesarean section in 1 patient (2 pregnancies) and radiofrequency ablation (RFA) in 1 case during the first trimester of pregnancy. All pregnancies had an uneventful course with a successful maternal and fetal outcome. However, there is no evidence-based algorithm for the evaluation and management of HCA during pregnancy, due to scarcity of cases. The conclusion not to discourage all women with HCA from pregnancy has, however, to be proven in a large multicentre study in which we will closely monitor pregnant patient with a HCA in a prospectively acquired database to give more insight in the behaviour of HCA during pregnancy. We hypothesized that pregnancy may be allowed in case of one or more known HCA < 5 cm, because HCA < 5 cm will not disturb the course of pregnancy. Whether it is justified to deny a young woman a pregnancy, as the biological behavior may be less threatening than presumed will be investigated in the 'Pregnancy And Liver adenoma Management' (PALM)-study.

The safety and efficacy of RFA for the treatment of HCA and liver adenomatosis (≥ 10 HCA) [7] is investigated in **chapter 5**. Minimal invasive treatment like RFA has provided to be safe and can be used effectively in the treatment of HCA. However, multiple ses-

sions are often required, and signs of residual HCA might persist in some patients despite repetitive treatment. Although surgical resection is the treatment of choice in many patients, RFA could be applied selectively for the treatment of HCA in patients not amenable for surgery due to the extensive involvement of the liver (e.g. liver adenomatosis) in patients who would require major hepatic resection otherwise or in patients with multiple right-sided lesions or patients with multiple HCA in both lobes of the liver. Moreover, RFA might also be useful for centrally located HCA in the liver. However, which patients should undergo surgical treatment and which patients should not remains a topic largely open for debate.

As previous said, HCA can be complicated by hormone induced growth and subsequently spontaneous rupture and bleeding of the tumor. **Chapter 6** describes a systematic review on the risk estimate for hemorrhage and rupture as reported in the literature. Hemorrhage and rupture is a common complication in patients with HCA. Hemorrhage was reported with an overall frequency of 27.2% of cases, and in 15.8% of the total number of HCA lesions. In 17.5% of cases rupture and intraperitoneal bleeding were reported. The risk of hemorrhage and rupture in HCA < 5 cm seems small. Prospective multicenter studies are warranted to establish the actual risk of hemorrhage and rupture for each subgroup of HCA as mentioned in **chapter 3** and to identify those patients who require aggressive treatment.

Last years great progress has been made in the area of HCA, especially regarding the pathological subtype classification, radiologic imaging and management of HCA during pregnancy. However, defining the right management strategy, once the diagnosis of HCA has been established, may be challenging. **Chapter 7** describes the current knowledge about diagnosis and treatment modalities of HCA and a decision-making model for HCA is proposed. However, in the near future new variables e.g. pathological subtypes, bleeding risks, age, pregnancy and multiple HCA should be included for more personalized medicine.

In **chapter 8** the studies performed in **chapter 2–7** are discussed. In addition, directions for further studies are pointed out.

CONCLUSIONS

Chapter 2: The management of HCA in the Netherlands is rather uniform, except in complex cases in which multiple factors may influence policy.

Chapter 3: Subtype classification of HCA has implications for treatment and follow-up.

Chapter 4: A 'wait and see' management may be advocated in pregnant women presenting with HCA < 5 cm in diameter.

Chapter 5: RFA can be used effectively in the treatment of HCA.

Chapter 6: Hemorrhage and rupture is a common complication in patients with HCA. However the risk of hemorrhage and rupture in HCA < 5 cm seems small.

Chapter 7: There is a great development in the field of HCA, especially in case of radiology, pathology and management during pregnancy. A decision-making model is proposed based on the current knowledge.

