MANAGEMENT OF BENIGN LIVER TUMORS
BEYOND CURRENT GUIDELINES

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"Come on now, all you young men, all over the world. You are needed more than ever now to fill the gap of a generation shorn by the War. You have not an hour to lose. You must take your places in Life's fighting line. Twenty to twenty-five! These are the years! Don't be content with things as they are. 'The earth is yours and the fulness thereof.' Enter upon your inheritance, accept your responsibilities . . . Don't take No for an answer. Never submit to failure. Do not be fobbed off with mere personal success or acceptance. You will make all kinds of mistakes; but as long as you are generous and true, and also fierce, you cannot hurt the world or even seriously distress her. She was made to be wooed and won by youth. She has lived and thrived only by repeated subjugations."

Sir Winston S. Churchill

My Early Life (1930)

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CHAPTER 1

General Introduction and Outline of the Thesis

Benign liver tumors

In recent years, the increased use and accuracy of diagnostic imaging has contributed significantly to the rising diagnosis of hepatic incidentalomas – incidentally diagnosed tumors which occur in about 15% of all people. Hepatic incidentalomas are observed in up to a third of individuals over 40 years old.[1–3] The majority of hepatic incidentalomas have limited clinical significance as they are benign and include hepatic cysts, focal fatty sparing, and benign liver tumors (BLT).[2] BLT comprise a heterogeneous group of tumors with distinct cellular origins, characterized by non-metastasizing, and non-invasive behavior – the tumors do not grow outside the liver invading other organs or spread through the body via the circulatory or lymphatic system. Most common BLT are hepatic hemangioma, focal nodular hyperplasia (FNH), and hepatocellular adenoma (HCA), which differ extensively in their clinical consequences.[3]

Complications, and hence clinical significance, of hepatic hemangiomas and FNH are limited.[4–8] Neither hemangioma nor FNH have a potential for malignant transformation, and they are both insensitive to steroid hormones such as estrogen and testosterone. Hepatic hemangiomas have an extremely rare risk of hemorrhage due to blunt trauma-induced tumor rupture.[9–11] Another important but very uncommon, complication is a consumptive coagulopathy (Kasabach-Merritt syndrome) caused by giant hemangiomas (≥10 cm).[9] Although not lethal, hemangiomas or FNH may sometimes cause abdominal discomfort and nausea by compression of gastrointestinal organs, potentially impairing patient's quality of life (QoL).[9,10]

Hepatocellular adenoma

History and epidemiology of HCA

The most clinically relevant BLT are HCA. HCA were first discovered in 1958 by Hugh A. Edmondson, when he discovered two HCA after 50 000 autopsies.[12] In 1973, Baum *et al.* were the first to potentially relate estrogen suppletion (by use of the oral contraceptive pill; OCP) with HCA formation.[13] After several case reports, Edmondson's case-control series definitely proved the estrogen-HCA relationship in 1976.[14–16] In 1977, Edmondson was also the first to publish observations of HCA regression after

the stop of OCP use, laying the cornerstone for conservative HCA management.[17] True HCA occurrence remains unclear, although the prevalence is estimated around 1:250 – 1:1 000, with an incidence of 3-4:100 000.[18–20] Most HCA are diagnosed in women aged 20-30 years, and occur about ten-fold more often in females than in males. A 30-40-fold increase of incidence is seen after chronic (>2 years) OCP use.[20,21]

HCA subtypes – a Janus-faced benign liver tumor

There are distinct HCA subtypes with individual risk profiles. HCA subtypes are diagnosed on histopathology through immunohistochemistry (IHC) or molecular analysis by next generation sequencing (NGS).[22,23] The latter has a higher sensitivity and is able to objectify mutations undetected by IHC.[24] Inflammatory HCA (I-HCA; 30-40%), mainly co-occur with obesity and/or metabolic syndrome.[22] Hepatocyte nuclear factor 1a (*HNF1A*) inactivated HCA (H-HCA; 30-40%) rarely bleed or show malignant transformation. *CTNNB1* mutated HCA (b-HCA; 10%) are at increased risk for malignant transformation to HCC, occur more often in men, and half of b-HCA are hybrid b-catenin/inflammatory HCA (b-IHCA).[22] B-HCA occur more often in males, and male sex is an independent additional driver of HCC formation, hence invasive treatment is recommended for HCA in male patients.[22] Finally, sonic hedgehog and roof plate spondin-2 HCA subtypes have recently been identified, each of which with a distinct clinical risk profile.[22,25] The remainder of HCA which cannot be differentiated (yet) are characterized as unclassified HCA (U-HCA; ±10%).

HCA etiology – key to formation and management strategy

Prolonged estrogen or testosterone exposure (*e.g.* OCP or androgenic steroids in obesity or by supplementation) is a key risk factor for HCA formation and growth.[16,22,26] The respective natural increase and reduction of estrogen during pregnancy and after onset of menopause can also increase or reduce HCA size.[27,28] Current clinical practice guidelines by the European Association of the Study of the Liver (EASL) discourage invasive treatment in HCA <5 cm, due to the limited risk of complications.[29] In HCA

≥5 cm the EASL guideline advises to await estrogen reducing lifestyle advices for six months, before escalating to (minimally) invasive treatment in HCA remaining ≥5 cm.[29]

HCA, and especially HCA ≥5 cm, are associated with (potentially severe) hepatic hemorrhage (10-15%), and transformation into hepatocellular carcinoma (HCC; 1.6%).[16,23,30,31] In addition to tumor size ≥5 cm, risk of HCA bleeding is increased in case of exophytic tumor growth, or when the tumor is located in the left lateral liver segments.[31] Risk of malignant transformation is enhanced by male sex, tumoral beta-catenin (*CTNNB1*) mutations, and telomerase reverse transcriptase promotor mutations.[22,30]

HCA are also known to occur in context of metabolic disease, such as glycogen storage disease (GSD). There are seven hepatic subtypes of GSD (0, Ia, Ib, III, VI, IX and XI), of which GSD type Ia (GSDIa) is the most common GSD subtype in the European population, with an incidence of 1:100 000.[32,33] GSDIa is a rare, inborn error of carbohydrate metabolism caused by mutations in the glucose-6-phosphatase catalytic subunit 1 (*G6PC1*) gene.[34,35] The GSDIa phenotype is characterized clinically with fasting intolerance, hepatomegaly and failure to thrive and biochemically with non-ketotic hypoglycemia, and hypertriglyceridemia. GSDIa patients, and especially patients with high serum triglyceride (TG) concentrations (>500 mg/dL or 5.65 mmol/L) are prone to HCA development.[36] No data is available on the association of *G6PC1* variants, or sex, and TG on HCA development, and the interaction between those potential risk factors. HCA are also described in GSDIb and GSDIII, albeit very rare.[37] Other GSD subtypes are not associated with HCA.

Another metabolic disease associated with HCA is *HNF1A*-associated maturity onset diabetes of the young (MODY), in which solely H-HCA are seen.[22] Although adenomatosis (presence of 10 or more HCA) can occur in all HCA subtypes, adenomatosis is especially associated with inherited metabolic disorders such as HNF1A-MODY and GSD1a.[38] Although GSDIa and HNF1A-MODY typically present during early childhood and adolescence, respectively, both may present at an adult age with mild metabolic symptoms, and should therefore always be considered in patients with hepatic adenomatosis.[39,40] Limited data on bleeding or malignant risk of HCA in the context of GSD and HNF1A-MODY are available, and an alternative management algorithm than currently used in non-metabolic-associated HCA might be needed.

BLT treatment options

Current European clinical practice guidelines from the European Association for the Study of the Liver (EASL) have been published in 2016 and provide clear and concise recommendations for BLT management.[29] The EASL clinical practice guideline recommends that MRI should be used for non-invasive tumor differentiation because of diagnostic accuracy. In addition, the guideline recommends that diagnosis and treatment of BLT should be managed by a multidisciplinary team (MDT) which includes a hepatologist, hepatobiliary surgeon, diagnostic and interventional radiologist, and pathologist, all with sufficient experience in BLT management.

The EASL guideline states that FNH rarely need treatment – OCP can safely be continued, and there is no contra-indication for pregnancy. Biopsy may be indicated for atypical tumors but only after MDT consultation. FNH should only be resected when causing mechanical complaints or in exceptional cases such as pedunculated, expanding, or exophytic growth. Follow-up is unnecessary when FNH are asymptomatic, irrespective of sex.

Accurate discrimination between HCA and FNH is of utmost importance as clinical and hence treatment consequences are divergent. High diagnostic sensitivity and specificity are obtained by contrast-enhanced magnetic resonance imaging (CE-MRI) with liver-specific contrast agents: respectively 92-96.9% and 91-100%, irrespective of tumor size.[41,42] Contrast-enhanced ultrasound (CEUS) has been reported to improve the specificity of CE-MRI (especially when using extracellular contrast agents) in small FNH (<3 cm).[43,44]

The current European clinical practice guideline acknowledges that HCA subtype diagnosis on CE-MRI is possible, yet histopathology remains the standard – especially for b-HCA and b-IHCA.[29] HCA treatment decisions are based on patient sex, HCA size and behavior, and HCA subtype, when available (**Figure 1**). Females diagnosed with HCA ≥5 cm are recommended to cease use of OCP and reduce overweight for six months, when applicable. Invasive treatment (*i.e.* transarterial embolization, percutaneous ablation, or resection) is advised if HCA size remains ≥5 cm or if ≥20% diameter growth is observed.[29] Invasive treatment is also indicated in all HCA in male patients and for b-HCA/b-IHCA. Stable HCA <5 cm do not require invasive

treatment and should be followed on an annual basis. HCA-induced hepatic bleeding with hemodynamic instability should be embolized and treated invasively if any viable HCA is observed during follow-up. HCA during pregnancy should be followed by US every 6-12 weeks, and non-exophytic HCA <5 cm do not necessitate elective cesarean section.[29]

Although the clinical practice guideline covers a multiplicity of subjects, several potential lacunas are present, which include safety and behavior of HCA ≥5 cm during pregnancy, specific recommendations on HCA due to metabolic diseases such as GSD, safety and behavior of HCA after ceasing OCP intake, and data on surgical outcomes after BLT resection. There are also no data on the current European management practices, and individual approaches of European experts to particular clinical FNH and HCA situations. Frequency and indication for resection of HCA, and specifically HCA <5 cm, have also not yet been evaluated.

Outline of the thesis

The significant intra- and intertumoral differences between the aforementioned BLT, and many nuances in BLT management, necessitate clear and ever improving clinical practice guidelines. Although clinicians are often determined not to undertreat (*e.g.* failing to perform invasive treatment whilst indicated) a BLT patient, overtreatment is equally wrong – especially for often relatively harmless tumors in young patients. Acquisition of novel data, continuing on previous work of scientific predecessors, is key to the evolution of therapeutic and diagnostic practices and may assist clinicians and patients in their decision-making process.

This thesis expands on multiple aspects of BLT management, in particular for HCA, beyond the current guidelines. These aspects include an analysis of current guidelines, management of BLT by European experts, conservative treatment of HCA, approach to HCA during pregnancy, surgical indications and short-term surgical outcomes of BLT, HCA in context of GSDIa, and BLT-QoL interaction. The thesis concludes with a general discussion of its content and exploration of future research areas in the BLT field.

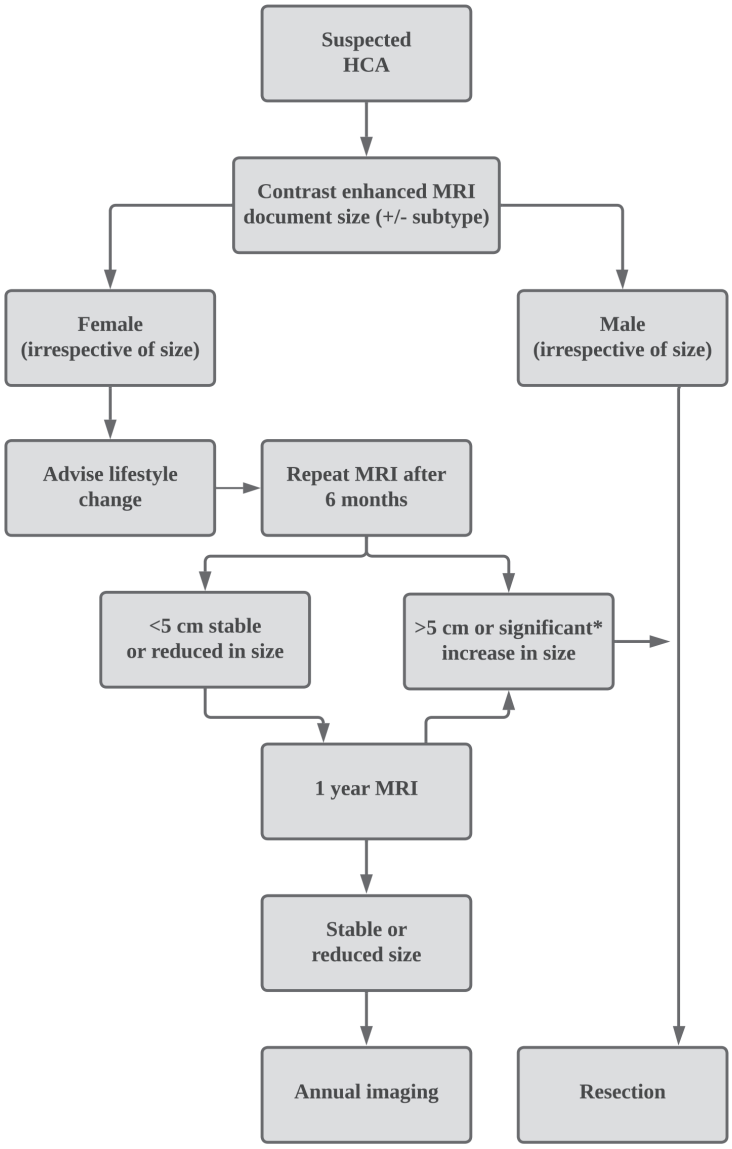

Figure 1. Management of HCA according to current European guidelines. *Significant increase in size is defined as ≥20% diameter. Abbreviations: HCA, hepatocellular adenoma.[29]

Management of BLT has many nuances and often multiple management strategies are feasible. In addition, current evidence is mostly retrospective of nature which compounds into potential international practice variation. **Chapter 2** provides a

scoping review of available international BLT guidelines, and compares and critically appraises guideline recommendations on diagnostics, management, and follow-up of hepatic hemangioma, FNH, and HCA.

Chapter 3 investigates the current European practices in HCA & FNH management strategies. An electronic survey was distributed to European radiologists, pathologists, surgeons, and gastroenterologists/hepatologists with BLT expertise. The survey consisted of two parts, first enquiring into local practices and approaches to standard situations, and secondly presenting eight fictive clinical vignettes which require decisions on diagnostics, treatment, and follow-up.

The HCA management calculus changes significantly when a HCA patient becomes pregnant. HCA <5 cm have been shown to be managed safely by close follow-up throughout pregnancy. **Chapter 4** investigates the behavior and complications of HCA ≥5 cm during pregnancy, labor, and the postpartum period in a combined observational cohort study and systematic literature review.

Induction of HCA regression through reducing estrogen exposure and lifestyle changes has been a successful conservative treatment strategy. However, specific factors influencing tumor regression have not been identified yet. In addition, no research has been performed on the bleeding safety of the wait-and-see strategy. **Chapter 5** consists of an observational cohort study on HCA diameter after stopping OCP intake, including a multivariate analysis of factors influencing HCA regression.

In specific cases, HCA resection is the treatment of choice**. Chapter 6** investigates the indications for HCA resection, stratifying indications for HCA <5 cm and HCA ≥5 cm in a nationwide observational cohort study using data from the Dutch Hepato Biliary Audit.

GSDIa patients are at increased risk to develop HCA during adolescence and adulthood, yet data on specific risk factors are currently lacking. Using a nationwide observational study design, **Chapter 7** explores the association of sex, *G6PC1* variants, and childhood serum TG concentrations as risk factors for GSDIa related HCA formation.

Chapter 8 evaluates surgical outcomes after BLT resection in a nationwide observational cohort study using data from the Dutch Hepato Biliary Audit. The study

includes all patients who underwent hepatic resection for FNH, HCA, and hepatic hemangioma during 2014-2019. Results were stratified for open and laparoscopic surgery using multivariate analysis after propensity score matching for surgical approach.

No prospective data are available on the influence of benign liver tumors and cysts on QoL. **Chapter 9** describes the study protocol for the BELIVER study – a nationwide prospective cohort study investigating the QoL of patients with clinically relevant BLT (*i.e.* FNH, hemangioma, HCA, and simple hepatic cysts).

In **Chapter 10**, the findings presented in this thesis will be summarized and discussed, together with an exploration of future perspectives of BLT research.

A thesis summary in Dutch is presented in **Chapter 11**.

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CHAPTER 2

Scoping Review of Clinical Practice Guidelines on the Management of Benign Liver Tumors

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Unstructured abstract

Benign liver tumors (BLT) are increasingly diagnosed as incidentalomas. Clinical implications and management vary across and within the different types of BLT. High-quality clinical practice guidelines are needed, because of the many nuances in tumor types, diagnostic modalities, and conservative and invasive management strategies. Yet, available observational evidence is subject to interpretation which may lead to practice variation.

Therefore, we aimed to systematically search for available clinical practice guidelines on BLT, to critically appraise them, and to compare management recommendations in a scoping review. All BLT guidelines published in peer reviewed, and English language journals were eligible for inclusion. Clinical practice guidelines on BLT were analyzed, compared, and critically appraised using the Appraisal of Guidelines, Research and Evaluation (AGREE II) checklist regarding hepatic hemangioma, focal nodular hyperplasia (FNH), and hepatocellular adenoma (HCA). PRISMA recommendations for scoping reviews were adhered to.

Ultimately, guidelines from the American College of Gastroenterology (ACG; 2014), Brazilian Society of Hepatology (SBH; 2015), and European Association for the Study of the Liver (EASL; 2016) were included. There was no uniformity in the assessment methods for grading and gravity of recommendations between guidelines. Among observed differences were: 1) indications for biopsy in all three tumors; 2) advice on oral contraceptives and follow-up in FNH and HCA; 3) use of an individualized approach to HCA, 4) absence of recommendations for treatment of HCA in men, and 5) approaches to HCA subtype identification on magnetic resonance imaging. Recognizing these differences can assist in harmonization of practice standards and identify unmet needs in research. This may ultimately contribute to improved global patient care.

Introduction

Hepatic incidentalomas are increasingly diagnosed due to the frequent use of diagnostic imaging. These pathologies have a prevalence of about 15% in general but are observed in up to 30% of individuals older than 40 years.[1–3] The majority of hepatic incidentalomas are benign and include hepatic cysts, focal fatty sparing, and benign liver tumors (BLT).[2] BLT comprise a heterogeneous group of tumors with distinct cellular origins, characterized by non-metastasizing, non-invasive behavior. Most common BLT are hepatic hemangioma, focal nodular hyperplasia (FNH), and hepatocellular adenoma (HCA), which differ extensively in their clinical consequences.[4]

Hepatic hemangiomas are hypervascular tumors not at risk for malignant transformation.[5] Rupture is extremely unlikely, often only after blunt trauma, and is associated with high mortality.[5] Large hepatic hemangiomas (≥5 cm) can cause abdominal pain and nausea by compression, or in rare cases cause consumptive coagulopathy (Kasabach-Merritt syndrome).[5]

FNH are solitary, well-circumscribed, unencapsulated masses including a central fibrous scar and not at risk for hemorrhage or malignant transformation.[6] Oral contraceptive pill (OCP) use and pregnancy do not affect FNH size or number.[7] Highest diagnostic sensitivity and specificity are obtained by hepatobiliary contrast-enhanced magnetic resonance imaging (CE-MRI): respectively 92-96.9% and 91-100%, irrespective of size.[8,9] Contrast-enhanced ultrasound (CEUS) has been reported to improve the specificity of CE-MRI (especially when using extracellular contrast agents) in small FNH (<3 cm).[10,11]

HCA are hypervascular tumors associated with potentially lethal hemorrhage (10%), and may transform into hepatocellular carcinoma (5%).[12–14] Prolonged androgen exposure (OCP, androgenic steroids, obesity) is the major risk factor for HCA formation and growth.[12,15,16] Cessation of OCP and weight loss can induce HCA regression.[15,17] HCA subtypes are diagnosed through either immunohistochemistry or molecular analyses and have specific morphological and etiological features, clinical characteristics, and behaviors.[13,16] Inflammatory HCA (I-HCA; 40-55% of HCA), mainly co-occur with obesity and/or metabolic syndrome.[16] Hepatocyte nuclear factor 1a (*HNF1A*)

inactivated HCA (H-HCA; 30-40% of HCA) rarely bleed or show malignant transformation.[16] Adenomatosis (≥10 HCA) is associated with metabolic disorders such as *HNF1A* maturity onset diabetes of the young and glycogen storage disease (GSD).[18,19] B-catenin activated HCA (b-HCA; 10%) are at increased risk for malignant transformation to hepatocellular carcinoma (HCC) and more often occur in men. Importantly, half of b-HCA are hybrid b-catenin/inflammatory HCA (b-IHCA).[16,20] Invasive treatment is always warranted if HCA are diagnosed in men, as most HCA in men are b-HCA, and male sex is an independent additional driver of HCC formation.[16] Two additional HCA-subtypes with corresponding phenotype, sonic hedgehog and roof plate spondin-2 HCA, have been identified.[16,21] The remainder are characterized as unclassified (U-HCA). Some reports have been able to differentiate HCA subtypes on CE-MRI, although no specific characteristics for b-HCA have yet been identified.[22,23]

The aforementioned intra- and intertumoral differences necessitate clear and consistent clinical practice guidelines to prevent (inter)national practice variation. Determining differences between current guidelines can provide a framework for practice standard harmonization, identify unmet needs in research, and ultimately contribute to improved patient care. Until now, it is unclear how many clinical practice guidelines on BLT management are available, what the quality of available guidelines is, and to what extent management recommendations differ. Therefore, we aimed to systematically search for available clinical practice guidelines on BLT, to critically appraise them, and to compare management recommendations in a scoping review.