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Nederlandse samenvatting en conclusies

SAMENVATTING

In **hoofdstuk 2** onderzochten we de huidige "expert opinies" met betrekking tot de diagnostiek en behandeling van het hepatocellulair adenoom (HCA) in Nederland. We concludeerden dat het beleid betreffende HCA in Nederland redelijk eenduidig is, behalve in situaties waarin meerdere factoren een rol spelen zoals bloeding, een zwangerschapswens of multipele laesies. In de meeste ziekenhuizen werd het beleid na multidisciplinair overleg bepaald. De diagnose werd gebaseerd op multifasische spiraal computed tomography (CT)- of magnetic resonance imaging (MRI)-series na contrast-toediening. Alle patiënten werd geadviseerd pilgebruik te staken en minstens één maal radiologische controle met MRI, CT of echografie uit te laten voeren. In alle ziekenhuizen had een conservatief beleid de voorkeur in die situaties waarbij het adenoom een diameter had kleiner dan 5 cm. Een tumorgrootte > 5 cm en buikklachten waren redenen om te reseceren. Echter, soms werd een resectie uitgevoerd indien er sprake was van een zwangerschapswens, kans op maligne ontaarding, groei van de tumor of indien er sprake was van twijfel aan de diagnose. Zwangerschap werd in de meeste klinieken niet afgeraden, echter een meerderheid van de centra koos toch voor invasieve therapie voorafgaand aan de zwangerschap om het risico op hormoon geïnduceerde ruptuur en bloeding teniet te doen. Naar onze mening lijkt het niet gerechtvaardigd om alle vrouwen met HCA < 5 cm een zwangerschap te onthouden. Er zijn geen gerandomiseerde gecontroleerde studies beschikbaar die een wetenschappelijke onderbouwing tonen voor de behandeling van HCA in verschillende omstandigheden. Daarnaast is het management van individuele patiënten vooral afhankelijk van het inzicht van de behandelende artsen. De behoefte aan een helder besluitvormingsmodel ligt voor de hand. Daarom moet toekomstig onderzoek zich richten op het management van HCA bij patiënten met multipele HCA, HCA > 5 cm, zwangerschap en bloedende laesies.

In **hoofdstuk 3** hebben we leveradenomen onderverdeeld in subgroepen op basis van pathologische bevindingen en onderzochten we de mogelijkheid om de pathologische bevindingen te correleren aan radiologische karakteristieken van state-of-the-art MRI. Recent is een moleculair and pathologisch classificatie systeem voor HCA ingevoerd door de Bordeaux groep. HCA werden onderverdeeld in vier grote subgroepen gebaseerd op morfologische criteria, moleculaire karakteristieken en door het gebruik van een panel van immunohistochemische markers [1-3]. We valideerden het classificatie systeem op 57 HCA laesies en concludeerde dat subtype classificatie door middel van morfologie en aanvullende immunohistochemische markers mogelijk is in > 90% van de HCA. Per

patiënt kunnen HCA van verschillende subtypen voorkomen. Focaal nodulaire hyperplasie (FNH) kan met hoge betrouwbaarheid worden aangetoond door gebruikt te maken van glutamine synthetase (GS), wat een typisch 'kaart-achtig' aankleuringspatroon van GS vertoont in het geval van FNH. De identificatie van β-catenine positieve laesies is van groot belang omdat β-catenine positieve laesies een kans op maligne transformatie lijken te hebben [4-6]. Echter interpretatie van nucleaire aankleuring van β-catenine kan moeilijk zijn doordat het aantal positieve cellen beperkt is en de aankleuring focaal is. Hierbij is moleculaire diagnostiek aanbevolen.

We confirmeerden specifieke MRI kenmerken die kunnen worden gebruikt voor de identificatie van de verschillende subgroepen van HCA, vooral voor het inflammatoire en L-FABP-negatieve HCA subtype. Het L-FABP-negatieve subtype kan met hoge betrouwbaarheid worden herkend en presenteert zich met diffuse afname in signaal intensiteit op 'uit fase' signaal beelden vanwege de aanwezigheid van vet in de laesie. In de helft van de inflammatoire adenomen vonden we een typische 'atol' teken op de MRI, gekenmerkt door een hyperintense signaal band op T2-gewogen pulse sequenties in de periferie van de laesie (zoals een atol) en iso-intensiteit van het centrum van de laesie ten opzichte van de omgeven lever (zoals de omgeven zee). De aanwezigheid van een typisch vaag afgebakend litteken in het HCA was significant geassocieerd met nuclaire aankleuring van β-catenine. In deze casus is chirurgische resectie of strikte follow-up aanbevolen. De klinische consequenties van de pathologische subtype classificatie voor de behandeling en follow-up moet worden vastgesteld. Een multicenter studie is wenselijk om specifieke klinische en pathologische kenmerken voor elk subtype te onderzoeken en om richtlijnen vast te stellen voor het management van elke individuele patiënt.

Er wordt gedacht dat HCA kan worden gecompliceerd door hormoon geïnduceerde groei en vervolgens spontane hemorragische ruptuur. In **hoofdstuk 4** hebben we voorgesteld niet alle vrouwen met een HCA een negatief zwangerschapsadvies te geven, gebaseerd op een studie waarin we twaalf vrouwen vervolgden met gedocumenteerde HCA gedurende een totaal van 17 zwangerschappen. In 4 casus was er sprake van groei van het HCA gedurende de zwangerschap. In 1 patiënt (2 zwangerschappen) resulteerden dit in een sectio caesarea en in 1 patiënt werd radiofrequente ablatie (RFA) therapie toegepast in het eerste trimester van de zwangerschap. Alle zwangerschappen hadden een gunstig verloop en een succesvolle maternale en foetale uitkomst. Door de schaarste aan zwangere patiënten met HCA is er echter geen evidence-based algoritme voor de evaluatie en het management van HCA gedurende de zwangerschap. De conclusie om niet alle vrouwen met HCA een zwangerschap te onthouden moet dan ook worden bewezen in een grote multicenter studie. In deze studie zullen wij zwangere patiënten met HCA nauwlettend volgen om meer inzicht te krijgen in het gedrag van HCA gedurende de zwangerschap. We maken hierbij gebruik van een prospectief verkregen database.

De hypothese is dat zwangerschap gerechtvaardigd is in geval van één of meerdere HCA < 5 cm, omdat HCA < 5 cm het verloop van de zwangerschap niet zal verstoren. Of het gerechtvaardigd is om een jonge vrouw een zwangerschap te ontraden, terwijl het biologisch gedrag minder bedreigend is dan wordt vermoed, zal worden onderzocht in de 'Pregnancy And Liver adenoma Management' (PALM)-studie.

We onderzochten de veiligheid en werkzaamheid van RFA voor de behandeling van HCA en lever adenomatosis (≥ 10 HCA) [7] in **hoofdstuk 5**. Een minimaal invasieve behandeling zoals RFA is veilig en effectief in de behandeling van HCA. Echter, er zijn vaak meerdere sessies nodig en er kan resterend HCA weefsel persisteren in sommige patiënten ondanks herhaalde behandeling. Hoewel chirurgische resectie de behandeling van keuze is bij veel patiënten, kan RFA selectief worden toegepast voor de behandeling van HCA bij patiënten die niet vatbaar zijn voor een operatie als gevolg van grote betrokkenheid van de lever (bijv. lever adenomatosis) en dus een grote leverresectie zouden moeten ondergaan, bij patiënten met meerdere rechtszijdige laesies of patiënten met multiple HCA in beide leverlobben. Daarnaast kan RFA ook de aangewezen therapie zijn voor centraal gelegen HCA in de lever. Welke patiënten een chirurgische behandeling moeten ondergaan en welke patiënten niet blijft echter een onderwerp open voor discussie.