Methods

A scoping literature review was performed including clinical practice guidelines on the management of BLT. Guidelines specifically developed for imaging or on gastroenterological pathologies in a specific context (*i.e.* pediatric population or pregnancy) were excluded. The review was performed according to the extended PRISMA recommendations for scoping reviews.[24] No formal review protocol was drafted prior to execution of the study.

Literature search

A systematic literature search was performed by two investigators using appropriate pre-specified search terms within the bibliographic databases of MEDLINE, EMBASE, and Web of Science, from inception, with the latest search on March 31st 2021. Only peer reviewedf papers (no pre-print), and only English articles were included. Reference lists of finally included papers were hand searched. Literature search and screening, and data extraction and appraisal were performed in duplicate by M.P.D.H. and V.E.D.M. A third reviewer (R.J.D.H.) was consulted for resolving any discrepancies.

Data extraction and critical appraisal

Guideline recommendations and recommendation strength were extracted and structured according to either recommendations in the applied systems of evidence grading or 'in text conclusions'. Oxford levels of evidence grade I was regarded as high-quality research, grade II-1 & II-2 as moderate quality, grade II-3 as low quality, and grade III as very low quality.[25] Guidelines were appraised with the Appraisal of Guidelines, Research and Evaluation (AGREE II) checklist.[26] AGREE II contains 23 items scored one (strongly disagree) to seven (strongly agree) points. Items span six domains: scope & purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence and an overall assessment. Scaled domain scores were calculated according to protocol by two reviewers.[26] A third reviewer was consulted in for resolving any points of discussion between the two reviewers.

Results

Quantity and quality of evidence

MEDLINE, EMBASE, and Web of Science queries provided 78, 189, and 176 results, respectively, leading to 367 original articles (**Figure 1**). Seventy-six duplicates were removed. Screening of titles and abstracts, resulted in exclusion of 348 publications. Full text screening of the 19 remaining publications lead to further exclusion of 16 publications. Three guidelines were identified: American college of gastroenterology

(ACG) clinical guideline "diagnosis and management of focal liver lesions" (2014), "diagnosis and treatment of benign liver nodules: Brazilian society of hepatology (SBH) recommendations" (2015), and European association for the study of the liver (EASL) "clinical practice guideline on the management of benign liver tumors" (2016).[27–29] Reference lists of the identified and included papers were hand searched but no additional clinical practice guidelines could be identified.

The AGREE II domain scores favored the EASL guideline in four out of six domains (**Figure 2**).[26] Two guidelines indicated grade and gravity of recommendations (**Table 1**). The ACG guideline used the four level Grading of Recommendations Assessment, Development, and Evaluation system[30] and used ACG guideline standards and Practice Parameters Committee guidance. The ACG guideline also stated used databases and search terms and specific author contributions. The EASL stated adoption from the GRADE system but practically used the five level U.S. Preventive Services Task Force scale with comparable definitions.[31] The EASL and SBH guidelines did not specify search terms or used databases. None of the guidelines presented a flow chart of the literature review results. All guidelines provided both explicit recommendations and in text advice.

Content of the guidelines

The ACG guideline included literature up to June 2013 on both benign and malignant liver tumors. Discussed benign entities are hepatic hemangioma, FNH, HCA, focal regenerative hyperplasia, simple hepatic cysts, biliary cystadenomas, polycystic liver disease, and hydatid cysts.[28] The SBH guideline did not mention a literature study timeframe; the most recent included publication dates September 2014. It includes hepatic hemangioma, FNH, HCA, simple hepatic cysts, hydatid cysts, cystadenomas, and polycystic liver disease.[27] The EASL guideline did not mention the time frame of the literature study either but included studies published up to July 2015.[29] It focused on hepatic hemangioma, FNH, and HCA. Nodular (or focal) regenerative hyperplasia is mentioned but referred to alternate reviews for recommendations on diagnostic features and management. It was the only guideline recommending use of a benign liver tumor

multidisciplinary team consisting of a hepatologist, hepatobiliary surgeon, diagnostic and interventional radiologists, and pathologist.

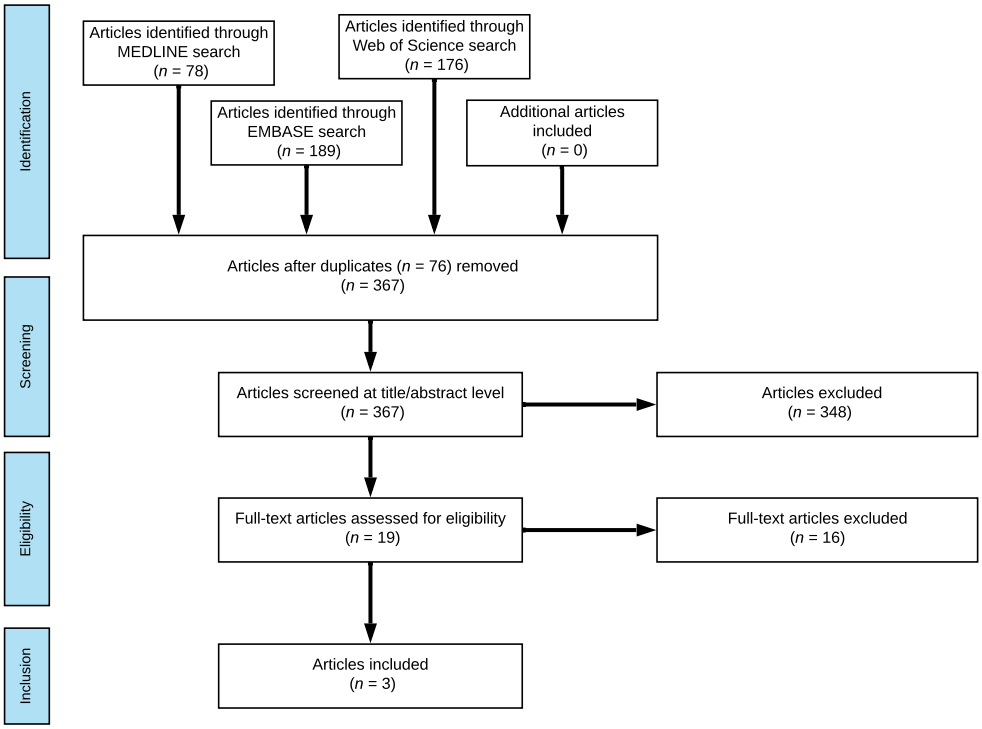

Figure 1. Flowchart of systematic literature search.

Hepatic hemangioma

The ACG and SBH guidelines discouraged percutaneous needle biopsy due to bleeding risk, in contrast to the EASL guideline (**Table 2**). Indications for surgical intervention differed slightly, as ACG guidelines included consideration of hemangiomas ≥10 cm, whilst the other guidelines only included surgery for symptomatic tumors. Follow-up recommendations were similar in ACG and EASL guidelines. The SBH guideline recommended follow-up through US in large hemangiomas and in pregnant patients. The SBH guideline was the only guideline to suggest liver transplantation as option for surgical treatment.

Table 1: Comparison of methodology in grading of evidence and strength of recommendation

	System for grading of evidence		
	ACG (2014)[25]	***SBH (2015)***[24]	***EASL (2016)***[27]
	High quality: Further research unlikely to change confidence of effect	No grading system applied	Grade I: Randomized, controlled trials
	Moderate quality: Further research likely to change the confidence in the estimate of the effect and may change the estimate		Grade II-1: Controlled trials without randomization
			Grade II-2: Cohort or case-control analytical series
	Low quality: Further research is very likely to change confidence in the estimate of the effect and likely to change the estimate		Grade II-3: Multiple time series, dramatic uncontrolled experiments
	Very low quality: Any estimate of effect is very uncertain		Grade III: Opinions of respected authorities, descriptive epidemiology
	Type and strength of recommendation		
R		Recommendations without definition of gravity	
S	"Factors influencing the strength of the recommendation include the quality of the evidence, presumed patient-important outcomes, and cost."	N/A	"The desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not."
W	"Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty: higher cost or resource consumption"	N/A	"The tradeoffs are less certain between the desirable and undesirable effects of an intervention."
t	In text conclusion	In text conclusion	

Abbreviations: ACG, American college of gastroenterology; SBH, Brazilian society of hepatology; EASL, European association for the study of the liver; S, strong recommendation; W, weak recommendation/ conditional recommendation.

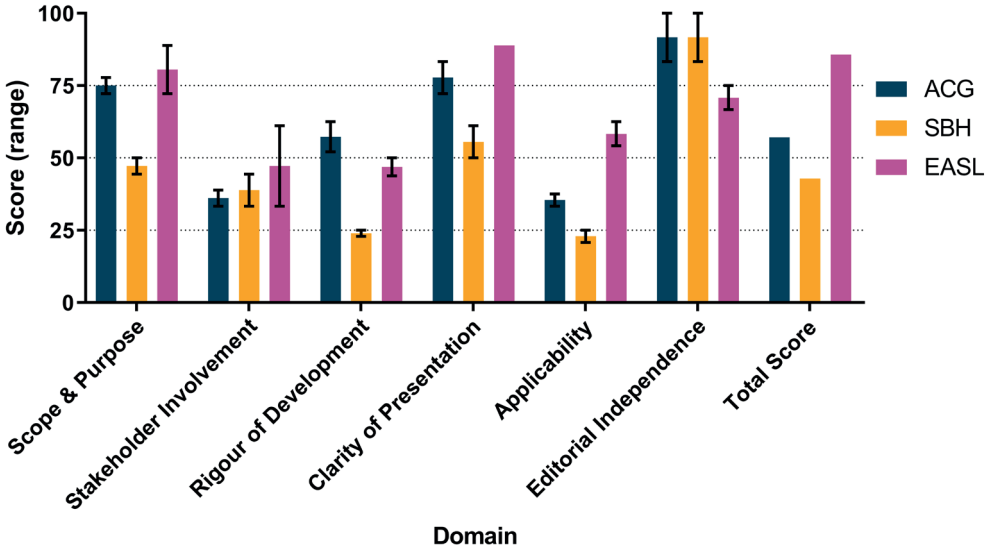

Figure 2. Agree II Scores of guidelines on benign liver tumors. AGREE II scores per domain as assessed by two reviewers. Domain scores calculated as instructed in AGREE II protocol.[26] Abbreviations: ACG, American college of gastroenterology; SBH, Brazilian society of hepatology; EASL, European association for the study of the liver.

Table 2: Comparison of guideline recommendations on hepatic hemangioma

	ACG (2014)[25]		*SBH (2015)*[24]		*EASL (2016)*[27]
Diagnostics	**S**	An MRI or CT scan should be obtained to confirm a diagnosis of hemangioma.	**R**	A finding on hepatic nodule(s) consistent with hemangioma on ultrasound should be confirmed by contrast-enhanced CT or MRI	**S**	In patients with a normal or healthy liver, a hyperechoic lesion is very likely to be a liver haemangioma. With typical radiology (homogeneous hyperechoic, sharp margin, posterior enhancement, and absence of halo sign) in a lesion less than 3 cm, ultrasound is sufficient to establish the diagnosis.
					S	In oncology patients or those with underlying liver disease, contrast enhanced imaging (CEUS, CT or MRI) is required.
			R	At hepatobiliary centers of excellence where there is absolute certainty of technical quality and professional skill, radiologic confirmation [by MRI or CT] of hemangioma may be unnecessary, as long as the patient has no known risk factors.	**S**	The diagnosis by contrast enhanced imaging is based on a typical vascular profile characterized by peripheral and globular enhancement on arterial phase followed by a central enhancement on delayed phases. MRI provides additional findings such as lesion signal on T1-, T2-weighted sequences, and diffusion-weighted imaging.
	S	Liver biopsy should be avoided if the radiologic features of a hemangioma are present.	**t**	Needle core biopsy carries a risk of life-threatening bleeding, and should only be considered in rare cases in which a diagnosis cannot be established conclusively despite the use of multiple imaging modalities and a suspicion of malignancy remains.	**t**	Percutaneous biopsy can be performed when the diagnosis cannot be achieved with imaging. Provided that a cuff of normal hepatic parenchyma is interposed between the capsule and the margin of haemangioma, needle biopsy is not contraindicated.

Table 2: Continued

	ACG (2014)[25]		*SBH (2015)*[24]		*EASL (2016)*[27]
Management	W	Pregnancy and the use of OCP or anabolic steroids are not contraindicated in patients with a hemangioma	R	The use of OCP or other hormonal therapies is not contraindicated in patients with hemangiomas.	W	Pregnancy and oral contraceptives are not contraindicated.
	W	Regardless of the size, no intervention is required for asymptomatic hepatic hemangiomas. Symptomatic patients with impaired quality of life can be referred for surgical or nonsurgical therapeutic modalities by an experienced team.	R	Patients with symptomatic giant hemangiomas or those presenting with compression of adjacent structures should be referred to a hepatobiliary center for assessment of surgical or nonsurgical treatment options such as enucleation, liver resection, arterial embolization, radiofrequency ablation, the efficacy of which remains unconfirmed.	S	Conservative management is appropriate for typical cases.
	t	Surgical intervention can be considered in large lesions (>10 cm), or in case of symptomatic compression or recurrent pain.	R	In the event of rare complications such as rupture (spontaneous or traumatic) or Kasabach-Merritt syndrome, surgical treatment is necessary.	S	In the presence of Kasabach-Merritt syndrome, growing lesions or lesions symptomatic by compression: refer to BLT-MDT*.
Follow-up	t	Follow-up imaging is not required in cases of classical hemangioma.	R	Once the diagnosis has been established conclusively, there is no need for systematic follow-up of asymptomatic patients with small nodules.	S	Due to its benign course, imaging follow-up is not required for typical haemangioma.
			R	Yearly or twice-yearly follow-up ultrasound is recommended for patients with hemangiomas >5 cm in size.		
			t	Conservative monitoring during pregnancy is advisable for patients with large tumors.		

Abbreviations: ACG, American college of gastroenterology; SBH, Brazilian society of hepatology; EASL, European association for the study of the liver; S, strong recommendation; W, weak recommendation/conditional recommendation; R, recommendation without definition of strength; t, in text advice; MRI, magnetic resonance imaging; CT, computed tomography; CEUS, contrast enhanced ultrasound; BLT-MDT, benign liver tumor dedicated multidisciplinary team; OCP, oral contraceptive pills. *BLT-MDT should consist of a hepatologist, hepatopancreatobiliary surgeon, diagnostic and interventional radiologist, and a pathologist.

Focal Nodular Hyperplasia

Guidelines differed slightly in their formulation of recommendations for FNH (**Table 3**). The ACG guideline recommended using MRI or CT for diagnostic confirmation, without specifying the modality or MR contrast agents. SBH and EASL guidelines concluded CE-MRI superiority for both FNH identification and FNH-HCA differentiation. The EASL guideline recommended biopsy for suspected FNH ≥3 cm if diagnosis is doubtful after CE-MRI or if uncertain in <3 cm tumors after CEUS. The ACG guideline recommended biopsy if FNH cannot be distinguished from hepatocellular adenoma, without discussing the role of MRI and CEUS. The SBH did not discuss the role of biopsy in FNH.

Results regarding the use of CEUS (combined with MRI) for focal liver tumors were published prior to ACG and SBH guideline publication.[32] Additional findings on CEUS use in FNH smaller than 3 cm, though, were published after July 2013.[10,11]

The SBH guideline had no advice regarding OCP use and concluded FNH's association with estrogens remains controversial. The SBH recommended follow-up every six months to two years, depending on tumor characteristics. The ACG recommended follow-up during 2-3 years in women when OCP are continued. The EASL guideline did not recommend any follow-up unless concurring underlying vascular liver disease is present.

Hepatocellular Adenoma

The guidelines differed moderately in HCA management recommendations (**Table 4**). All guidelines recommended use of biopsies when imaging is inconclusive, and biopsy is necessitated for treatment decisions. Yet, none of the guidelines provided specific biopsy indications or a strict diagnostic workup. The EASL guideline preconditioned the consideration by a BLT multidisciplinary team prior to biopsy. All guidelines mentioned HCA subtype differentiation through MRI but differed in nuances. The ACG guideline described specific MRI characteristics for b-HCA and biopsy might prove unnecessary due to MRI HCA subtype characterization. The SBH guideline noted identification of all HCA subtypes through MRI. The EASL guideline reported accurate characterization of H-HCA or I-HCA, excluding b-HCA and U-HCA. B-HCA MRI features differed between ACG and EASL guidelines.

Table 3. Comparison of guideline recommendations on focal nodular hyperplasia

	ACG (2014)[25]		*SBH (2015)*[24]		*EASL (2016)*[27]	
Diagnostics	S	An MRI or CT scan should be obtained to confirm a diagnosis of FNH. A liver biopsy is not routinely indicated to confirm the diagnosis.	R	A diagnosis of FNH suggested by US findings should be confirmed by dynamic CT or MRI.	S	CEUS, CT, or MRI can diagnose FNH with nearly 100% specificity when typical imaging features are seen in combination.
					S	MRI has the highest diagnostic performance overall. The highest diagnostic accuracy by CEUS is achieved in FNH less than 3 cm.
					S	If imaging is atypical refer to a BLT-MDT*.
			R	If central scars and/or other signs indicative of FNH are absent and there is diagnostic uncertainty between HCA and FNH, the use of liver specific contrast agents is indicated.	t	Perform [hepatobiliary] contrast enhanced MRI first. Perform a CEUS when the diagnosis is uncertain and the lesion is <3 cm. Perform biopsy in case of doubt in lesions >3 cm or after CEUS.
Management	S	Asymptomatic FNH does not require intervention.	R	If a diagnosis of FNH is confirmed, conservative management is indicated. There is no specific treatment.	W	Treatment is not recommended in absence of symptoms.
			R	Exceptionally large nodules associated with symptoms or compression of adjacent structures should be considered for surgical resection.	S	Refer to a BLT-MDT* if the patient is symptomatic.
	W	Pregnancy and the use of OCP or anabolic steroids are not contraindicated in patients with FNH.	t	Its [FNH] potential association with estrogens is controversial and certainly less evident than that observed in HCA. [No advice given].	t	There is no indication for discontinuing OCPs and follow-up during pregnancy is not necessary.
Follow-up	W	Annual ultrasound for 2–3 years is prudent in women diagnosed with FNH who wish to continue OCP use. Individuals with a firm diagnosis of FNH who are not using OCP do not require follow-up imaging.	R	Follow-up imaging is recommended for patients with FNH, who are generally asymptomatic. Control scans may be performed every six months to two years, depending on the disease course.	W	For a lesion typical of FNH follow-up is not necessary, unless there is underlying vascular liver disease.

Abbreviations: ACG, American college of gastroenterology; SBH, Brazilian society of hepatology; EASL, European association for the study of the liver; S, strong recommendation; W, weak recommendation/conditional recommendation; R, recommendation without definition of strength; t, in text advice; MRI, magnetic resonance imaging; CT, computed tomography; US, ultrasound CEUS, contrast enhanced ultrasound; FNH, focal nodular hyperplasia; BLT-MDT, benign liver tumor dedicated multidisciplinary team; OCP, oral contraceptive pills. *BLT-MDT should consist of a hepatologist, hepatopancreatobiliary surgeon, diagnostic and interventional radiologist, and a pathologist.

The ACG guideline defined b-HCA as "heterogeneous with no signal dropout on T1 out-of-phase sequences, isointense on T1 and T2 sequences, with strong arterial enhancement and delayed washout". The EASL guideline observed b-HCA as "mainly heterogeneously hyperintense on T2- and hypointense on T1-weighted sequences, with a central scar but no signal loss on chemical shift sequences".Conservative management was similar with regards to cessation of OCP and anabolic steroids. The ACG guideline additionally included cessation of hormone-containing intra-uterine devices, in contrast to SBH and EASL guidelines. Only the EASL guideline recommended weight loss.