Zoals eerder beschreven kan HCA worden gecompliceerd door hormoon geïnduceerde groei en vervolgens ruptuur en bloeding van de tumor. **Hoofdstuk 6** beschrijft een systematisch review over de risico-inschatting voor bloeding en ruptuur zoals gerapporteerd in de literatuur. Bloeding en ruptuur is een veel voorkomende complicatie bij patiënten met HCA. Bloeding werd beschreven in 27,2% van de patiënten, en in 15,8% van het totaal aantal HCA laesies. In 17,5% van de patiënten was er sprake van ruptuur en intraperitoneale bloeding. Het risico op bloeding en ruptuur in HCA < 5 cm lijkt klein. Een prospectieve multicenter studie is nodig om het werkelijke risico op bloeding en ruptuur voor elke subgroep van HCA, zoals vermeld in **hoofdstuk 3**, te bepalen en om vast te stellen welke patiënten met HCA een agressieve behandeling dienen te ondergaan.

De afgelopen jaren is er grote vooruitgang geboekt op het gebied van HCA, vooral wat betreft de pathologische subtype classificatie, radiologische beeldvorming en het management van HCA gedurende de zwangerschap. Het bepalen van de juiste managementstrategie zodra de diagnose HCA is gesteld kan echter een uitdaging zijn. **Hoofdstuk 7** beschrijft de huidige kennis over de diagnose en de behandelingsmodaliteiten van HCA. Daarnaast is een beslissingsmodel voor HCA voorgesteld. In de nabije toekomst moeten echter nieuwe variabelen zoals pathologische subtypes, bloeding

risico's, leeftijd, zwangerschap en multipele HCA worden opgenomen voor een meer geïndividualiseerd beleid.

In **hoofdstuk 8** worden de bevindingen uit de **hoofdstukken 2–7** bediscussieerd. Tevens worden enkele aanknopingspunten voor verder onderzoek gegeven.

CONCLUSIES

Hoofdstuk 2: Het beleid van HCA in Nederland is eenduidig, behalve in complexe casus waarin meerdere factoren van invloed kunnen zijn op het beleid.

Hoofdstuk 3: Subclassificatie van HCA maakt het mogelijk beleid voor behandeling en follow-up beter te definiëren.

Hoofdstuk 4: Een afwachtend beleid is gerechtvaardigd bij zwangere vrouwen die zich presenteren met HCA < 5 cm in diameter.

Hoofdstuk 5: RFA kan effectief worden gebruikt bij de behandeling van HCA.

Hoofdstuk 6: Bloeding en ruptuur is een veel voorkomende complicatie bij patiënten met HCA. Het risico op bloeding en ruptuur in HCA < 5 cm lijkt echter klein.

Hoofdstuk 7: Er is een belangrijke ontwikkeling op het gebied van HCA, in het bijzonder wat betreft radiologie, pathologie en het management van HCA gedurende de zwangerschap. Een besluitvormingsmodel is voorgesteld op basis van de huidige kennis.

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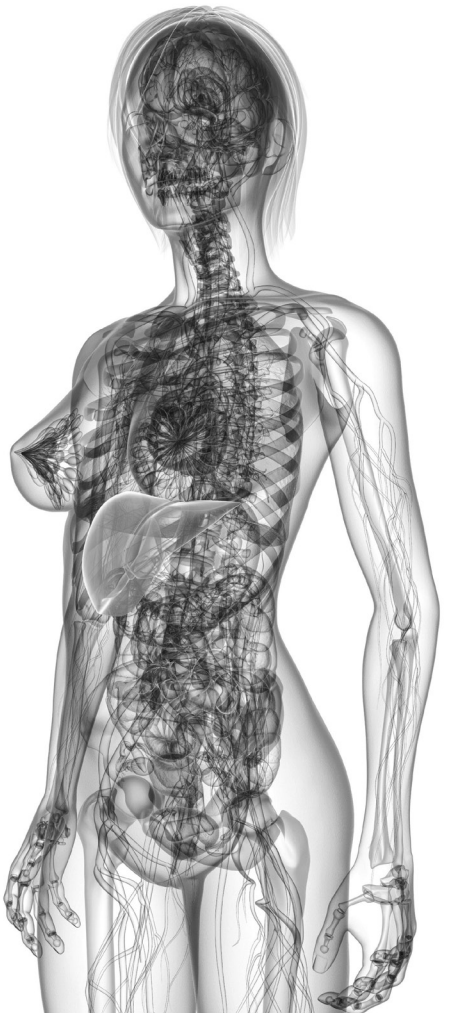
Chapter 10