The ACG guideline did not mention male patients as specifically eligible for preemptive intervention. All guidelines described HCA diameter ≥5 cm as indication for (minimally) invasive intervention in females. Evaluation of prior lifestyle alteration effect was not included by the ACG and SBH guidelines. Management in the EASL guideline was individualized and gave recommendations based on patient sex, HCA size, HCA behavior after lifestyle changes, and patients with multiple HCA. Results regarding the effect of weight loss on HCA diameter were also reported after the publication of the ACG and SBH guidelines.[15] The individualized strategy provided by the EASL guideline was proposed (but not yet clinical practice) in a review published within the ACG and SBH timelines.[13] The SBH guideline advised resection of all HCA prior to pregnancy. The ACG and EASL recommended a case-by-case approach. The EASL guideline specified close follow-up by US, radiologic or surgical intervention if growth occurs, and safety of vaginal delivery in non-exophytic HCA <5 cm. Follow up intervals differed as the ACG advised twelve-months, the SBH guideline six-months, and the EASL guideline twelve months after an initial six-month evaluation of diameter after lifestyle changes. The ACG guideline advised liver transplantation only as definitive treatment of HCA in context of GSD, or as last resort in severe HCA induced hemorrhage. The EASL guideline states liver transplantation is not recommended in multiple HCA but might be considered in individuals with underlying liver disease.

Table 4: Comparison of guideline recommendations on hepatocellular adenoma

	ACG (2014)[25]		*SBH (2015)*[24]		*EASL (2016)*[27]
Diagnostics	**t** Although CT can be used to diagnose HCA, recent findings suggest that not only can MRI be used to diagnose HCA, but it can also identify the subtypes of HCA based on the imaging patterns, obviating the need for biopsy to distinguish these subtypes. MRI enhanced with gadobenate dimeglumine or gadoxetate disodium can be very effective in differentiating HCA from FNH and other lesions. [Specific MRI findings of H-HCA, I-HCA and b-HCA are described.]	**R**	The imaging modality of choice for suspected cases of HCA is MRI, which may also define subtype. [Mentions H-HCA, I-HCA & b-HCA to have specific MRI findings.]	**S**	MRI is superior to all other imaging modalities and due to its intrinsic properties to detect fat and vascular spaces it offers an opportunity to subtype HCA up to 80%
				S	The positive identification of H-HCA or inflammatory HCA is achievable with MRI with >90% specificity. By contrast, identification of b-HCA and its distinction with U-HCA and hepatocellular carcinoma is not possible by any imaging technique
				S	Identification of b-HCA and distinction from unclassified HCA or HCC is not possible with any current imaging technique
	S Obtaining a biopsy should be reserved for cases in which imaging is inconclusive and biopsy is deemed necessary to make treatment decisions	**R**	Percutaneous liver biopsy should be reserved for cases of diagnostic uncertainty in which definition of management is dependent on biopsy findings.	**t**	Biopsy may be considered within a BLT-MDT* to exclude malignancy. Resection is advised in case of b-HCA.

Table 4: Continued

	ACG (2014)[25]		*SBH (2015)*[24]		*EASL (2016)*[27]	
Management	W	In hepatocellular adenomas ≥5 cm, intervention through surgical or nonsurgical modalities is recommended, as there is a risk of rupture and malignancy [No explicit mentioning of indication for resection in all men.]	t	The high risk of malignant transformation of HCA in male patients means that surgical resection is always indicated, regardless of tumor size.	W	Treatment decisions are based on gender, size and pattern of progression
					W	Base management of multiple HCAs on the size of the largest tumor progression.
					W	In women, a period of 6 months observation after lifestyle change is advised and resection is indicated for nodules ≥5 cm and those continuing to grow
					W	HCA resection is recommended irrespective of size in men and in any instance of proven β-catenin mutation
					W	A bleeding HCA with hemodynamic instability should be embolized and residual viable lesion on follow-up imaging is an indication for resection.
					W	The management of patients with multiple HCA should be based on the size of the largest tumor.
					W	Hepatic resection might be considered in unilobular disease, and in those cases with more widespread HCA, resection of the largest adenomas may be an option.
					W	Liver transplantation is not recommended in multiple HCA, but might be considered in individuals with underlying liver disease.
	S	OCP, hormone-containing IUD, and anabolic steroids are to be avoided in patients with hepatocellular adenoma	R	OCP or anabolic androgenic steroids should be discontinued if in use.	S	Upon HCA diagnosis, lifestyle changes such as discontinuation of OCP as well as weight loss should be advised. [No IUD mentioned.]
	W	Pregnancy is not generally contraindicated in cases of hepatocellular adenoma <5 cm and an individualized approach is advocated for these patients.	R	Surgical resection is indicated in women of childbearing age with lesions ≥5 cm and in men, regardless of lesion size. As gestation may lead to growth of HCA, resection should be offered to women with large nodules (even if <5 cm) who wish to become pregnant.	t	Monitor HCA in pregnant women by US every 6-12 weeks. Pursue vaginal delivery in case of non-exophytic HCA <5 cm. Consider embolization for growing lesions. Prior to 24 weeks, surgery may be preferred, especially in peripherally located smaller lesions.

Table 4: Continued

	ACG (2014)[25]		*SBH (2015)*[24]		*EASL (2016)*[27]
Follow-up	**W** If no therapeutic intervention is pursued, lesions suspected of being hepatocellular adenoma require follow-up CT or MRI at 6-12-month intervals. The duration of monitoring is based on the growth patterns and stability of the lesion over time.	**R**	If surgical intervention is not indicated, the progression of HCA should be monitored by follow-up imaging every 6 months. [No end mentioned].	**W**	In women, lesions less than 5 cm should be reassessed at 1 year, and annual imaging adopted thereafter.
				t	There is no robust data on the timeline to define stable disease.

Abbreviations: ACG, American college of gastroenterology; SBH, Brazilian society of hepatology; EASL, European association for the study of the liver; S, strong recommendation; W, weak recommendation/conditional recommendation; R, recommendation without definition of strength; t, in text advice; MRI, magnetic resonance imaging; CT, computed tomography; US, ultrasound; HCA, hepatocellular adenoma; H-HCA, hepatocyte nuclear factor 1a inactivated HCA; I-HCA, inflammatory HCA; b-HCA, beta catenin mutated HCA; U-HCA, unclassified HCA; BLT-MDT, benign liver tumor dedicated multidisciplinary team; OCP, oral contraceptive pills; IUD, intrauterine device. *BLT-MDT should consist of a hepatologist, hepatopancreatobiliary surgeon, diagnostic and interventional radiologist, and a pathologist.

Discussion

The current review identified and indexed the currently available clinical practice guidelines on the management of BLT, critically appraised them and compared management recommendations. Three clinical practice guidelines were identified and included in the analysis, originating from the North American (ACG), South American (SBH), and European (EASL) continent. Some differences in guideline quality were observed between guideline domains. Differences in the recommendations were identified in diagnostic workup, management, and follow-up of hepatic hemangioma, FNH, and HCA.

Multiple causes may explain the identified differences. First, ACG and SBH guidelines did solely focus on BLT but described (pre-)malignant tumors and cysts too. As the EASL guideline only focused on BLT, its authors had the possibility to provide a more in-depth overview. Second, discrepancies among the three guidelines could be a consequence of the moderate quality of the available and included (observational) evidence. This creates room for different – and equally justifiable – interpretations. Lastly, ACG and SBH guidelines were published up to two years before the EASL guideline. Novel insights emerged in this time-interval could explain differences in recommended treatment strategies.

There were different inclusions of available literature by the guidelines, leading to differences in recommendations on CEUS use. Interpretation of literature also differed between guidelines. For example, one report reported on 177 patients using estrogen-containing OCP for nine years and excluded any influence of estrogens on FNH behavior.[7] It was published within the scope of all guidelines but only the EASL guideline completely dismissed FNH patients from interventions and follow-up. Safety of percutaneous biopsy in hemangioma also varied, with ACG and SBH guidelines discouraging it due to hemorrhage risk. No references regarding safety of biopsy are provided by the ACG guideline. The SBH guideline referred to two publications.[33,34] These, however, do not explicitly discourage biopsy. The study by Klotz *et al.* discourages biopsy because hepatic angiosarcoma (1% of all hepatic tumors) is part of the differential diagnosis, with significant bleeding risk.[33] The other publication, by Caseiro-Alves *et al.,*

provides evidence supporting safety of hemangioma biopsy.[34] The EASL guideline did not discourage biopsies. It refers to a paper dating from 1998 by Caldironi *et al.,* which observed two minor bleedings in 114 biopsies.[35]

Another example is differing recommendations on the follow-up of FNH. The SBH guideline recommends follow-up because of their cited risk of potential misdiagnosis of fibrolamellar HCC as FNH.[36,37] However, these publications used outdated imaging and histopathologic techniques, and current diagnostics are highly capable in differentiating HCC from FNH.[9,38–40] The ACG guideline advices a conservative stance due to rarity of FNH induced HCC formation or hepatic rupture.[41–43] However, it does not cite literature for its recommendation of follow-up of FNH in female patients using OCP. The EASL guideline states there is insufficient evidence to support or refute elective surgery for FNH.[44] However, it emphasizes the very low probability of FNH induced complications.[45,46]

The extent to which the guidelines advise HCA subtype identification on MRI differed. The SBH guideline stated H-HCA, I-HCA, and b-HCA can be discriminated on MRI. This guideline referred to a retrospective study which described 34 I-HCA, 11 H-HCA and 3 b-HCA.[47] The cited study focused on gadolinium chelate (Dotarem), and although the authors described accurate characteristics for H-HCA and I-HCA, an insufficient number b-HCA cases were included to allow identification of discriminating features. The EASL guideline takes a more conservative stance and states that even though the subtype identification on imaging holds promise, future studies should prove feasibility for a wider application of MRI subtype differentiation of HCA than in the highly specialized centers. The EASL guideline mainly appreciates H-HCA and I-HCA as distinguishable on MRI, and includes three other retrospective studies from 2008-2015 in addition to the paper included by the SBH.[47–50] The three additional papers also included 12 b-HCA cases, of which 6 were investigated after Gadoxetic acid (Primovist)-enhanced MRI. The ACG guideline states that biopsy for HCA subtype identification is obviated by MRI guided diagnostics, referring to a retrospective study from 2008 which included 15 H-HCA, 27 I-HCA, and 2 b-HCA cases.[48] Multiple publications on this topic consulted by the EASL guidelines, where not discussed in

the ACG and SBH guidelines.[47–49] A critical evaluation of the methodology of all the aforementioned imaging studies spans beyond the scope of the current review. Though, we opine that non-invasive HCA subtype identification can be considered when HCA demonstrate obvious signs of H-HCA or I-HCA. The current evidence does not allow for b-HCA discrimination, especially considering the malignant potential which this subtype associates with.

Recommendations on HCA during pregnancy were limited in the included ACG guideline. Both EASL and the ACG guideline on liver disease during pregnancy recommend growing or HCA ≥5 cm to be treated by radiologic or surgical intervention.[29,51] The SBH guideline approached HCA more aggressively by advocating resection prior to pregnancy in all cases. All guidelines agreed upon the safety of hemangiomas and FNH during pregnancy. Additional recommendations on liver disease during pregnancy, including BLT, can be found elsewhere.[51–53]

Some liver transplantations have been performed for hepatocellular adenomatosis, yet this should not be applied standardly in the context of the current donor organ shortage and transplantation associated morbidity.[54] Both ACG and EASL made limited recommendations on the role of liver transplantation. Both guidelines stated it should only be applied for GSD (associated adenomatosis) as an exception, though finally only warranted as it is a broader therapy for the carbohydrate metabolism dysfunction.[55] The ACG guideline also suggested to use liver transplantation for severe HCA induced hemorrhage, which has been successfully been performed.[56] BLT are also known to occur in pediatric patients but none of the guidelines provided recommendations on this subpopulation.[57]

The current manuscript included all available gastroenterology guidelines on BLT but excluded specific radiology guidelines, or guidelines on subtopics which could potentially contain recommendations on benign liver tumors in a specific context (*i.e.* pregnancy or in the pediatric setting). Another potential limitation is the subjective nature of the AGREE II questionnaire for critical appraisal. This may have introduced a potential risk of bias which, however, was at least in part mitigated using two independent scoring researchers.

BLT are rare, but increasingly observed as incidentalomas. Albeit being benign, some tumors may cause potential serious complications, necessitating clear and complete guidelines. The current inclusion of only three guidelines demonstrates the need of further development of guidance for clinicians. Ideally, novel guidelines would be drafted by multidisciplinary panels with representatives of all relevant specialty associations to ensure homogeneity on subtopics like imaging, need for pathology, and surgical interventions. Formulation of a global consensus statement is also needed. Differing designs of the health care systems could prevent a truly one-size-fits-all approach. Though, consensus could be attained through a Delphi method with participation of allied international associations to ensure elimination of potential treatment variation. Lastly, future drafting of guidelines could be performed according to AGREE or RIGHT reporting guidelines to ensure quality and comparability.[58,59]

Guideline authors could provide a framework to ensure comparable strategies on major topics such as diagnostics or treatment, with the opportunity to adjust the guideline to local practice and preference. The aim of such an approach is patient care improvement, and optimal use of (scarce) health care budgets. Second, analysis of BLT guidelines uncovered a potential future research agenda. Currently, none of the guidelines provided recommendations on HCA in patients with HNF1A-MODY or GSD, while albeit rare, these are known for their high HCA prevalence.[18] Additionally, no large series on molecular HCA subtypes and behavior in men have been performed, nor has the role of artificial intelligence in BLT characterization extensively been explored.

Since publication of the EASL guideline, several HCA papers have been published which may carry significant consequences for future guidelines. One report observed the currently used six-month period for evaluation of lifestyle alterations to be potentially too short for sufficient HCA regression, especially in large HCA.[60] Another highly debated subject is the management of HCA prior to, during, and after pregnancy. A major prospective study observed sub-5 cm HCA to be safe during pregnancy, whilst a combined cohort study and systematic review observed only HCA induced hemorrhages in HCA >6.5 cm and observed HCA to cause (lethal) postpartum hemorrhage in rare cases.[53,61] HCA smaller than 5 cm have been observed safe to discharge from follow-up

after the menopause.[62] In addition, there has been reporting on the novel identification of sonic hedgehog activated HCA and roof plate-specific spondin-2 gene rearranged HCA, the increased application and accuracy of CEUS and MRI for diagnostics, occurrence of HCA in men prior to diabetic symptoms in HNF1A-MODY, and conservative and (minimally) invasive HCA management by transarterial embolization.[18,21,63–65] Next generation sequencing of HCA in men revealed frequent change of HCA or HCC diagnosis and several b-HCA which were not diagnosed by immunohistochemistry, which could warrant a more prominent role for genetic sequencing in HCA (subtype) diagnostics.[20] Regarding the minimally invasive treatment of symptomatic hemangioma transarterial embolization and lipiodolization was observed to be safe and effective in a systematic review including 1284 pooled patients.[66] These new insights might warrant an update of (harmonized) clinical practice guidelines in the near future.

Our observations might have influence on two important topics: (i) creation of global clinical practice uniformity, and (ii) identifying areas of future research. First, although comparing and analyzing clinical practice guidelines may not directly benefit medical professionals or patients, our observations clearly show significant differences in BLT guideline design, content, and considerations between continents. This may encourage global professionals in expanding their scope when facing clinical dilemmas. Additionally, guideline authors and policy makers could take previously drafted guidelines into account when updating recommendations. This could create uniformity by raising global awareness of the differences in approaching various BLT.

In conclusion, three guidelines on BLT were identified, and several differences were identified on diagnostic workup and management of hepatic hemangioma, FNH, and HCA after comparison. These included: use of a dedicated BLT multidisciplinary team for management decisions, indications for biopsy, timing and duration of follow-up, conservative management of FNH, diagnosis of HCA subtypes on MRI, and (conservative) management of HCA. These differences could lead to a practice variation, and thereby to varying outcomes. By recognizing these differences, future research and debate should be focused on both harmonization of clinical practice standards and remaining lacunas for BLT to achieve best patient care worldwide.

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CHAPTER 3

Variation in the Management of Benign Liver Tumors: A European Survey and Case Vignette Study

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Abstract

Background

Management of benign liver tumors (BLT), including focal nodular hyperplasia (FNH) and hepatocellular adenoma (HCA), is multidisciplinary by nature and subject to practice variation. We aimed to evaluate variation in clinical management of FNH and HCA in Europe.

Methods

We distributed an online survey (November 2021-March 2022) among 294 European BLT experts. The survey included general questions on local practice and questions based on eight clinical vignettes. The clinical vignettes focused on FNH or HCA management in the setting of sex, lifestyle modification (*i.e.* oral contraceptive discontinuation and weight loss), and pregnancy.

Results

The survey response rate was 32% and respondents included surgeons (38%), gastroenterologists/hepatologists (25%), radiologists (8%), and pathologists (1.6%) from ten European countries. We observed practice variation regarding lifestyle modification and imaging follow-up in patients with FNH, and with regard to the management of HCA >5cm before and during pregnancy. Finally, the management of HCA >5 cm after lifestyle modification deviated from EASL guideline recommendations.

Discussion

Our survey illustrates substantial variability in FNH and HCA management in Europe. Several areas were identified for future research and guideline recommendations, including FNH follow-up and the management of HCA >5 cm. We propose the organization of Delphi consensus meetings to prioritize new areas of research and update current guidelines to optimize management for all patients with benign liver tumors.

Introduction

Benign liver tumors (BLT) are increasingly detected due to the growing use of diagnostic imaging.[1–3] The diagnosis and management of BLT is challenging due to the heterogeneity in tumor (sub)types and the variable clinical risk of adverse outcomes.[4]

The majority of clinically relevant BLT are focal nodular hyperplasia (FNH) and hepatocellular adenoma (HCA).[3] FNH are typically solitary, well-circumscribed, non-encapsulated tumors.[4–6] FNH are not at risk of malignant transformation or hemorrhage – neither in male, nor in female.[4,6] In addition, oral contraceptive pill (OCP) use and pregnancy do not affect FNH size, or number.[7] Due to these characteristics, follow-up of FNH is not recommended by the European guideline for management of BLT.[4] The challenge of FNH management is its differentiation from HCA on diagnostic imaging. Contrast-enhanced magnetic resonance imaging (CE-MRI) with hepatobiliary contrast agent has the strongest diagnostic and discriminatory power in differentiating these two BLT.[8,9] The current European clinical practice guideline only recommends invasive FNH treatment in case of (significant) mechanical complaints by compression of abdominal viscera or exophytic or pedunculated growth.[4,10] HCA are most frequently diagnosed in middle-aged women.[3,4] HCA are associated with sustained high estrogen exposure, by prolonged use of OCP, and/or obesity.[10,11]

The main complications of HCA, *i.e.* hemorrhage and transformation to hepatocellular carcinoma[4,12–15], are related to both tumor size and subtype of the adenoma. Both complications are extremely rare in HCA <5 cm. Key to non-invasive management of HCA is the ability of HCA to regress after estrogen reduction by the cessation of OCP intake and/or weight loss.[16,17] In female patients with HCA >5 cm (without signs of pre-malignancy on MRI [*e.g.* diffusion restriction] or histopathology [*e.g.* cellular atypia]), cessation of OCP intake and weight loss is advised, and tumor size is evaluated after six months. In male patients, however, immediate invasive treatment of all HCA is recommended irrespective of tumor size due to the high risk of malignant transformation.[4] The risk of malignant transformation in male patients is associated with the male sex itself and due to higher prevalence of beta-catenin activated HCA (b-HCA) subtype.[12,14,18]

Currently, there is a single European guideline for management of BLT, published by the European Association for the Study of the Liver (EASL). There are no data available, however, on European daily clinical management of FNH and HCA.

Insight into real-world management strategies of FNH and HCA may identify areas of improvement for future research, guideline adjustment, and guideline implementation. We therefore conducted an online survey among European medical specialists involved in BLT treatment. Our study aimed to evaluate potential variation in clinical practice and real-world management of FNH and HCA in Europe.

Methods

Study design

A European survey study was performed among medical experts involved in BLT management. Experts and expert centers were selected based on authorship on a FNH or HCA oriented publication. Publications were identified by one author from the MEDLINE database (PubMed) using the following search query: "focal nodular hyperplasia OR FNH OR "Focal Nodular Hyperplasia"[Mesh] OR hepatocellular adenoma OR hepatic adenoma OR "Adenoma, Liver Cell" [Mesh]" on September 15th 2021. Included medical specialties were (hepatobiliary) surgeons, gastroenterologists and hepatologists, (intervention) radiologists, and pathologists. Experts and expert centers were identified and contacted through the "corresponding author" contact information of the identified scientific publications.

Survey design and data collection

The survey was designed by a multidisciplinary team consisting of a hepatologist (FJCC), hepatobiliary surgeon (VEM), and radiologist (RJDH), and reviewed by multiple specialists. The survey included general questions regarding medical specialty, level of training, and experience in treating FNH and HCA. Thereafter, the survey consisted of two parts: 1) an enquiry regarding local daily clinical practice, including organization of the local multidisciplinary team (MDT), available diagnostic techniques and treatment strategies for FNH and HCA patients; and 2) eight fictive clinical vignettes of FNH or HCA patients, enquiring on diagnostic and treatment strategies.

Vignette case description included information on patient sex, patient age, patient weight (body mass index), (previous) use of estrogen-containing OCP, pregnancy, imaging modality and results, and tumor behavior during a specified follow-up period (**Table 1**). It was also stated none of the patients experienced potentially tumor-related symptoms and diagnostic tumor markers (*i.e.* alpha-fetoprotein, des-gamma-carboxy prothrombin, carcinogenic embryonic antigen, carbohydrate antigen 19-9) were within normal range. Imaging by CE-MRI with liver-specific contrast agents was available for all vignette patients, and all tumors were described as pathognomonic on imaging, without any atypia. Respondents were instructed on the above-mentioned general characteristics of the included clinical vignettes and were advised to manage the vignette scenarios regardless of the modalities available for the respondent in daily practice. Agreement on management of the clinical vignettes was defined as ≥75% agreement between respondents. Medical management decisions were categorized according to the recommendation as provided by the respondent: additional diagnostics, non-invasive treatment (*e.g.* weight loss, OCP cessation, other), (minimally) invasive treatment, and follow-up. Vignettes were categorized into three clinical categories: 1) male and female patients with FNH; 2) HCA during pregnancy; and 3) female patients with HCA ≥5 cm.

CHERRIES guidelines were adhered to in study design and manuscript preparation.[19] The Medical Ethical Committee of the University Medical Center Groningen confirmed that the Law on Medical Scientific Research involving human beings (WMO) did not apply (MEC 2019-290). The study was registered prior to initiation in the local research registry (UMCG RR#201900347). A collaborator authorship was offered for all respondents who returned a completed survey.

Survey invitations were only distributed by email using REDCap (Vanderbilt University, Tennessee, USA) electronic data capture tools hosted at the University Medical Center Groningen.[20,21] The voluntary survey was open for inclusions from November 2021-March 2022. Three reminders were sent by email after the initial invitation. Conditional questions were used, *e.g.* preferred follow-up modality was only displayed if respondents opted for follow-up at all. The survey included a maximum of 216 items, although not all were shown to each respondent due to conditionality.

The survey consisted of 11 web pages: background information and instructions (page 1, 3 items), personal information (page 2, 9 items), part I – local practices (page 3, 44 items), and part 2 – cases 1-8 (pages 4-11, 160 items). The REDCap integrated completeness check was used. Respondents were able to review and change answers through a "back" button. All participants received a unique survey weblink. No visitor rates were monitored. No cookies, IP checks, log file analyses, or registrations were used. No questionnaire timestamp analysis was performed.

Statistical analyses

Only fully completed surveys were included in final analysis. Dichotomous data were presented as proportions. Variable distribution was assessed by plotting histograms. Categorical variables were expressed as number (*n*) and percentage (%). Variables were analyzed using appropriate statistical tests for variable type and distribution. Parameters with two-tailed $p < 0.05$ were considered statistically significant. No statistical corrections were applied. All analyses were performed in R version 4.1.0.® (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). Study data were collected and managed using REDCap electronic data capture tools (Vanderbilt university, Tennessee, USA) hosted at the University Medical Center Groningen.[20,21]

Results

A link to the survey was emailed to 294 European experts. Ninety-five (32%) experts responded. Thirty-three experts were excluded from analysis due to declining of the invitation (*n*=22), or partial completion of the survey (*n*=12). Sixty-one (21%) respondents were included in the final analysis. (**Figure 1a**).

Profile of respondents

The 61 included respondents originated from a total of ten European countries (**Figure 1b**), and included 24 (39%) surgeons, 15 (25%) gastroenterologists/hepatologists, 19 (31%) (interventional) radiologists, 1 pathologist (1.6%), and 2 research associates (3.3%).

Table 1. Overview of included fictive FNH & HCA patients

Vignette	Age (year)	Sex	BMI (kg/m²)#	Age of OCP use	Pregnancy	PA	Imaging (interval)
				FNH			
Case 1: FNH in male patient	31	M	26	N/A	N/A	-	CE-MR with liver specific contrast†: 1 FNH 6.0 cm
Case 2: Growing FNH in female patient, current OCP use	28	F	24	16	No	-	**First** MRI: 1 FNH 4.0cm **Second** (6 months), CE-MRI with liver specific contrast†: 1 FNH 7.0 cm, +75% growth
Case 3: Stable FNH during pregnancy	31	F	22	15-29	2nd trimester	IHC	**First** (3 months pre-pregnancy), CE-MRI with liver specific contrast†: 1 FNH 6.0 cm **Second** (6 months, 2nd trimester), US: 1 FNH 6.0 cm
				HCA before or during pregnancy			
Case 4: Stable HCA >5 cm and wish to become pregnant	31	F	24	17-28	Strong wish	-	**First** (stop OCP), CE-MRI with liver specific contrast†: 1 HCA 6.8 cm **Second** (six months later), CE-MRI with liver specific contrast†: 1 HCA 6.5 cm **Third** (12 months later after 2nd), CE-MRI with liver specific contrast†: 1 HCA 6.6 cm
Case 5: Growing HCA >5 cm during pregnancy	28	F	28	16-26	2nd trimester	-	**First** CE-MRI with liver specific contrast†: HCA 4.5 cm **Second** (12 months later, 8 weeks gestation), US: 1 HCA 5.0 cm **Third** (6 weeks after 2nd, 14 weeks gestation), US: 1 HCA 6.0 cm, +33% growth **Fourth** (6 weeks after 3rd, 20 weeks gestation), US: 1 HCA 7.0 cm, +56% total growth
Case 6: Stable exophytic HCA >5 cm and wish to become pregnant	32	F	24	15-31	No	I-HCA on NGS	**First** (stop OCP), CE-MRI with liver specific contrast†: 1 exophytic HCA 7.1 cm + 5 HCA <5.0 cm **Second** (6 months after 1st), CE-MRI with liver specific contrast†: 1 exophytic HCA 7.0 cm + 5 HCA <5.0 cm
				HCA >5 cm, 6 months after OCP stop and weight loss			
Case 7: HCA >5 cm, and <30% regression*	26	F	27 (32)	16-26§	No	-	**First** (stop OCP), CE-MRI with liver specific contrast†: 1 HCA 9.0 cm **Second** (6 months after 1st), CE-MRI with liver specific contrast†: 1 HCA 7.6 cm, -16% regression
Case 8: HCA >5 cm, and >30% regression*	24	F	26 (28)	17-24§	No	-	**First** (stop OCP), CE-MRI with liver specific contrast†: 1 HCA 12.0 cm **Second** (6 months after 1st), CE-MRI with liver specific contrast†: 1 HCA 8.1 cm, -32.5% regression

*According to RECISTv1.1 criteria 30% regression defines (clinically relevant) "partial response"[25]; #BMI six months after first imaging in brackets; §OCP stopped six months before second imaging. † Hepatobiliary contrast equals liver specific contrast agents *e.g.* Primovist or Eovist. Abbreviations: FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; BMI, body mass index; OCP, oral contraceptive pill; PA, histopathology; M, male; F, female; IHC, immunohistochemistry; CE-MRI, contrast-enhanced magnetic resonance imaging; US, ultrasound; NGS, next generation sequencing.

Ninety-eight percent of respondents worked in tertiary referral hospitals or university medical centers. Ninety percent of respondents currently works as attending/consultant specialist, and 59% had more than 10 years of experience in treatment of BLT.

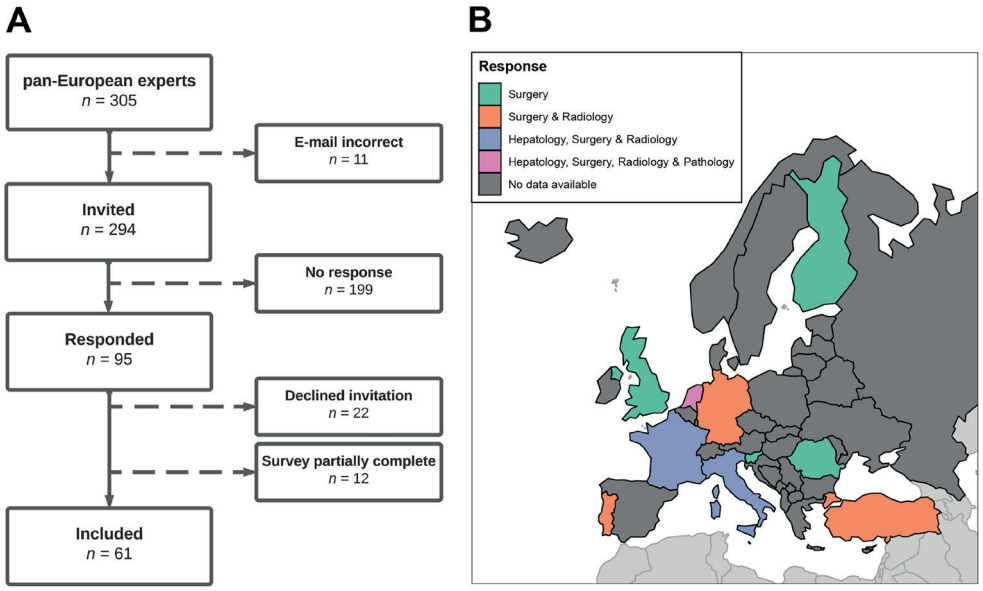

Figure 1. Overview of participating European experts on BLT. (A) Flow-chart of survey responses. (B) Participating medical specialists per included European country. Abbreviations: BLT, benign liver tumors.

Survey results part I; general questionnaire

Local practice

Fifty-three respondents (87%) participated in a MDT, of whom 96% had weekly meetings and all of whom included a gastroenterologist or hepatologist and a surgeon. Fifty-two (98%) respondents participated in an MDT that included a radiologist, 42 (79%) participated in an MDT that included an interventional radiologist and/or a pathologist, and 18 (34%) respondents participated in an MDT that included other specialists, namely radiotherapists (11%), oncologists (44%), or nuclear medicine physicians (17%). Thirty-one (51%) respondents participated in an MDT that included a gastroenterologist or hepatologist, hepatobiliary surgeon, diagnostic radiologist, interventional radiologist, and pathologist (*i.e.* EASL guideline BLT-MDT

recommendation). Outpatient BLT patients were managed by gastroenterologists/hepatologists and surgeons (75% of the respondents), gastroenterologists/hepatologists only (20%), or surgeons only (4.9%).

Diagnostic techniques

All (100%) respondents preferred a hepatobiliary contrast agent to differentiate FNH form HCA. Sixteen (26%) respondents used contrast-enhanced ultrasound (CEUS) as additional tool for FNH-HCA differentiation.

HCA subtype diagnosis on CE-MRI was accepted if the diagnosis was inflammatory (I-HCA) by 29 (48%) respondents, by 28 (46%) for H-HCA, and by 19 (31%) for b-HCA/b-IHCA. Molecular diagnostics on histopathology was available for 50 (82%) respondents, and was used on all HCA samples by 60% of the respondents. Twelve (20%) respondents used this technique mainly when b-HCA/b-IHCA was suspected on immunohistochemistry, 6 (9.8%) when b-HCA/b-IHCA was diagnosed on immunohistochemistry, and 14 (23%) when no subtype could be identified on immunohistochemistry (unclassified HCA; U-HCA).

Clinical management of FNH

Thirty-seven (61%) respondents would discharge male asymptomatic FNH patients from follow-up when diagnosed with hepatobiliary CE-MRI. Female patients with an asymptomatic FNH (diagnosed by hepatobiliary CE-MRI) were discharged without follow-up by 50 (82%) of the respondents, whereas 11 (18%) would continue follow-up, and 3 (4.9%) of the respondents would advise life-style interventions. The proposed follow-up included CE-MRI (n=3), unenhanced MRI (n=1), or US (n=4) for 6 months up to 3 years at intervals of 6-12 months. Four (6.6%) respondents commented follow-up would stop if FNH proved stable after 1-3 years.

Clinical management of HCA and pregnancy

For patients with CE-MRI- or biopsy-proven HCA <5 cm with a pregnancy wish, 54 (89%) respondents recommended follow-up according to the algorithm used in the PALM study protocol (*i.e.* evaluation of pregnant patients with HCA <5 cm by

ultrasound (US) at 14 (±3), 20, 26, 32, and 38 weeks of gestation, and 6-12 weeks postpartum).[22,23] Other respondents would advise follow-up by US every 1 (*n*=1), 2 (*n*=1), 3 (*n*=1), or 6 (*n*=1) months, or "according to the follow-up scheme by the gastroenterologist" or "close follow-up but not according to the PALM study protocol". Two respondents recommended pre-emptive treatment (transarterial embolization, radiofrequency ablation, or surgery).

For patients with CE-MRI- or biopsy-proven HCA 5-10 cm pre-emptive treatment was recommended by 52 (85%) of the respondents, and 7 (12%) recommended follow-up without pre-emptive treatment according to the PALM study protocol.[22,23]

For HCA >10 cm pre-emptive treatment was recommended by 55 (90%) respondents, 4 (6.6%) recommended follow-up without pre-emptive treatment according to the PALM study protocol, and the remaining 2 (3.3%) respondents would await the six-month effect of stopping OCP or could not decide on a specific treatment. HCA >5 cm (non-exophytic) on itself was considered a contraindication for pregnancy by 11 (18%) respondents.

Clinical management of large (>5 cm) HCA

Forty-eight (79%) respondents advised against routine HCA resection, regardless of tumor regression, when tumor size remained >5 cm after six months of weight loss and stopping OCP. Fifty-two (85%) respondents would continue follow-up of a female patient with HCA <5 cm while still ovulating, compared with 56% for a post-menopausal patient. Follow-up duration for ovulating women varied from 1-10 years or "up to menopause". For post-menopausal patients, follow-up duration varied from 1-15 years.

Survey results part II: clinical vignette-based questionnaire

Clinical vignettes 1-3: FNH

FNH in a male patient

The respondents agreed (agreement defined as >75% consensus) that additional diagnostics, weight loss, or invasive treatment were unnecessary. Six (9.8%) respondents advised additional diagnostic testing by either percutaneous biopsy (*n*=4) or additional imaging (*n*=4) (**Figure 2 – Case 1**). One respondent (1.6%) opted for surgical resection.

Follow-up imaging was advised by 23 (38%) respondents, mostly by US (13%), or CE-MRI (18%). The advised follow-up interval was mainly 3 (*n*=5) or 6-months (*n*=11).

Growing FNH <5 cm during OCP use

The respondents agreed that additional diagnostics, weight loss, or invasive treatment were not necessary. Thirteen (21%) respondents advised additional diagnostic testing by percutaneous liver biopsy (*n*=10), or additional imaging (*n*=3) (**Figure 2 – Case 2**). Twenty-three (38%) respondents would cease OCP intake and 11 (18%) advised weight loss. Four (4.9%) respondents opted for invasive treatment, either by resection (*n*=3) or embolization (*n*=1). Follow-up imaging was advised by 45 (74%) respondents, mostly by CE-MRI (*n*=27) or US (*n*=12). The advised follow-up interval was mainly 3 (26%) or 6-months (62%).

Stable FNH during pregnancy

The respondents agreed that additional diagnostics, weight loss, or invasive treatment were not necessary. Only two (3.3%) respondents advised additional diagnostic testing by hepatobiliary CE-MRI (*n*=1), or hepatobiliary CE-MRI and CEUS (*n*=1) (**Figure 2 – Case 3**). Only 1 (1.6%) respondent advised weight loss. Almost two-third (*n*=50) of the respondents advised against follow-up imaging of the patient, whereas 18 (30%) respondents would advise follow-up imaging by US, mostly (61%) according to PALM study protocol. Four (6.6%) respondents would rather use liver-specific CE-MRI for follow-up.

Clinical vignettes 4-6: HCA during pregnancy

Stable HCA >5 cm and wish to become pregnant

The respondents agreed on starting follow-up, and on not discouraging pregnancy. Twenty-one (34%) respondents would perform additional diagnostic testing, mostly by percutaneous liver biopsy (*n*=16) or CE-MRI (*n*=5) (**Figure 2 – Case 4**). Forty (66%) respondents recommended pre-emptive invasive treatment, either by resection (*n*=26), embolization (*n*=13), or ablation (*n*=1). Fifty respondents (82%) would perform follow-

up imaging, mostly by CE-MRI (*n*=24) or US (*n*=20). The suggested follow-up interval was either 3 (*n*=8), 6 (*n*=15), or 12 (*n*=14) months.

Growing HCA >5 cm during pregnancy

The respondents agreed that additional diagnostics or weight loss were not necessary and agreed on starting follow-up. Fourteen (23%) respondents would perform additional diagnostic testing, either by unenhanced MRI (*n*=5), CE-MRI (*n*=4), US (*n*=3), or by CEUS (*n*=1) (**Figure 2 – Case 5**). Eleven (18%) respondents advised weight loss. Thirty-four (56%) respondents would perform invasive treatment, either by embolization (*n*=19) or resection (*n*=14). Almost 90% of respondents would closely follow the patient during pregnancy, mostly (77%) according to the PALM study protocol. Twelve (20%) respondents proposed an alternative follow-up protocol: either by US (*n*=6), by CE-MRI (*n*=4), by unenhanced MRI (*n*=1), or by unenhanced computed tomography (CT; *n*=1), with follow-up after 1-2 months (*n*=7) or 6 months (*n*=5).

Stable exophytic HCA >5 cm and wish to become pregnant

The respondents agreed that additional diagnostics were not necessary and agreed on advising invasive treatment and on starting follow-up. Four (6.6%) respondents would perform additional diagnostics either by percutaneous biopsy (*n*=3) or CE-MRI (*n*=1). Sixteen (26%) of respondents would advise weight loss (**Figure 2 – Case 6**). Forty-nine (80%) respondents opted for invasive therapy, mostly resection (*n*=44). Fifty-five (90%) respondents would closely follow the patient during pregnancy, 24 (39%) respondents according to the PALM study protocol. Thirty-one respondents (51%) proposed an alternative follow-up protocol: either by CE-MRI (*n*=19) , by US (*n*=6), by unenhanced MRI (*n*=3), by CEUS (*n*=2), or by unenhanced CT (*n*=1), with follow-up after 3 (*n*=6), 6 (*n*=19), or 12 months (*n*=6).

Clinical vignettes 7 & 8: HCA >5 cm after six months of lifestyle therapy

On both clinical vignettes of female patients with HCA >5 cm after six months of conservative therapy, respondents agreed that additional diagnostics or invasive treatment were not necessary and opted to monitor patients by follow-up imaging.

Recommendations were comparable for HCA>5 that showed more (Case 8) or less (Case 7) than 30% regression (*i.e.* the RECISTv1.1 cut-off for partial tumor regression[24]) after six months of lifestyle interventions (**Figure 2 – Case 7 & 8**). Nine respondents (15%) would perform invasive therapy, of whom 8 would consider resection, and 1 transarterial embolization (TAE). Follow-up was proposed by ≥95% of respondents, 58% of whom would use CE-MRI, 20% unenhanced MRI, and 20% US. Respondents advised to follow-up patients after 6 months (70%), or 12 months (22%).≥95% of respondents, 58% of whom would use CE-MRI, 20% unenhanced MRI, and 20% US. Respondents advised to follow-up patients after 6 months (70%), or 12 months (22%).

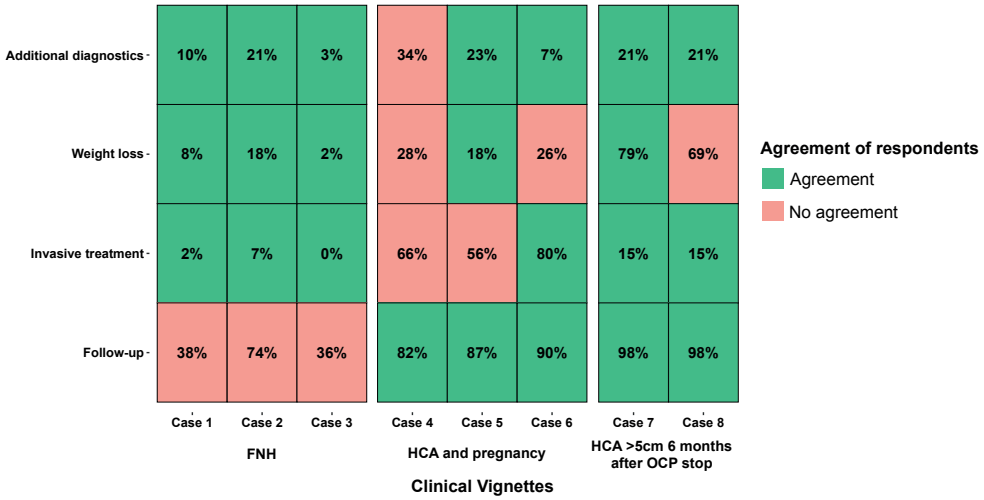

Figure 2. Response of included European experts to eight fictive clinical vignettes on FNH and HCA patients. Values represent percentage of respondents opting for management options, *i.e.* additional diagnostics or follow-up per case. Management agreement was defined as ≥75% of respondents opting for either yes or no.
Case 1: Hepatobiliary CE-MRI diagnosed FNH in male patient.
Case 2: Growing hepatobiliary CE-MRI diagnosed FNH in female patient with OCP use.
Case 3: Stable CE-MRI diagnosed FNH in pregnant patient.
Case 4: Stable hepatobiliary CE-MRI diagnosed HCA >5 cm and pregnancy wish.
Case 5: Growing hepatobiliary CE-MRI diagnosed HCA >5 cm during pregnancy.
Case 6: Stable exophytic hepatobiliary CE-MRI diagnosed HCA >5 cm and pregnancy whish.
Case 7: Hepatobiliary CE-MRI diagnosed HCA >5 cm with <30% regression 6 months after OCP stop†
Case 8: Hepatobiliary CE-MRI diagnosed HCA >5 cm with >30% regression 6 months after OCP stop†
Abbreviations: CE-MRI, contrast-enhanced magnetic resonance imaging; FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; OCP, oral contraceptive pill.
† 30% regression is defined as a clinically relevant, "partial response" according to RECISTv1.1[24]

Discussion

This international expert survey study demonstrates variation in the clinical management of FNH and HCA in Europe. We observed practice variation regarding lifestyle modification and imaging follow-up in patients with FNH, and with regard to the management of larger (>5 cm) HCA before and during pregnancy. In addition, most (>75%) respondents advised against routine resection of HCA >5 cm after lifestyle modifications, which deviates from EASL guideline recommendations.