Dankwoord

List of publications

Curriculum Vitae

PhD portfolio



Dankwoord

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List of publications

1. **S.M. van Aalten**, T. Terkivatan, R.A. de Man, D.J. van der Windt, N.F.M. Kok, R.S. Dwarkasing, J.N.M. IJzermans. Diagnosis and treatment of HCA in the Netherlands: Similarities and differences. Digestive Surgery 2010; 27(1):61-7.

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3. **S.M. van Aalten**, J. Verheij, T. Terkivatan, R.S. Dwarkasing, R.A. de Man, J.N.M. IJzermans. Validation of a liver adenoma classification system in a tertiary referral centre: Implications for clinical practice. Journal of Hepatology 2011; 55(1):120-5.

4. **S.M. van Aalten**, T. Terkivatan, E. van der Linden, J. Verheij, R.A. de Man, J.N.M. IJzermans. Management of liver adenoma by radiofrequency ablation. Digestive Surgery 2011; 28(3):173-7.

5. **S.M. van Aalten**, M.G. van Vledder, T. Terkivatan, R.A. de Man, T. Leertouwer, J.N.M. IJzermans. Safety and efficacy of radiofrequency ablation for hepatocellular adenoma. Journal of Vascular and Interventional Radiology 2011; 22(6):787-93.

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Curriculum vitae

Susanna Maria (Sanne) van Aalten was born on March 30th 1984 in Breda, The Netherlands. After graduation from high school at the Nassau secondary school in Breda in June 2002, she started medical school at the Erasmus University Rotterdam. During her study she did an internship at the Department of Surgery of the Sardjito General Hospital in Yogyakarta, Indonesia and she conducted research at the Msambweni District Hospital in Msambweni, Kenya. In March 2009, she graduated from medical school, after which she started working as a surgical resident at the Department of Surgery of the Erasmus University Medical Center in Rotterdam (prof.dr. J.J.B. van Lanschot). In October 2009 she started as a PhD student at the Department of Surgery at the Erasmus University Medical Center in Rotterdam, under supervision of prof.dr. J.N.M. IJzermans and dr. R.A. de Man, which has resulted in this thesis. From June 2011 until December 2011 she worked as a surgical resident at the Department of Surgery at the Maasstad Hospital in Rotterdam (dr. E. van der Harst). In January 2012 she started her general surgical training at the IJsselland Hospital in Rotterdam (supervisors: dr. I. Dawson and prof.dr. J.N.M. IJzermans).

PhD Portfolio

Summary of PhD training and teaching

Name PhD student: Susanna Maria van Aalten
Erasmus MC Department: Surgery

PhD period: Okt 2009 – Dec 2011
Promotor: Prof.dr. J.N.M. IJzermans
Supervisor: Dr. R.A. de Man

1. PhD training	Year	Workload (ECTS)
General courses		
Introduction to clinical research	2010	0.9
Biostatistics for clinicians	2010	1.0
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2010	1.0
Seminars and workshops		
Journal club	2009-2011	3.0
CPO Minicursus voor Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen	2010	0.3
Schrijven van een wetenschappelijke publicatie	2010	0.3
Presentations		
National conferences	2009	2.0
National conferences	2010	4.0
International conferences	2010	7.0
National conferences	2011	2.0
International conferences	2011	5.0

2. Teaching	Year	Workload (ECTS)
Lecturing		
Lecturing at department of pathology	2010	0.5
Supervising practicals and excursions, Tutoring		
Examination of Basic Life Support (EHBO) of medical students	2009-2010	1.0