Our survey was divided into two parts. The first part consisted of general questions regarding local practice, diagnostic techniques, and clinical management of FNH and HCA, while the second part consisted of fictitious vignettes in three categories: FNH (in male and female patients), HCA before and during pregnancy, and HCA >5 cm six months after lifestyle modification.

Several observations stand out from the results of general part of the survey. Almost 90% of the respondents participated in a MDT that included a gastroenterologist/hepatologist and a surgeon. Only 59% of the respondents, however, participated in a BLT-MDT as defined by the EASL guideline, which also includes (at least) a diagnostic and interventional radiologist and a pathologist. Regarding diagnostic techniques, CEUS, a modality with excellent FNH-HCA differentiating capacity in tumors <3 cm, was only used by 21% of respondents.[25,26] CEUS can be considered prior to biopsy when results from hepatobiliary CE-MRI prove inconclusive. Most (82%) respondents had molecular (*i.e.* next generation sequencing) HCA subtype diagnostics available in their center, a technique that can reveal b-catenine mutations unobserved on immunohistochemistry.[27] Interestingly, non-invasive subtype diagnosis on CE-MRI was also accepted for b-HCA/b-IHCA by about a third of respondents. Although non-invasive HCA subtype identification with MRI has made significant progress in recent years[28,29], no large studies on MRI-based b-HCA/b-IHCA identification have been performed, and biopsy should always be considered if b-HCA/b-IHCA are suspected.

Regarding clinical management, we observed comparable responses on the general and the vignette-based parts of the survey. Although the respondents agreed that that additional diagnostics, weight loss, or invasive treatment were not necessary in FNH in

all clinical vignettes, disagreement, was observed regarding the need to follow-up FNH patients in both the general and vignette-based part of or survey. Indeed, a significant minority of respondents would continue imaging follow-up in male (almost 40% of respondents) and female (18% of respondents) patients with FNH. In addition, 74% of the respondents would continue imaging follow up and 38% would cease OCP intake in female FNH patients using OCP when tumor growth was reported, whilst OCP has been proven to have no influence on FNH number or size, and FNH might grow and reduce in size spontaneously.[7] Although FNH was described as pathognomonic on imaging in our survey, lingering uncertainty on potential HCA occurrence instead of FNH, which carries significant clinical consequences, might explain these results. Regarding HCA before or during pregnancy, respondents agreed that additional diagnostics (*i.e.* biopsy) were unnecessary, that close follow-up (according to PALM study protocol) should be advised during pregnancy, that treatment of stable HCA <5cm is not warranted, and that pre-emptive invasive treatment of exophytic HCA should be performed. No agreement was observed regarding the need for invasive treatment of HCA >5 cm before and during pregnancy, although most of the respondents opted for invasive therapy. The latter observation illustrates the limited amount of evidence on HCA >5 cm during and after pregnancy, whilst HCA <5 cm have been observed as safe during pregnancy and the postpartum period.[23,30]

The current EASL-guideline recommends invasive treatment of all HCA >5 cm after six months of OCP cessation and weight loss. Most (85%) respondents, however, advised against routine invasive treatment of these HCA, provided that these tumors decreased in size. Respondents provided similar responses with regards to intervention and follow-up between the two vignettes with more or less than 30% tumor diameter reduction (*i.e.* the RECISTv1.1 cut-off for partial tumor regression).[24] Follow-up of HCA after OCP cessation is safe[17], and six months wait-and-see might be too short for large HCA (*i.e.* >7-10 cm) to regress to sub-5 cm size. Consequently, prolongation of the six-month period has been suggested.[31] Half of the respondents would advise to continue follow-up of postmenopausal patients with HCA <5 cm, although there is evidence for safety and good prognosis of HCA after menopausal onset, which has

been argued to allow for safe discontinuation of follow-up.[32] A few respondents advised CE-MRI for pregnant patients. The teratogenicity of CE-MRI, however, has not been refuted yet and pregnancy is therefore still considered a contraindication for CE-MRI. If truly indicated, an unenhanced MRI may be performed but only from the second trimester onwards.

The current study may be limited by its sample size, yet all specialties and various European countries were represented. In addition, only a limited number of clinical vignettes could be presented due to constraints of time for the respondents to fill in the survey. However, we have selected and presented some of the most controversial and relevant clinical situations in the field of BLT management.

Future studies and clinical practice guidelines could focus on the areas uncovered in the current survey to provide additional data for European professionals. Using the Delphi method could improve clinical (and scientific) consensus on management using currently available data as well as identify areas of future research.[33] These areas include diagnostic and follow-up strategies for FNH-HCA differentiation, HCA >5 cm before, during, and after pregnancy, HCA in post-menopausal women, management of HCA >5 cm after six-months of lifestyle changes, and duration of follow-up in HCA <5 cm. Reduction of European clinical ambiguity on BLT may decrease unwarranted treatment variation and could improve patient care.

In conclusion, our survey illustrates substantial variability in FNH and HCA management among European expert centers. Several areas were identified for future research and guideline recommendations, including FNH follow-up and the management of HCA >5 cm. We propose the organization of Delphi consensus meetings to prioritize new areas of research and update current guidelines to optimize management for all patients with benign liver tumors.

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CHAPTER 4

Behavior and Complications of Hepatocellular Adenoma During Pregnancy and Puerperium: A Retrospective Study and Systematic Review

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Abstract

Background

Hepatocellular adenomas (HCA) are benign liver tumors at risk of hemorrhage. The influence of pregnancy on HCA growth and potential bleeding remains unclear. This study investigates HCA-associated behavior and bleeding complications during or shortly after pregnancy.

Methods

(I) Single center retrospective cohort study of HCA during and after pregnancy. (II) Systematic literature review.

Results

The retrospective study included 11 patients, of which 4 with HCA ≥5 cm. In only two patients HCA showed growth during pregnancy. In this local cohort, no HCA-related hemorrhages occurred during median follow-up of 34 months (interquartile range 19-58 months). The systematic review yielded 33 studies, totaling 90 patients with 99 pregnancies. Of 73 pregnancies without prior HCA-related intervention, 39 HCA remained stable (53.4%), 11 regressed (15.1%), and 23 (31.5%) progressed. Fifteen HCA-related hemorrhages occurred in HCA measuring 6.5-17.0 cm. Eight patients experienced bleeding during pregnancy, two during labor and five postpartum.

Discussion

Although hemorrhage of HCA during or shortly after pregnancy is rare and only reported in HCA ≥6.5 cm, it can be fatal. Pregnancy in women with HCA, regardless of size, warrant a close surveillance strategy. Observational studies on behavior and management of HCA ≥5 cm during and immediately after pregnancy are needed.

Introduction

Hepatocellular adenomas (HCA) are rare, benign liver tumors. HCA can be complicated by bleeding (15-20%) and malignant transformation (4-5%). These complications are related to tumor diameter, and typically occur in HCA ≥5 cm.[1–6] HCA growth can be stimulated by estrogen, either of endogenous (*i.e.* from adipose tissue) or exogenous origin.[1,6–8] Consequently, obesity or weight loss and chronic use or cessation of oral contraceptive pills (OCP) can either lead to HCA stimulation or regression.[7,9,10]

HCA are classified into subtypes, diagnosed through either immunohistochemistry or molecular analyses with specific morphological and etiological features, clinical characteristics, and behaviors.[2,6] Inflammatory HCA (I-HCA; 40-55% of HCA), hepatocyte nuclear factor 1a (*HNF1A*) inactivated HCA (H-HCA; 30-40% of HCA) rarely bleed or show malignant transformation, beta-catenin activated HCA (b-HCA; 10%) are at risk for malignant transformation to hepatocellular carcinoma (HCC). Importantly, half of b-HCA are hybrid b-catenin/inflammatory HCA (b-IHCA).[6] Finally, sonic hedgehog and roof plate spondin-2 HCA have been identified, the former being prone for hemorrhage.[6,11] U-HCA is diagnosed if analyses cannot identify any subtype. Pregnancy-associated estrogen increase may lead to HCA growth and potentially (lethal) hemorrhage.[12] Risk of gestational HCA hemorrhage, however, is largely unknown. Consequently, diagnostic strategy, follow-up, and management of HCA during pregnancy, remain controversial, especially in HCA ≥5 cm.

Current guidelines provide limited recommendations regarding diagnostics, treatment, or mode of delivery on HCA diagnosed prior to or during pregnancy.[13–16] We reviewed our records to evaluate the behavior, complications, and outcome of HCA during gestation and puerperium at our center. Subsequently, a literature review was performed to compare our data with the current literature.

Methods

This study consists of two sections: (1) a single center retrospective study; and (2) a systematic review of the current literature. This study was approved by the local medical ethical committee (METc2020/064-UMCG/RR2020000071).

Retrospective analysis of HCA during pregnancy and puerperium

Electronic patient files of patients with HCA diagnosed prior to or during pregnancy during January 2010-December 2020 were retrospectively investigated. HCA size and number were extracted from radiology reports. HCA size on either cross-sectional imaging or ultrasound (US) was reported during diagnosis, latest observation before pregnancy, latest observation during pregnancy, and last observation. If no recorded measurement during pregnancy was available, measurements up to two weeks post-partum were used. Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were applied.[17] Paraphrased criteria are: "complete regression" defined by disappearance of all tumors, "regression" defined by ≥30% regression, "growth" defined by ≥20% increase in diameter, and "stable" defined by neither sufficient growth for being classified as "growth" nor sufficient regression for "regression". Extraction of all measurements was supervised by a radiologist (R.J.D.H.). Lastly, HCA related complications, invasive treatments, methods of delivery, and duration of follow-up were extracted.

Statistical analyses

Continuous variables were described using the median with interquartile range (IQR) or range, whereas nominal and ordinal variables were described using totals, frequencies, and percentages. The statistical analyses were performed using IBM SPSS statistics v23.0 (SPSS Inc., Chicago, IL, USA).

Systematic review on HCA during pregnancy and puerperium

A systematic literature search was performed by two investigators using pre-specified search terms within the electronic bibliographic databases of MEDLINE, EMBASE, and Web of Science, from inception with the latest search on July 10th 2020. Manual reference checks of accepted papers in recent reviews and included papers were performed to supplement the electronic searches. The review protocol was registered at the International Prospective Register of Systematic Reviews; CRD42020181650.[18] Literature search and screening, and data extraction and appraisal were performed in duplicate by M.P.D.H. & C.S.S.

Literature screening

Case reports, case series, and cohort studies from English-language journals were included if they reported on HCA during pregnancy. Reports with missing HCA size were included to reduce publication bias. Bibliographic filters were applied for exclusion of conference abstracts, non-English articles, systematic reviews, and animal studies. Duplicates were excluded manually. Two investigators first independently screened titles and abstracts, and thereafter full texts. Duplicate removal and article screening was performed using the web based, open-access software CADIMA.[19] No blinding strategies were employed. A third investigator (V.E.M.) resolved discrepancies.

Data extraction and critical appraisal

The retrospective study adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[20] The design, conduct, and reporting of the review were according to Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[21] Data were independently extracted in duplicate from included articles in a standardized form. Surgical interventions and HCA size were quoted if explicit reporting of resected hepatic segments or absolute HCA size was missing. Data were presented on a per pregnancy base. Individual patients from cohort studies were pooled together with case reports and case series if sufficient information was provided and reported separately if not. Separately reported cases were excluded from data synthesis but included in the discussion of data. Two independent investigators appraised levels of evidence using the Oxford Centre for Evidence-based Medicine Level of Evidence (OCEBM) scale, the Newcastle-Ottawa Scale (NOS), and the Enhancing the Quality and Transparency of Health Research Network consensus-based Clinical Case Reporting (EQUATOR-CARE) guidelines.[22–25]

Definitions

HCA size behavior in the included studies was extracted and categorized into growing, stable, or regressing. RECISTv1.1 definitions were applied if possible.[17] Extraction of all measurements was supervised by a radiologist (R.J.D.H.).

Results

Retrospective analysis of HCA during pregnancy and puerperium

From a total cohort of 332 HCA patients, 11 patients were identified with HCA diagnosed either prior to or during pregnancy (**Table 1**). All patients had a history of OCP use. Median (IQR) age of diagnosis was 26 years (25-30). Two patients were diagnosed with hepatic adenomatosis (*i.e.* ≥10 HCA). Five HCA with subtype analysis on histopathology were diagnosed as I-HCA, and one I-HCA was diagnosed on contrast-enhanced magnetic resonance imaging (CE-MRI). Other patients had a median (IQR) of 2 HCA (1-3). Median (IQR) size at diagnosis was 27 mm (24-63), and prior to pregnancy 28 mm (14-63). Four out of 11 patients had HCA >5 cm (36.4%). Two HCA grew during pregnancy; both HCA <5 cm. All HCA among the four patients with HCA >5 cm showed stable behavior during pregnancy. Postpartum, 6 HCA were stable, and 5 regressed (complete regression in two patients). There were 2 Cesarean sections (CS), 1 due to HCA size (67 mm), and 1 because of fetal breech position. No HCA induced hemorrhages were observed during the median (IQR) follow-up period of 34 months (19-58). No (minimally) invasive treatments for HCA were performed prior to or during pregnancy. No relation was observed between HCA behavior after pre-pregnancy OCP cessation and HCA behavior during or after pregnancy.

Systematic review of the literature on HCA during pregnancy and puerperium

Quantity and quality of included evidence

Among 311 unique articles identified in the search, 33 fell within the scope of the study (**Figure 1**). Twenty-eight case reports and case series were included.[12,26–53] Five cohort studies were included.[3,12,54–56] All included cohort studies scored ≥6on the NOS and provided OCEBM level three evidence. None of the included case series adhered to CARE guidelines. Data from 28 case reports or series and one cohort study were pooled, resulting in 90 patients during 99 pregnancies (**Table 2**).[12,26–53] OCP status was reported in most studies (79%).[26,28,30,42–45,52] Four cohort studies reported insufficient information on patient characteristics, HCA size, and HCA behavior for reporting and pooling of individual patients.[3,54–56] One case report and one cohort study reported on hepatocyte

nuclear factor 1a maturity onset diabetes of the young (HNF1A-MODY)-associated HCA.[40,55] One cohort study described glycogen storage disease (GSD)-associated HCA.[56]

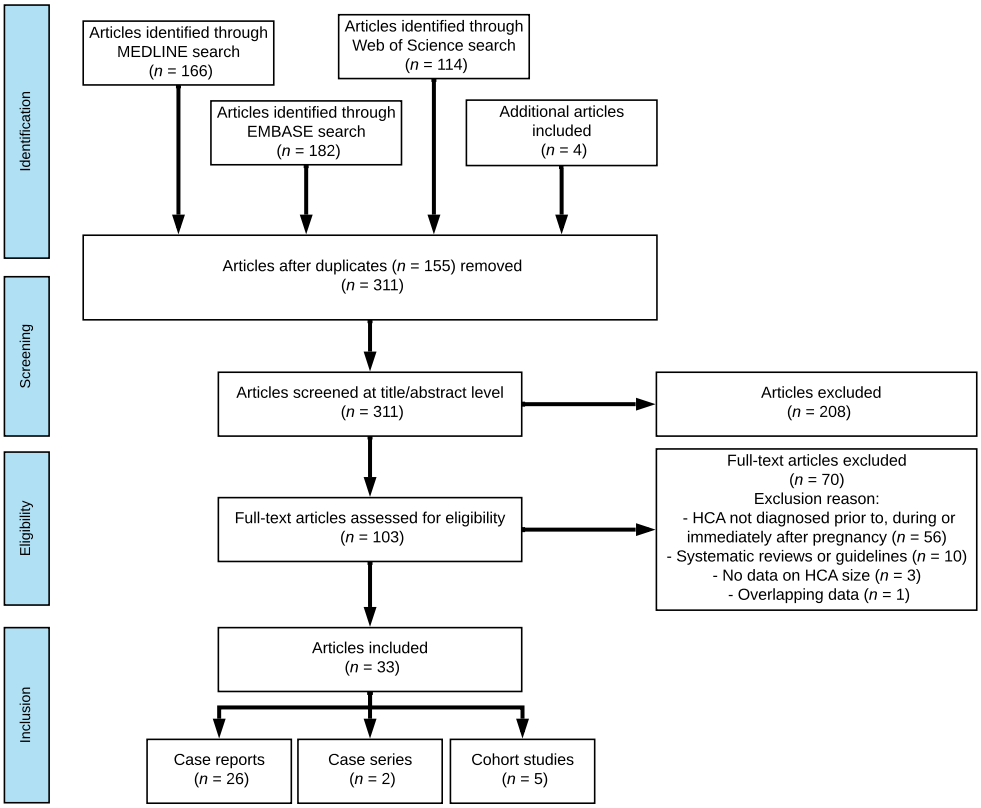

Figure 1. Flowchart of systematic literature search.
Abbreviations: HCA, hepatocellular adenoma.

Table 1. Overview of baseline, gestational, and postpartum characteristics of patients with HCA during pregnancy

Case ID	Age of diagnosis (years)	No. of HCA	HCA Subtype	Timing of HCA diagnosis	HCA size at diagnosis (mm)	HCA size last observation prior to pregnancy (mm)	HCA size during pregnancy (mm, trimester)	HCA behavior during pregnancy	HCA behavior postpartum	HCA size postpartum (mm)	Follow-up postpartum (months)	HCA bleeding complication	Mode of delivery & indication for CS
A	37	4	I-HCA	Prior to pregnancy	63	63	67, 3rd trimester	Stable	Stable	67	34	None	CS, HCA size
B	26	1	I-HCA*	Prior to pregnancy	104	82	91, 3rd trimester	Stable	Stable	66	19	None	Vaginal
C	26	2	No subtype analysis	Prior to pregnancy	15	14	36, 3rd trimester	Growth	Stable	19	69	None	Vaginal
D	17	1	N/A	Prior to pregnancy	27	28	Unobservable	N/A	Regression	18	24	None	Vaginal
E	31	3	I-HCA	Prior to pregnancy	62	62	57, 3rd trimester	Stable	Stable	51	2	None	Vaginal
F	24	>10	I-HCA	Prior to pregnancy	36	30	31, 3rd trimester	Stable	Stable	31	67	None	Vaginal
G	26	3	N/A	Prior to pregnancy	24	11	11, 3rd trimester	Stable	Complete regression	4	9	None	Vaginal
H	30	>10	I-HCA	Prior to pregnancy	24	24	31, 2 weeks postpartum	Growth	Regression	18	58	None	Vaginal
I	26	1	N/A	Prior to pregnancy	27	16	14, 3rd trimester	Stable	Regression	9	47	None	CS, breech position
J	28	1	N/A	Prior to pregnancy	18	10	Unobservable	Complete regression	Complete regression	0	29	None	Vaginal
K	25	2	I-HCA	3rd week gestation	63	63	71, 3rd trimester	Stable	Stable	65	58	None	Vaginal

Abbreviations: OCP, oral contraceptive pill; HCA, hepatocellular adenoma; I-HCA, inflammatory hepatocellular adenoma. *HCA subtype diagnosis made on contrast-enhanced magnetic resonance imaging.

Table 2. Behavior of HCA during gestation and puerperium of all studies included in the systematic review

Author (year)	Patient ID-pregnancy	Timing of HCA diagnosis	Largest HCA at diagnosis (cm)	No. of HCA	HCA behavior after OCP stop	HCA behavior during pregnancy	HCA diameter at start (cm)	HCA diameter at end (cm)	Behavior postpartum
				HCA <5 cm					
Cobey (2004)[26]	1-1	Prior to pregnancy	-	1	-	-	-	4.0	Stable
	1-2	Prior to pregnancy	4.0	1	-	Growth	4.0	10.7	Growth
Fujita (2006)[27]	2	Prior to pregnancy	3.0	2	-	Growth (Surgery + RFA)	3.0	4.0	Regression
Wilson (2011)[28]	3	During, 3rd trimester	3.4	3	-	Stable	-	-	Stable
Noels (2011)[29]	4	Prior to pregnancy	All <5 cm	3	Stable (Surgery)	Stable	-	-	-
Noels (2011)[29]	5-1	Prior to pregnancy	<5 cm	1	Regression	Stable	-	-	Regression
	5-2	Prior to pregnancy	<5 cm	1	Regression	Stable	-	-	Regression
Noels (2011)[29]	6-1	Prior to pregnancy	All <5 cm	"Multiple"	-	Growth to >5 cm	3.2	7.5	Regression & stable
	6-2	Prior to pregnancy	All <5 cm	"Multiple"	-	Growth to >5 cm	4.0	-	Regression & stable
Noels (2011)[29]	7	Prior to pregnancy	All <5 cm	"Multiple"	Regression	Stable	-	-	-
Noels (2011)[29]	8-1	Prior to pregnancy	All <5 cm	3	-	Growth, <5 cm	-	-	Regression
	8-2	Prior to pregnancy	All <5 cm	3	-	Stable	-	-	-
Noels (2011)[29]	9-1	During, unreported	≥5 cm	1	-	Growth to >5 cm	-	-	Regression
	9-2	During, unreported	≥5 cm	1	-	N/A (RFA)	-	-	Not visible on US
Noels (2011)[29]	10	Prior to pregnancy	All <5 cm	"Multiple"	Stable (Surgery)	Stable	-	-	Regression
Noels (2011)[29]	11	Prior to pregnancy	<5 cm	1	Regression	-	-	-	Regression
Klompenhouwer (2017)[30]	12	Prior to pregnancy	4.6	-	-	Growth	4.6	6.5	Regression
Klompenhouwer (2017)[30]	13	Prior to pregnancy	3.0	-	-	Stable	3.0	3.0	Stable
Gaspersz (2020)[12]	14-61	Prior to pregnancy	All <5 cm	-	Regression *n*=26 Stable *n*=14 N/A *n*=11	Regression 22% Stable 53% Growth 25% (TAE *n*=1)	2.3 (1.9-3.9)[§]	Growth of 1.4 (0.8-1.9)[§]	All uncomplicated

*TAE procedure prior to pregnancy. #RFA during 1st trimester. †Co-occurring HNF1A-MODY. ‡Two TAE and one electroporation procedures prior to pregnancy. § Median (IQR). Abbreviations: HCA, hepatocellular adenoma; OCP, oral contraceptives; MRI, magnetic resonance imaging; CE-CT, contrast-enhanced computed tomography; US, ultrasound; TAE, transarterial embolization; RFA, radiofrequency ablation; HNF1A-MODY; hepatocyte nuclear factor 1A maturity onset diabetes of the young; LT, liver transplantation.

Table 2. Behavior of HCA during gestation and puerperium of all studies included in the systematic review (continued)

Author (year)	Patient ID-pregnancy	Timing of HCA diagnosis	Largest HCA at diagnosis (cm)	No. of HCA	HCA behavior after OCP stop	HCA behavior during pregnancy	HCA diameter at start (cm)	HCA diameter at end (cm)	Behavior postpartum
			HCA 5-10 cm						
Antoniades (1975)[31]	62	Postpartum	6.5	1	-	-	-	-	N/A, resected
Lansing (1976)[32]	63	Postpartum	7.5	1	-	-	-	-	N/A, resected
Hibbard (1976)[33]	64	During, 3rd trimester	"⅓ of right hepatic lobe"	1	-	-	-	-	N/A, death
Kent (1977)[34]	65	During, 3rd trimester	7.0	1	-	-	-	-	-
Kent (1977)[34]	66	During, labor	"½ of right hepatic lobe"	1	-	-	-	-	-
Kent (1978)[35]	67	During, labor	"⅓ of right hepatic lobe"	1	-	-	-	-	N/A, death
Monks (1986)[36]	68	During, 3rd trimester	8.0	1	-	-	-	-	N/A, resected
Terkivatan (2000)[36]	69	During, 1st trimester	9.0	1	-	N/A (Surgery)	9.0	-	N/A, resected
Jabbour (2005)[38]	70	Prior to pregnancy	6.0	3	-	Growth (Surgery)	-	-	N/A, resected
Santambrogio (2009)[39]	71	Prior to pregnancy	5.0	1	-	Growth to ≥5 cm	5.0	12.0	N/A, LT
Wilson (2011)[28]	72	Prior to pregnancy	5.0	"Multiple"	-	Stable (Surgery)	-	-	N/A, resected
Noels (2011)[29]	73	Prior to pregnancy	One ≥5 cm	2	Regression	Stable	-	-	-
Noels (2011)[29]	74	Prior to pregnancy	One ≥5 cm	3	Stable (Surgery)	Stable	-	-	Not visible on US
Noels (2011)[29*]	75-1	Prior to pregnancy	One ≥5 cm	2	Growth (TAE)	Stable	-	-	Regression & stable
	75-2	Prior to pregnancy	One ≥5 cm	2	Growth (TAE)	Stable	-	-	-
Noels (2011)[29#]	76	Prior to pregnancy	One ≥5 cm	"Multiple"	No OCP	Stable (RFA)	-	-	Regression (RFA)

Table 2. Continued

Author (year)	Patient ID-pregnancy	Timing of HCA diagnosis	Largest HCA at diagnosis (cm)	No. of HCA	HCA behavior after OCP stop	HCA behavior during pregnancy	HCA diameter at start (cm)	HCA diameter at end (cm)	Behavior postpartum
Jeannot (2012)[40 †]	77	During, 2nd trimester	6.0	>30	-	-	-	-	-
Scheffer (2014)[41 ‡]	78	Prior to pregnancy	5.2	1	Stable (TAE & EP)	Regression	6.9 cm^3	5.2 cm^3	-
Gryspeerdt (2017)[42]	79	During, 2nd trimester	9.0	1	-	- (Surgery)	9.0	-	N/A, resected
Sanford (2020)[43]	80	During, 3rd trimester	6.5	1	-	-	-	-	Regression (TAE)
			HCA ≥10cm						
Baird (1971)[44]	81	During, 3rd trimester	16.0	1	-	-	-	-	N/A, death
Motsay (1972)[45]	82	Postpartum	10.0	1	-	-	-	-	N/A, resected
Stenwig (1975)[46]	83	During, 3rd trimester	10.0	1	-	-	-	-	N/A, resected
Hayes (1977)[46]	84	Postpartum	10.0	1	-	-	-	10.0	N/A, death
Stock (1985)[48]	85	During, 1st trimester	18.0	1	-	Growth (Abortion)	-	-	Necrosis after abortion, resection
Tsang (1989)[49]	86	During, 2nd trimester	15.0	3	-	-	-	-	N/A, resected
al-Otaibi (1995)[50]	87	Postpartum	17.0	1	-	-	-	-	Regression
Hill (1997)[51]	88	During, 2nd trimester	10.0	3	-	Stable (Resection)	-	-	N/A, resected
Stoot (2006)[52]	89	During, 3rd trimester	10.0	4	-	-	-	10.0	-
Bernstein (2019)[53]	90	During, 3rd trimester	16.1	1	-	-	-	-	Regression (TAE + Resection)

*TAE procedure prior to pregnancy. #RFA during 1st trimester. †Co-occurring HNF1A-MODY. ‡Two TAE and one electroporation procedures prior to pregnancy. § Median (IQR). Abbreviations: HCA, hepatocellular adenoma; OCP, oral contraceptives; MRI, magnetic resonance imaging; CE-CT, contrast-enhanced computed tomography; US, ultrasound; TAE, transarterial embolization; RFA, radiofrequency ablation; HNF1A-MODY; hepatocyte nuclear factor 1A maturity onset diabetes of the young; LT, liver transplantation.

Table 3. Treatment and outcomes of HCA induced hemorrhage in studies included in the systematic review

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	Timing of HCA induced hemorrhage	Treatment	Postoperative course	Maternal outcome	Fetal outcome
				HCA 5-10 cm				
Antoniades (1975)[31]	62	6.5	1	5 Weeks postpartum	Segment resection	Uncomplicated	Alive	Alive
Lansing (1976)[32]	63	7.5	3	9 Days postpartum	Lobectomy	Uncomplicated	Alive	Alive
Hibbard (1976)[33]	64	"⅓ of right hepatic lobe"	1	3rd Trimester	None, patient deceased	No surgery performed	Death	Death
Kent (1977)[34]	65	7.0	1	3rd Trimester	Tumor shelled out	Uncomplicated	Alive	Alive
Kent (1977)[34]	66	"½ of right hepatic lobe"	1	During labor	None, patient deceased	No surgery performed	Death	Alive
Kent (1978)[35]	67	"⅓ of right hepatic lobe"	1	During labor	None, patient deceased	No surgery performed	Death	Death
Monks (1986)[36]	68	8.0	1	3rd Trimester	Segment resection	Postoperative transfusions	Alive	Alive
Santambrogio (2009)[39]	89	12.0	1	1 Day postpartum	Primary: gauze packing	Uncomplicated	Alive	Alive
					Secondary: liver transplantation	Uncomplicated		
Sanford (2020)[43]	80	6.5	1	3rd Trimester	Primary: gauze packing, cautery coagulation, TAE	Uncomplicated	Alive	Alive
					Secondary: gauze removal & segment resection	Liver abscess, percutaneous drainage (led to pulmonary & right external iliac vein embolism)		
					Tertiary: segment resection	Uncomplicated		

Table 3. Continued

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	Timing of HCA induced hemorrhage	Treatment	Postoperative course	Maternal outcome	Fetal outcome
				HCA ≥10 cm				
Baird (1971)[44]	81	16.0	1	3rd Trimester	Hysterectomy & mattress sutures	Intraoperative death	Death	Death
Stenwig (1975)[46]	83	10.0	1	3rd Trimester	Segment resection	Uncomplicated	Alive	Death
Hayes (1977)[47]	84	10.0	1	5 Days postpartum	Gauze packing	Death 7 days postoperative	Death	Alive
Tsang (1989)[49]	86	15.0	1	2nd Trimester	Primary: gauze packing & arterial ligation Secondary: tumor shelled out	Uncomplicated	Alive	Abortion
al-Otaibi (1995)[50]	87	17.0	4	2 Weeks postpartum	Segment resection	Unreported	Alive	Alive
Stoot (2006)[52]	89	10.0	1	3rd Trimester	TAE postpartum	Uncomplicated	Alive	Alive

Abbreviations: HCA, hepatocellular adenoma; TAE, transarterial embolization.

Table 4. Indications and outcomes of elective invasive procedures of studies included in the systematic review

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	Timing of invasive procedure	Procedure type	Indication for procedure	Procedure outcome	Procedure related complications
				HCA <5 cm				
Cobey (2004)[26]	1-1	-	1	Postpartum, 1 year	"Resection"	HCA growth	Full resection	Uncomplicated
	1-2	4.0	1	Postpartum, 1 year	"Resection"	HCA growth	Full resection	
Fujita (2006)[27]	2	3.0	2	During, 2nd trimester	Enucleation + RFA	HCA growth	Residual HCA stable	-
Wilson (2011)[28]	3	3.4	3	During, 3rd trimester	Percutaneous biopsy	Tumor diagnosis	HCA diagnosis	Severe HCA induced hemorrhage requiring 2 surgeries and ICU. Fetus and mother survived.
Noels (2011)[29]	4	All <5 cm	3	Prior to pregnancy	Lap. s2/3 resection	Unreported	Residual HCA stable	-
Noels (2011)[29]	5	All <5 cm	"Multiple"	Prior to pregnancy	Lap. s3/6 resection	Unreported	Residual HCA stable	Uncomplicated
Noels (2011)[29]	9-1	≥5 cm	1	Prior to 2nd pregnancy	RFA	HCA size	No residual HCA	Uncomplicated
Gaspersz (2020)[12]	1 patient	All <5 cm	-	During, 2nd trimester	1 case: TAE	HCA growth	Stable at 5.1 cm	Subphrenic abscess, drainage
Motsay (1972)[45]	82	5.2	1	Postpartum, 3 weeks	Right "lobectomy"	Pain	Full resection	

Table 4. Continued

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	Timing of invasive procedure	Procedure type	Indication for procedure	Procedure outcome	Procedure related complications
				HCA 5-10 cm				
Terkivatan (2000)[37]	69	9.0	1	1: During, 1st trimester 2: During, 1st trimester	1: Percutaneous biopsy 2: s2/3 resection	1: Tumor diagnosis 2: HCA size	1: HCA/well differentiated HCC diagnosis 2: Full resection	1: Uncomplicated 2: Uncomplicated
Jabbour (2005)[38]	70	6.0	3	During, 2nd trimester	Open "partial right resection"	HCA growth	Full resection	Uncomplicated
Wilson (2011)[28]	72	5.0	"Multiple"	During, 2nd trimester	Lap. s2/3 + 6 resection	HCA size	Full resection	-
Noels (2011)[29]	74	One ≥5 cm	3	Prior to pregnancy	s4 resection	Unreported	Residual HCA stable	-
Noels (2011)[29]	75-1	One ≥5 cm	2	Prior to pregnancy	TAE	Unreported	Residual HCA stable & regression	-
	75-2	One ≥5 cm	2	Prior to pregnancy	TAE	Unreported	Residual HCA stable & regression	-
Noels (2011)[29]	76	One ≥5 cm	"Multiple"	During, 1st trimester	RFA	HCA growth	RFA: regression, other stable	Uncomplicated
Gryspeerdt (2017)[42]	79	9.0	1	During, 2nd trimester	Lap. s2/3 resection	HCA size	Full resection	Uncomplicated
Sanford (2020)[43]	80	6.5	1	Postpartum, 4 months	Converted lap. S2/3 resection	Residual collection	Full resection	Uncomplicated

Table 4. Continued

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	Timing of invasive procedure	Procedure type	Indication for procedure	Procedure outcome	Procedure related complications
				HCA ≥10 cm				
Scheffer (2014)[41]	78	10.0	1	Prior to pregnancy	1: 2 x TAE 2: Electroporation	HCA size	1: No effect on HCA diameter 2: 90% size reduction	Uncomplicated, uncomplicated pregnancy
Stock (1985)[48]	85	18.0	1	1: During, 1st trimester 2: During, 1st trimester 3: Six weeks after termination	1: Fine needle aspiration 2: Abortion 3: Partial left "segmentectomy"	1: Tumor diagnosis 2: HCA size 3: Tumor necrosis	1: HCA diagnosis 2: No effect on diameter. Hemorrhagic tumor congestion & necrosis 3: Full Resection	1: Uncomplicated 2: Uncomplicated 3: Uncomplicated
Hill (1997)[51]	88	10.0	3	During, 2nd trimester	Open s2-4 + 8 resection	HCA size	Full resection	Uncomplicated
Bernstein (2019)[53]	90	16.1	1	1: Postpartum, 6 days	1: TAE	1: HCA size	1: Some necrosis	1: Infected post-necrotic hematoma, drainage
				2: Postpartum, 2 months	2: "Partial hepatectomy"	2: epigastric pain & residual HCA	2: Full resection	2: uncomplicated

Abbreviations: HCA, hepatocellular adenoma; TAE, transarterial embolization; RFA, radiofrequency ablation; lap, laparoscopic; HCC, hepatocellular carcinoma; ICU, intensive care unit admittance.

Table 5. Mode and outcomes of delivery of all studies included in the systematic review

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	HCA hemorrhage during pregnancy	Mode of delivery & indication for CS	Maternal Outcome	Fetal outcome
			HCA <5 cm				
Cobey (2004)[26]	1-1	-	1	None	Vaginal delivery	Alive	Alive
	1-2	4.0	1	None	CS: HCA size	Alive	Alive
Fujita (2006)[27]	2	3.0	1	None	Vaginal delivery	Alive	Alive
Wilson (2011)[28]	3	3.4	2	Biopsy induced, 3rd trimester	CS: circulatory shock after HCA biopsy	Alive	Alive
Noels (2011)[29]	4	All <5 cm	3	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	5-1	<5 cm	1	None	Vaginal delivery	Alive	Alive
	5-2	<5 cm	1	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	6-1	One ≥5 cm	"Multiple"	None	CS: indication unreported	Alive	Alive
	6-2	One ≥5 cm	"Multiple"	None	CS: indication unreported	Alive	Alive
Noels (2011)[29]	7	All <5 cm	"Multiple"	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	8-1	All <5 cm	3	None	Vaginal delivery	Alive	Alive
	8-2	All <5 cm	3	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	9-1	≥5 cm	"Multiple"	None	Vaginal delivery	Alive	Alive
	9-2	≥5 cm	"Multiple"	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	10	All <5 cm	"Multiple"	None	CS: indication unreported	Alive	Alive
Noels (2011)[29]	11	<5 cm	1	None	Vaginal delivery	Alive	Alive
Klompenhouwer (2017)[30]	12	4.6	-	None	Unreported	Alive	Alive
Klompenhouwer (2017)[30]	13	3.0	-	None	Unreported	Alive	Alive
Gaspersz (2020)[12]	14-61	All <5 cm	-	None	Vaginal delivery *n*=45 CS *n*=6, unrelated to HCA	All alive	All alive

Table 5. Continued

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	HCA hemorrhage during pregnancy	Mode of delivery & indication for CS	Maternal Outcome	Fetal outcome
			HCA 5-10 cm				
Antoniades (1975)[31]	62	6.5	1	Postpartum	Vaginal delivery	Alive	Alive
Lansing (1976)[32]	63	7.5	1	Postpartum	Vaginal delivery	Alive	Alive
Hibbard (1976)[33]	64	"⅓ of right hepatic lobe"		3rd Trimester	No delivery	Death	Death
Kent (1977)[34]	65	7.0	1	3rd Trimester	CS: circulatory shock	Alive	Alive
Kent (1977)[34]	66	"½ of right hepatic lobe"	1	During labor	Vaginal delivery (complicated)	Death	Alive
Kent (1978)[35]	67	"⅓ of right hepatic lobe"	1	During labor	Vaginal delivery (complicated)	Death	Death
Monks (1986)[36]	68	8.0	1	3rd Trimester	CS: circulatory shock & failure to progress	Alive	Alive
Terkivatan (2000)[37]	69	9.0	1	None	Vaginal delivery	Alive	Alive
Jabbour (2005)[38]	70	6.0	3	None	Vaginal delivery	Alive	Alive
Wilson (2011)[28]	72	5.0	"Multiple"	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	73	One ≥5 cm	2	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	74	One ≥5 cm	3	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]*	75-1	One ≥5 cm	2	None	Vaginal delivery	Alive	Alive
	76-2	One ≥5 cm	2	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]#	76	One ≥5 cm	"Multiple"	None	Vaginal delivery	Alive	Alive
Jeannot (2012)[40]†	77	6.0	>30	None	Vaginal delivery	Alive	Alive
Scheffer (2014)[41]‡	78	5.2	1	None	Vaginal delivery	Alive	Alive
Gryspeerdt (2017)[42]	79	9.0	1	None	Vaginal delivery	Alive	Alive
Sanford (2020)[43]	80	6.5	1	3rd Trimester	CS: circulatory shock	Alive	Alive

Table 5. Continued

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	HCA hemorrhage during pregnancy	Mode of delivery & indication for CS	Maternal Outcome	Fetal outcome
			HCA ≥10 cm				
Baird (1971)[44]	81	16.0	1	3rd Trimester	No delivery	Death	Death
Motsay (1972)[45]	82	10.0	1	None	Vaginal delivery	Alive	Alive
Stenwig (1975)[46]	83	10.0	1	3rd Trimester	CS: circulatory shock & fetal bradycardia	Alive	Death
Hayes (1977)[47]	84	10.0	1	Postpartum	CS: pre-eclampsia & fetal distress	Death	Alive
Stock (1987)[48]	85	18.0	1	None	No delivery	Alive	Abortion
Tsang (1989)[49]	86	15.0	3	2nd Trimester	Spontaneous abortion	Alive	Abortion
al-Otaibi (1995)[50]	87	17.0	1	Postpartum	Unreported	Alive	Alive
Hill (1997)[51]	88	10.0	3	None	CS: failure to progress	Alive	Alive
Stoot (2006)[52]	89	100	4	3rd Trimester	Vaginal delivery (induced after hemorrhage)	Alive	Alive
Santambrogio (2009)[39]	71	12.0	1	Postpartum	CS: abruptio placentae	Alive	Alive
Bernstein (2019)[53]	90	16.1	1	None	CS: HCA size	Alive	Alive

*TAE procedure prior to pregnancy. #RFA during 1st trimester. †Co-occurring HNF1A-MODY. ‡Two transarterial embolization and one electroporation procedures prior to pregnancy. Abbreviations: HCA, hepatocellular adenoma; CS, cesarean section.

Results from pooled data

Response to gestation and puerperium of non-bleeding HCA

Ninety patients during 99 pregnancies with non-bleeding HCA were pooled (**Table 2**). Besides patients 76 and 88, and five out of 48 patients in a cohort study, all had a history of OCP use (92%).[12,29,51] HCA was diagnosed prior to pregnancy in 67 patients with 74 pregnancies (75%). HCA was diagnosed during pregnancy in 18 patients, including 11 in the third trimester and two during labor. HCA was diagnosed postpartum in five patients.

HCA behavior without prior intervention was observed during 73 pregnancies. HCA were ultimately treated in four of these pregnancies (**Tables 2, 3, 4; patients 2, 70, 72 and one of patients 14-61**). Untreated HCA remained stable in 39 (53.4%) pregnancies. Eleven HCA demonstrated spontaneous regression (15.1%). Twenty-three HCA demonstrated growth (31.5%), seven exceeding 5 cm in size (patients 1, 6-1, 6-2, 9-1, 71, and two of patients 14-61). HCA in patient 71 demonstrated the most remarkable growth, progressing from 5 to 12 cm.[39] Postpartum HCA behavior was observed in 18 pregnancies and showed growth on one occasion (patient 1).The remainder of HCA demonstrated either stability or regression.

Fifty-one of the 99 studied pregnancies (patients 14-61) were derived from a prospective cohort study focusing solely on HCA <5 cm.[12] This observational study investigated 48 women during 51 pregnancies with HCA evaluations by US at 14 (±3), 20, 26, 32, and 38 weeks of gestation, and 6-12 weeks postpartum. It was the only study applying RECISTv1.1 criteria. Median (IQR) HCA size was 2.3 cm (1.9-3.9) prior to pregnancy. The cohort included 2 H-HCA, 16 I-HCA, 12 U-HCA, and 18 HCA without subtype determination. There were no HCA-related indications for Cesarean section. HCA demonstrated growth in 13 pregnancies (25%), exclusively during the second and third trimester. No bleedings were reported.

HCA induced bleeding during pregnancy and puerperium

Fifteen HCA bleeding episodes were reported in HCA sized 6.5-17 cm (**Table 3**). Eight bleedings occurred during pregnancy, two during labor, and five postpartum. In all 15 patients the bleeding episode was the presenting symptom of their HCA. Seven out of eight HCA-related hemorrhages during pregnancy occurred in the third

trimester. The two bleeding cases occurred during labor in HCA measuring "⅓ to ½ of right hepatic lobe".[34,35] HCA subtype could not be related to bleeding. Only one bleeding I-HCA was observed (case 79).[42] Four out of five HCA induced postpartum bleedings occurred during the first two weeks after delivery.

Three patients deceased before any intervention could be performed. Bleeding treatment was successful in 10 out of 12 remaining cases (**Table 3**). Four patients underwent primary gauze packing with secondary segment resection (*n*=2) or secondary liver transplantation (*n*=1), one patient deceased prior to secondary surgery. Other interventions were primary segment resection (*n*=6), transarterial embolization (TAE) (*n*=1), and mattress sutures (*n*=1). Although the hemorrhage incidence was low in pooled pregnancies, mortality was reported. Fatal outcome was observed in five out of 15 mothers and five out of 15 fetuses, including one abortion in the second trimester. Three pregnancies had fatal outcome for both mother and fetus.

Outcome of invasive interventions during pregnancy

Three reports described percutaneous HCA biopsy during pregnancy. Two were safely performed during 12 weeks of gestation (**Table 4; patients 69 & 85**).[37,48] One biopsy (**Table 4; patient 3**) in a 3.4 cm HCA at 32 weeks of gestation was complicated by severe hepatic hemorrhage.[28] Treatment consisted of emergency laparotomy with CS, and hepatic gauze packing. Shortly after, second look laparotomy was performed with simultaneous HCA resection, followed by short intensive care unit admittance. Both mother and the newborn survived.

Seventeen patients underwent HCA-related invasive procedures prior to, during, or after pregnancy during 18 pregnancies (**Table 4**). Seven pregnancies featured prior treatment: 3 patients with TAE (one with successive percutaneous electroporation), three with hepatic resection, and one with percutaneous radiofrequency ablation (RFA). Six patients underwent hepatic surgery during pregnancy, five of whom during the second trimester. Indications for surgery were HCA size ≥5 cm in four patients and HCA growth in two. Postpartum interventions were performed in two patients. Right lobectomy was performed in patient 84 due to postpartum abdominal pain.[45] TAE was performed in patient 90 resulting in necrosis and infected hematoma with residual HCA, necessitating partial hepatectomy.[53] Patients 84

and 90 account for the observed intervention-related complications: a subphrenic abscess, and an infected hematoma; both were treated by percutaneous drainage.[45,53]

Safety of vaginal delivery

Ninety-five deliveries were observed in 99 pregnancies. Two pregnancies had fatal outcome for the mother and unborn child due to hemorrhage, and two pregnancies were aborted (one spontaneous). Of full-term pregnancies, 73 (77%) resulted in vaginal delivery (**Table 5**). There were 19 CS for varying indications, with among them eight emergency procedures. Fourteen patients with HCA ≥5 cm delivered vaginally. Hepatic hemorrhage during labor occurred twice (patients 66 & 67), resulting in maternal and fetal death in the latter patient.[34,35] HCA size of these two patients spanned "⅓ to ½ of the right liver lobe". Method of delivery was unreported in three pregnancies.[30,50]

Results from non-pooled data

One single center retrospective study reported surgical interventions and outcomes in 122 HCA patients.[3] The report included nine patients with HCA during pregnancy and observed "moderate progression" without reporting actual size.

Another retrospective cohort study on hepatic adenomatosis reported 29 out of 36 included females (81%) with pregnancy prior to HCA diagnosis.[54] Four patients became pregnant after HCA diagnosis. In one patient, HCA progression was observed after pregnancy. Information on HCA size during pregnancy was not reported. One patient presented with uncontrollable and ultimately lethal hemorrhage in an undiagnosed 15 cm-sized HCA during pregnancy (pregnancy stage and comorbidities were unreported). One patient underwent resection of the largest HCA prior to pregnancy. HCA size, surgical outcomes, and behavior of remnant HCA were missing. It included six *HNF1A* germline mutated patients but did not report on pregnancies in this subgroup.

HCA due to metabolic disease

Two studies reported solely on metabolic disease associated HCA. A retros-pective study on 24 HNF1A-MODY patients with hepatic adenomatosis reported on fourteen pregnancies in eight women without bleeding complications.[55] Three patients had

imaging available: stable disease was observed twice, and regression once. HCA size was not reported. One patient experienced pre-pregnancy hemorrhage (and regression thereafter) in a 7 cm HCA following ovarian stimulation.

The other report described 32 GSD type I patients during pregnancy and included four HCA cases.[56] Two patients showed increase in HCA size or number and one patient had stable disease. Clinical course and HCA size of the latter patient was not reported. There were no HCA-related complications.

Discussion

This study aimed to evaluate HCA behavior, bleeding complications, mode of delivery, and outcomes of invasive treatment during pregnancy and puerperium. It concerned both a retrospective cohort study and a systematic review. The retrospective study included 11 patients, of whom 4 had HCA ≥5 cm. In two patients, HCA growth was observed during pregnancy; both in HCA <5 cm. All HCA with available subtype identification were diagnosed as I-HCA. No complications occurred during pregnancy, puerperium, or postpartum follow-up.

A systematic review was performed to compare our data with the current literature, especially regarding HCA size and bleeding risk association, including 29 studies. Ninety patients (99 pregnancies) in whom HCA were diagnosed before, during, or after pregnancy were reported. HCA remained stable in 39/73 treatment-naive pregnancies (53.4%). Eleven HCA demonstrated spontaneous regression (15.1%). Twenty-three HCA demonstrated growth (31.5%), seven exceeding >5 cm diameter. Fifteen cases of HCA–associated hemorrhage were included, none occurred in the first trimester and all HCA measuring ≥6.5 cm.[33,34,36,43,44,46,49,52] Eight HCA bled during gestation, seven in the third trimester. The remaining seven bleeding cases occurred during labor (n=2) or postpartum (n=5).

Prior studies have observed HCA regression, especially in large HCA, after OCP cessation or weight loss due to estrogen level reduction.[7,9] Strong regression after estrogen level reduction might arguably predict HCA behavior during pregnancy. Yet, this relationship was neither observed in the systematic review, nor in the retrospective study.[12,29]

The current manuscript concerns the second systematic review on HCA during or after pregnancy. The other review focused on focal nodular hyperplasia, hepatic hemangiomas, HCA, and HCC during and after pregnancy, including literature up to 2004.[26] The authors identified 26 reports on HCA and added one local case, totaling 27 pregnancies. The study already reported six postpartum bleeding HCA – yet this potentially hazardous period remains underexposed in clinical practice.[13] Postpartum HCA bleeding might result from HCA regression and necrosis by postpartum declining estrogen levels. Larger HCA might regress and necrotize more extensively causing HCA membrane rupture, yet not all postpartum bleeding HCA showed necrosis.[32]

Accurate HCA diagnosis is vital for optimal management. HCA are diagnosed best non-invasively through CE-MRI (sensitivity 92-97% and specificity 91-100%).[57–60] Pregnancy, however, is still considered a contraindication for CE-MRI by most radiologists because fetal exposure to contrast agents may potentially lead to various skin conditions, stillbirth, and neonatal death.[61] MR exposure itself during the first trimester may be safe but many clinical practice guidelines remain restrictive and await further evidence. Hence, gestational liver tumor diagnosis can be performed through unenhanced MRI in the second or third trimester and thereafter monitored by US (or MRI). Gold standard remains histopathology, although biopsy-associated hepatic hemorrhage may occur (patient 3). Biopsies should therefore only be performed in selected cases with severe treatment implications, and only during early gestation.

Multiple invasive treatment strategies were applied. Elective, uncomplicated, hepatic resections were performed up to the second trimester.[27,28,37,38,42,51] No minimally invasive strategy was identified as superior due to limited observations. Three patients were treated by US-guided RFA: two during pregnancy (patients 2 & 75) and one prior to the second pregnancy (patient 9-2).[27,29] TAE proved less effective with more complications. These observations are anecdotal and cannot be extrapolated to definite conclusions. Previous series have demonstrated effectiveness and safety for TAE and RFA in HCA patients.[62,63]

Several risk factors for symptomatic HCA bleeding, have been identified including diameter ≥5 cm, exophytic growth, hemorrhage observed on imaging, presence of central or peripheral arteries on imaging, sonic hedgehog subtype, and hepatic parenchymal

steatosis >30%.[6,64] Especially H-HCA are less likely to bleed.[6] We suggest not to include HCA subtype into treatment consideration, as this would implicate invasive (biopsy) as well as non-invasive (CE-MRI) diagnostics with its accompanying risk of gestational complications. However, HCA treatment may be considered in selected cases in which one or more risk factors are present. Drafting of a strict treatment algorithm is warranted but unfortunately not feasible with the currently available data. Nevertheless, several recommendations can be made.

(1) Management and surveillance of HCA in pregnancy should always be individualized and performed by a multidisciplinary team.[13] A well-performed observational cohort study by Gaspersz *et al.* prospectively followed 51 pregnancies with HCA <5 cm (median HCA size 2.3 cm) without bleeding complications.[12] In the current literature review, hemorrhage was only observed in women with HCA ≥6.5 cm in size. Although a reasonable estimate of the true risk of HCA hemorrhage in relation to size during pregnancy remains unknown, it seems safe to apply a watchful waiting strategy to women with HCA up to 5-6.5 cm. Close surveillance with US every 6 weeks should be mandatory, however, for any pregnant woman with HCA, regardless of size.

(2) Treatment of bleeding HCA during pregnancy should be decided by bleeding severity and gestational term. TAE may be preferred over surgery in minor, intra-tumoral bleedings during the first or second trimester. Surgery, however, is indicated when intra-abdominal, and especially third trimester, bleeding occurs. Fetal monitoring during surgery is essential, and an obstetrician/gynecologist should be on standby for emergency delivery when signs of fetal or patient (circulatory) distress are observed. Pre-emptive treatment, for example by TAE or surgery, may be considered in women who wish to become pregnant in case of large HCA (*e.g.* size ≥6,5-10cm) but only after evaluating HCA size/behavior for at least six months after OCP cessation and lifestyle changes/weight loss. Management and surveillance should always be individualized and performed by a multidisciplinary team.

(3) If high diagnostic suspicion for malignancy arises, unenhanced MRI may be performed from the second trimester onwards. Postpartum confirmation by CE-MRI or biopsy of equivocal tumors is recommended.

(4) Pre-emptive (minimally) invasive treatment of HCA during pregnancy cannot be recommended due to potential risks of teratogenic effects of (anesthesia accompanying) surgery or TAE-associated radiation, and risk of surgery induced (premature) labor without strong evidence for any benefit.

The systematic review is limited by a publication bias of included studies and patients. Substantial underreporting of HCA patients with successful and uncomplicated pregnancies is most likely. Another potential limitation is the inclusion of only retrospective studies, except one report.[12] The quality of included retrospective studies was appraised as moderate to high. The information on HCA behavior only warranted limited conclusions as exact HCA size was only systematically analyzed in the prospective study.[12] None of the included case reports adhered to CARE guidelines, however, all patients were sufficiently described for data pooling.

Concluding, most pregnancies with HCA did not demonstrate HCA-related bleeding complications, and hemorrhage was only observed in HCA ≥6.5 cm. Current guidelines provide limited recommendations for pregnant HCA patients.[13–16] Pregnant HCA patients should be referred to centers with sufficient experience on complex hepatobiliary pathology, (radiological) intervention facilities, and adequate supportive care infrastructure. Close surveillance and adequate diagnostic and treatment escalation decided by a multidisciplinary team is recommended. The current findings warrant a prospective observational cohort study on behavior and treatment strategies of HCA ≥5 cm during gestation and puerperium.

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CHAPTER 5

The Effect of Oral Contraceptive Pill Cessation on Hepatocellular Adenoma Diameter: A Retrospective Cohort Study

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Abstract

Background

Hepatocellular adenoma (HCA) is a rare, sex hormone driven, benign liver tumor. HCA >50 mm are associated with hemorrhage and malignant transformation. Guidelines recommend cessation of oral contraceptive pills (OCP) for size reduction, however, it is currently unknown how HCA respond to cessation of OCP. We sought to investigate the effect of OCP cessation on HCA size.

Methods

A retrospective cohort study was performed including HCA patients who stopped OCP intake within six months of imaging between 2005-2018. Biometrics and hormonal medication use were evaluated with self-designed questionnaires. Response of the largest HCA was evaluated according to Response Evaluation Criteria in Solid Tumors (RECISTv1.1). Cox regression was performed for analysis of factors influencing HCA regression.

Results

Seventy-eight HCA patients were included, diagnosed at a median (IQR) age of 32 (26-41) years. Follow-up was 1.6 (0.4-2.9) years. HCA size at diagnosis ranged 10-167 mm. After a median time of 1.3 (0.6-2.6) years after OCP cessation, 37.2% of HCA showed ≥30% regression, 5.1% complete regression, 56.4% stability, and 1.3% progression. No HCA induced complications were observed during follow-up. Cox regression analysis demonstrated a significant association of HCA size with rate of regression; 50 ≤HCA <100 mm (HR 2.4, 95% CI 1.1-5.3; $p<0.05$), HCA ≥100 mm (HR 8.3, 95% CI 3.3–21.6; $p<0.001$).

Discussion

Ninety-eight percent of HCA remained stable or regressed after OCP cessation. A longer wait-and-see period was associated with a larger proportion of regressing HCA, without HCA related complications during follow-up.

Introduction

Hepatocellular adenomas (HCA) are rare, hormone driven benign liver tumors. They mainly develop in young women in their reproductive age. While HCA have an incidence rate around one per million per year in the general population, long term (>2 years) users of oral contraceptive pills (OCP) have 30 to 40-fold increased risk of developing HCA.[1–3] Main complications are (potentially lethal) hemorrhage (15-20%) and malignant transformation to hepatocellular carcinoma (HCC) (5%).[4–6] HCA of ≥50 mm size are especially at risk for these complications.[4,5,7–9]

HCA can be classified into subtypes. Inflammatory HCA (I-HCA) comprise 40 to 55% and are most common in patients with obesity and/or metabolic syndrome. They are associated with prolonged estrogen exposure.[6] Hepatocyte Nuclear Factor 1a inactivated HCA (H-HCA) comprise 30 to 40% of HCA and bleed only in rare cases. They are seen in patients with significantly less estrogen exposure than I-HCA, suggesting a higher estrogen sensitivity or alternative pathofysiology.[6] Less common are the b-catenin activated adenomas (b-HCA). b-HCA have an increased tendency to transform into HCC and are mostly seen in men. Half of b-HCA are hybrid b-catenin / inflammatory HCA.[6] B-HCA are diagnosed through immunohistochemical analysis of glutamine synthetase. Finally, there are unclassified HCA and sonic hedgehog activated HCA, each accounting for 5 to 10% of HCA.

Sex hormones, or androgens stimulate both de novo formation as well as growth of HCA.[2,10] Hence, women using OCP and those using anabolic steroids are particularly at risk of HCA development. Extra gonadal estrogen is most notably formed by adipose tissue which accounts for 10 to 50% of total estrogen production.[11] Estrogen synthetization rate has been proven to increase with obesity.[12] Vital for a non-invasive management of HCA is that regression can be induced by reduction of circulating estrogen levels, which occurs naturally after the onset of the menopause, or after substantial weight loss.[13]

In addition, HCA are known to form in patients with metabolic disorders such as Glycogen Storage Disease (GSD) and Hepatocyte Nuclear Factor 1A Maturity Onset Diabetes of the Young (HNF1A-MODY). The incidence, etiology, behavior, and treatment of these HCA differ from androgen induced HCA.

The clinical guideline for treatment of benign liver tumors was published by the European Association for the Study of the Liver in 2016.[14] It advices an initial conservative and estrogen level reducing treatment through lifestyle changes in females diagnosed with HCA larger than 50 mm. This reduction is mainly accomplished by weight loss and cessation of all hormonal medication.[15,16] OCP containing progesterone only are excluded, as this hormone has no role in HCA physiology. If during follow-up HCA increase significantly in size (>20%), or if after 6 months of wait-and-see policy HCA remain equal to or larger than 50 mm, resection is advised.

It is well established that OCP are the main risk factor for HCA formation and growth, and that HCA show regression after cessation. However, detailed information on exact OCP use in HCA patients, and HCA behavior after OCP cessation is still lacking. The age of commencement, total duration, and age of cessation of OCP have not yet been observed to influence rate of regression, although research is lacking. Secondly, the current European Association for the Study of the Liver guideline does not take HCA diameter at baseline into account – a 6 month wait-and-see period is advised for all HCA equal to or larger than 50 mm. This period could prove to be frankly too short for regression of large HCA to sub 50 mm size. The aim of this study was to evaluate the response of HCA after OCP cessation, and to evaluate any factors associated with this response.

Methods

Study design and population

All female HCA patients treated at the University Medical Center Groningen between 2005 and 2018 were included. After obtaining informed consent, patients were subjected to a self-designed questionnaire regarding biometrical information, comorbidities, and exact intake of all hormonal medication such as OCP. Analysis was performed on female HCA patients with a history of estrogen containing OCP intake and consecutive imaging available. Baseline imaging was defined as imaging within six months prior to or after OCP cessation. The minimum amount of follow up was at least one scan obtained by either magnetic resonance imaging (MRI) or computed

tomography (CT), six months after OCP cessation or six months after baseline imaging if the HCA was imaged after cessation. Patients were excluded if: OCP intake was stopped after an HCA induced or post biopsy hemorrhage (as tumor diameter could not be observed accurately thereafter), had HCA in concordance with glycogen storage disease or HNF1A-MODY, or if they did not comply with the local opt out research registry. The study protocol was approved by the UMCG ethics committee (UMCG research registry 201700324 - METc 2017/270).

HCA response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[17] These criteria recommend that lesion response should only be evaluated using CT or MRI acquired imaging. Lesions should not be smaller than 10 mm and should be measured in their longest diameter. As advised, lesions were measured in the transversal plane on post contrast series. Imaging from CT was only used when MRI was not available. Response criteria are: "complete response" defined by disappearance of all lesions, "partial response" defined by at least 30% regression, "progressive disease" defined by at least 20% increase of diameter, and "stable disease" defined by neither sufficient growth for being classified as "progressive disease" nor regression for "partial response".

Endpoints

Primary endpoint was HCA response to cessation of OCP as defined by the RECIST criteria. Secondary outcomes were HCA related complications, frequency, indications, and outcomes of invasive treatment, and independent predictors of the rate of HCA regression.

Data collection and definitions

Relevant information was obtained from electronic patient files and a self-designed questionnaire. Obesity was defined by body mass index (BMI) above 30 kg/m^2 and was measured at baseline. One target lesion per patient was followed, defined by the single largest HCA at baseline imaging. These were classified into HCA <50 mm, 50 ≤HCA <100 mm, and HCA ≥100 mm.

Data analysis

Continuous variables were described using the median with interquartile range (IQR), whereas nominal and ordinal variables were described using totals, frequencies, and percentages. Normality was tested using the Shapiro-Wilk test. The Student's t-test or Mann-Whitney U test were used to investigate differences between groups for continuous variables and the chi-square or Fisher exact test for categorical variables. For comparison of three groups either ANOVA or the Kruskal-Wallis test was used. Spearman's Rank-Order was used for analysis of correlation for non-parametric values. A *p*-value ≤0.05 was considered statistically significant. Cox proportional-hazard modeling was used to determine factors that are independently associated with >30% regression in HCA diameter. Patients will be categorized into < or ≥ median values. Categories will be made 1) on less than and 2) equal to or larger than the median. Variables with a *p*-value <0.10 at univariate analysis were included in the multivariate analysis. The statistical analyses were performed using IBM SPSS statistics version 23.0 (SPSS Inc., Chicago, IL, USA). Figures were generated with GraphPad Prism version 5 (GraphPad Software, La Jolla, CA, USA).

Results

Study population and baseline characteristics

In total, 267 HCA patients were treated at the UMCG between 2005 and 2018. Twenty-one patients with concurring GSD, 6 HNF1A-MODY patients, and 2 male patients diagnosed with HCA were excluded. Of the remaining 238 patients, another 116 were excluded as their OCP use outmatched the inclusion criteria. Thirty-one patients in whom an intervention was performed before the effect of the lifestyle advices could be observed, and 13 patients in whom no observation of OCP cessation was possible, were also excluded, thereby leaving 78 patients available for analysis (**Figure 1**).

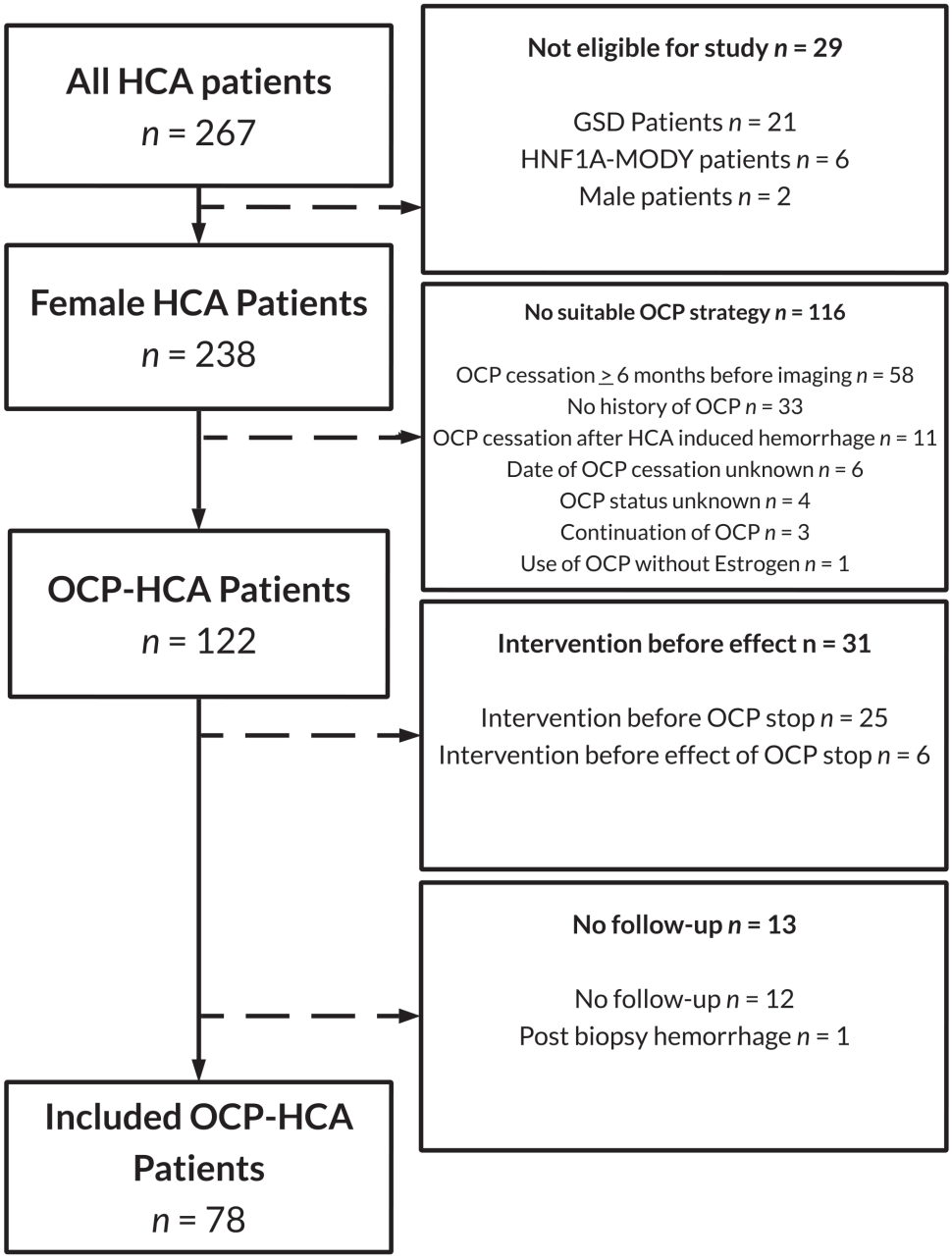


Figure 1. Flowchart of included patients. Abbreviations: HCA, hepatocellular adenoma; GSD, glycogen storage disease; HNF1A-MODY, hepatocyte nuclear factor 1a inactivated maturity onset diabetes of the young; OCP, oral contraceptive pill.

HCA were diagnosed at a median age of 32 (27-41) years. About a third of patients had obesity and 11.5% had a BMI ≥40 kg/m^2. HCA size at diagnosis ranged from 10 mm to 167 mm and had a median size of 49 mm. Patients started the intake of OCP at a median age of 15 (14-17) years and stopped after 15 (10-24) years of intake. Two thirds of patients took an estrogen/progesterone combination preparation containing less than 50 μg estrogen, 3.8% took a preparation with 50 μg, and estrogen dosage was unknown in 21 patients (26.9%). Obese patients were more often diagnosed with larger HCA, as the median size of the HCA was 37 (27.5-79.5) mm in patients with a BMI ≤30 kg/m^2 compared to 57.5 (45.0-94.3) mm of patients with BMI ≥30 kg/m^2 (p=0.01). Age at diagnosis, however, was similar (34.0 vs. 32.5 years; p=0.74). A Spearman's rank-order correlation was performed to analyze the correlation of the age of commencement and total duration of OCP intake to HCA size at diagnosis. Earlier commencement was not associated with larger HCA ($r_s(11)$)=0.085, p=0.53), and neither was total duration of OCP intake ($r_s(11)$)=0.050, p=0.71) (**Table 1**).

Table 1. Baseline Characteristics

HCA size at diagnosis	<50 mm *n*=39	≥50 – <100 mm *n*=26	≥100 mm *n*=13	*p*-value
Female	39 (100%)	26 (100%)	15 (100%)	-
Age at diagnosis, years	31.0 (26.0-40.0)	36.5 (29-44)	31.0 (24.5-41.0)	0.21*
Body Mass Index, kg/m²	27.0 (22.9-33.4)	32.0 (25.7-35.3)	30.6 (28.1-34.3)	0.08*
Oral Contraceptive Use				
Age at start, years	15.0 (14.0-16.0)	16.0 (14.0-18.0)	15.0 (14.0-17.0)	0.62^
Age at cessation, years	31.0 (27.0-40.0)	33.0 (29.0-41.0)	29.5 (25.0-39.3)	0.47*
Duration of intake, years	13.0 (7.0-27.0)	17.0 (11.5-23.8)	17.0 (10.5-23.0)	0.85*

Values are given in median (IQR) or *n* (%). * = Kruskal-Wallis test, ^ = ANOVA.

HCA Response to OCP cessation

At the end of follow-up 4 HCA demonstrated a complete response (5.1%), 29 HCA (37.2%) showed a partial response, 44 HCA (56.4%) remained stable, and 1 HCA (1.3%) showed progression (**Figure 2**). The HCA that demonstrated growth progressed from 10 to 16 mm during 7 months, however, no further follow-up was available. All of the 4 HCA with a complete response were smaller than 50 mm at diagnosis.

Of the remaining 35 HCA <50 mm, 8 demonstrated a partial response (20.5%), 1 was progressive (2.6%), and 26 (66.7%) remained stable. None of the HCA <50 mm progressed to a ≥50 mm diameter. Thirty-nine HCA were larger than 50 mm at diagnosis, median size at diagnosis 86 (60 – 110) mm and final diameter 55 (41 – 81) mm after 1 (0.4 – 2.9) year.

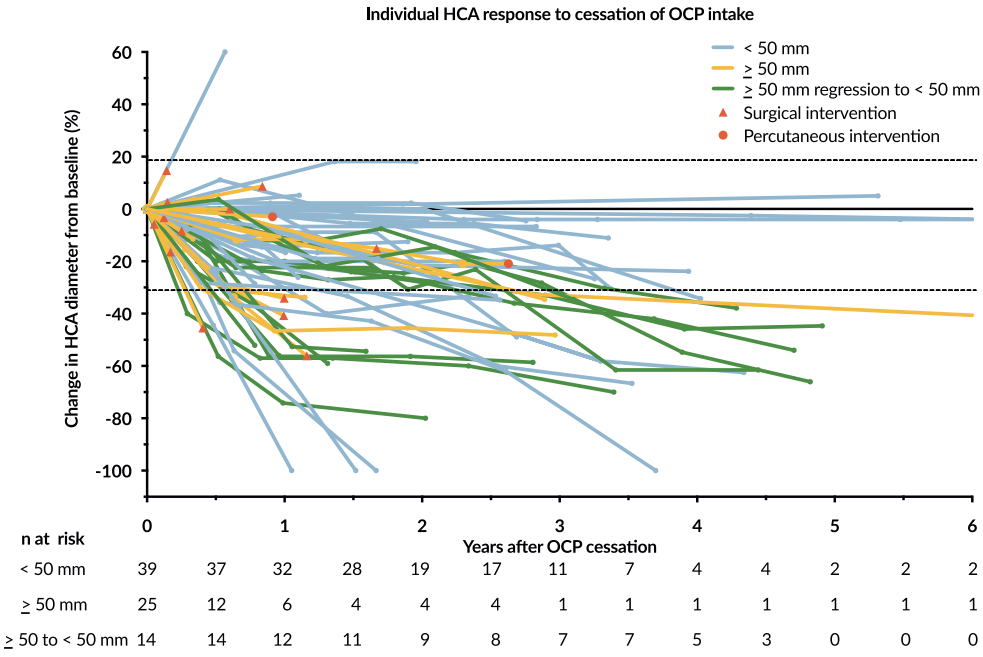


Figure 2. Spider plot of the relative change of largest HCA diameter from baseline over time
Patients (*n*=78) are color coded based on overall response. Horizontal dashed lines represent Response Evaluation Criteria In Solid Tumors version 1.1 guideline for partial response (≥30% decrease in target lesion) and progressive disease (≥20% increase in target lesion). Abbreviations: HCA, hepatocellular adenoma; OCP, oral contraceptive pill. Legend: Blue, HCA diameter <50 mm; Orange, HCA diameter >50 mm; Green, HCA diameter >50 mm at baseline, regression to <50 mm size; Red triangle, surgical intervention; Red circle, percutaneous intervention

In this subgroup stable disease was seen in 18 HCA (46.2%), and 21 HCA (53.8%) demonstrated a partial response. Fourteen patients (35.9%) of the latter group regressed to <50 mm size from a median diameter of 65.5 (56.5-95.5) mm after a median follow-up of 1.3 (0.9-3.3) year. Analysis of response per HCA subtype was not possible due to insufficient patient numbers for HCA subtypes other than I-HCA (**Table 2**).

HCA related complications

No HCA related complications occurred during follow up. Although two b-HCA were observed, at risk for malignant transformation, there were no cases of actual malignant degeneration to HCC during the follow-up period.

Table 2. HCA Response and management after cessation of OCP

	Included patients with HCA *n*=78
T0: HCA Diagnosis	
HCA diameter at diagnosis, mm	49.0 (30.8 – 86.0)
Interval between OCP cessation – T0, months	0 (-0.8 – 1.0)
No. of observed HCA	78
First follow-up (T1)	
HCA diameter at first follow-up, mm	50 (27.0 – 65.0)
Interval between T0 – T1, months	5.4 (4.1 – 6.4)
No. of observed HCA	59
Second follow-up (T2)	
HCA diameter at second follow-up, mm	41.0 (24.0 – 61.0)
Interval between T0 – T2, months	11.6 (9.9 – 13.2)
No. of observed HCA	42
Total follow-up time, years	1.1 (0.5 – 2.6)
HCA subtype	
H-HCA	2 (2.6%)
I-HCA	23 (29.5%)
b-HCA	-
b-IHCA	2 (2.3%)
U-HCA	2 (2.3%)
No histopathology or subtype analysis available	49 (62.8%)
Management	
Conservative	60 (76.9%)
Intervention	18 (23.1%)

Abbreviations: HCA, hepatocellular adenoma; H-HCA, hepatocyte nuclear factor 1A inactivated HCA; I-HCA, inflammatory HCA; b-HCA, b-catenin activated HCA; b-IHCA, hybrid b-HCA/I-HCA; U-HCA, unclassified HCA. Values are given in median (IQR) or *n* (%). For HCA subtype explanation, see introduction.

Interventions

Eighteen patients underwent invasive treatment for HCA, at a median of 8.5 (5.8 – 14.1) months after diagnosis (**Table 3**). Most cases were treated through either segment resection (*n*=10) or (extended) hemi-hepatectomy (*n*=5). Open thermal ablation of an

additional lesion was performed in three patients with segment resections. Three cases were treated through minimally invasive percutaneous treatment – radiofrequency or microwave ablation or trans-arterial embolization. Almost two thirds of ≥50 mm HCA (25 out of 39) remained larger than 50 mm in size and thus were potential candidates for surgery. Nearly a quarter of patients in whom HCA were resected, the indication for surgery was the inability to exclude (well-differentiated) HCC at either MRI or histopathologic analysis. All of these HCA demonstrated washout on contrast-enhanced MRI. Percutaneous biopsy was performed in two patients, which had a suspicion for malignant characteristics on immunohistochemical analysis. No HCC were found and only one case had a beta catenin mutation (**Table 4**).

There were two major complications and one minor complication (urine tract infection) postoperatively. One patient developed an abdominal incisional hernia after an open Couinaud segment 2, 3, and 6 resection requiring reoperation for mesh repair. Another patient experienced biliary leakage after a left hemihepatectomy requiring a reoperation with a Roux-en-Y hepaticojejunostomy.

Table 3. Patients with invasive treatment

	Included patients with HCA *n*=18
Age at treatment, years	32 (32.0-39.5)
HCA and OCP characteristics	
HCA diameter at baseline, mm	93.5 (71.5-120.8)
HCA diameter before intervention, mm	80.5 (61.0-102.3)
Interval between cessation of OCP and intervention, months	11.0 (4.8-14.3)
Treatment type	
Resection	15 (83.3%)
Percutaneous thermal ablation	2 (11.1%)
Transarterial embolization	1 (5.6%)
Indication	
HCA size ≥50 mm after lifestyle advices	9 (50.0%)
Unable to rule out malignancy	4 (22.2%)
Patient's own wish	3 (16.7%)
HCA induced symptoms	1 (5.6%)
Wish to become pregnant	1 (5.6%)

Abbreviations: HCA, Hepatocellular Adenoma; OCP, Oral Contraceptive Pill. Values are given in median (IQR) or *n* (%).

Table 4. Patients with suspected malignancy

Case 1	
Age at diagnosis, years	32
HCA diameter at diagnosis, mm	112
HCA diameter at last follow up, mm	100
Total follow up duration, months	12
MRI, type and findings	MRI gadoxetic acid: wash out on venous phase
Percutaneous histopathology	I-HCA: no b-Cat activation, though some malignant characteristics
Postoperative histopathology	b-IHCA
Type of intervention	Segment II, III resection
Case 2	
Age at diagnosis, years	32
HCA diameter at diagnosis, mm	75
HCA diameter at last follow up, mm	86
Total follow up duration, months	3
MRI, type and findings	MRI gadoxetic acid: atypical HCA, wash out on venous phase
Percutaneous histopathology	N/A
Postoperative histopathology	HCA, no subtype
Type of intervention	Segment II, III and caudal part of VI resection
Case 3	
Age at diagnosis, years	48
HCA diameter at diagnosis, mm	73
HCA diameter at last follow up, mm	61
Total follow up duration, months	2
MRI, type and findings	MRI gadoxetic acid: wash out on venous phase
Percutaneous histopathology	N/A
Postoperative histopathology	I-HCA, no signs of malignancy
Type of intervention	Right hemihepatectomy
Case 4	
Age at diagnosis, years	49
HCA diameter at diagnosis, mm	167
HCA diameter at last follow up, mm	110
Total follow up duration, months	12
MRI, type and findings	MRI gadoteridol: washout on portal venous phase
Percutaneous histopathology	b-IHCA: positive
Postoperative histopathology	I-HCA: glutamine synthetase neg., b-Cat expression on membrane
Type of intervention	Right hemihepatectomy

Abbreviations: HCA, Hepatocellular Adenoma; b-Cat, b-Catenin. For HCA subtype explanation, see introduction.

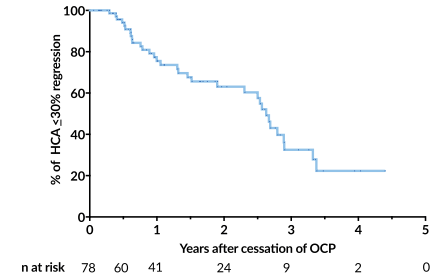
Factors associated with HCA regression

Longitudinal HCA diagnosis in the total cohort was analyzed (**Figure 3).** HCA diameter at baseline was significantly related to the rate of HCA regression (**Figure 3b**). Duration of OCP intake was not related to the rate of HCA regression (**Figure 3c**). Increased BMI was associated with larger HCA diameter at diagnosis. Analysis using Kaplan-Meier analysis, however, did not demonstrate a relation of BMI with the rate of HCA regression (**Figure 3d**). Next, a Cox proportional-hazard model was performed for univariate analysis of factors influencing regression including the following variables: BMI, total duration of OCP use, age of OCP commencement, age of HCA diagnosis, and largest HCA diameter categorized into <50 mm, 50≤HCA<100 mm and ≥100 mm (**Table 5**). Only HCA diameter was associated with rate of regression. Compared to HCA smaller than 50 mm, both HCA categorized 50 to 100 mm and larger than 100 mm were significantly more likely to regress 30% or more. They demonstrated a hazard ratio with 95% confidence interval of 2.37 (1.1 – 5.3) and 8.39, (3.3 – 21.6) respectively. No multivariate analysis was performed as none of the other variables demonstrated a univariate *p*-value <0.10.

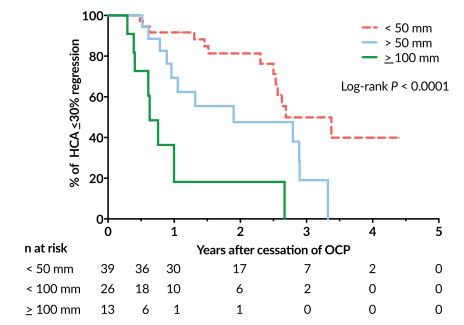
Table 5. Univariate analysis of HCA regression to >30% of baseline size by the Cox proportional-hazards

	Variable	Univariate analysis		
		Hazard Ratio	95% Confidence Interval	*p*-value
Weight, kg/m^2	<30 vs. ≥30	1.273	0.630 – 2.574	0.50
Start of OCP use	<15 vs. ≥15	1.102	0.491 – 2.475	0.81
Duration of OCP use	<15 vs. ≥15	0.880	0.401 – 1.935	0.75
Age of HCA diagnosis	<32 vs. ≥32	0.868	0.435 – 1.733	0.69
Largest HCA diameter	<50 vs. ≥50 to <100	2.368	1.057 – 5.304	**0.04**
	<50 vs. vs. ≥100	8.394	3.260 – 21.612	**<0.001**

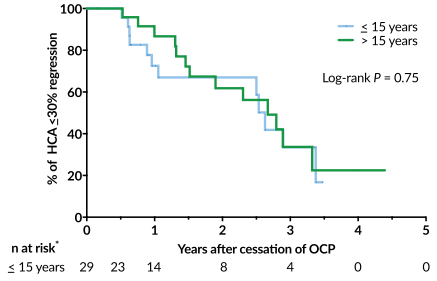
Abbreviations: HCA, Hepatocellular Adenoma; OCP, Oral Contraceptive Pill.



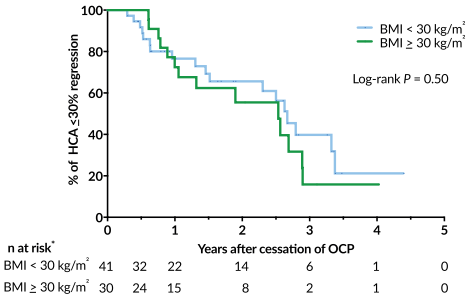
A Regression to 30% of baseline size, all HCA



B Regression to 30% of baseline size, by HCA size at baseline



C Regression to 30% of baseline size, by duration of OCP intake



D Regression to 30% of baseline size, by body mass index

Figure 3. Kaplan-Meier curves for the percentage of HCA showing 30% or more regression. (A) All HCA, (B) subdivided by initial HCA diameter, (C) duration of OCP use (*22 missing cases) and (D) BMI (*7 missing cases). Abbreviations: HCA, hepatocellular adenoma; OCP, oral contraceptive pill; BMI, body mass index.

Discussion

To our knowledge, this is the first study measuring the radiological HCA response after cessation of OCP using the RECIST criteria. We observed at least 30% regression in almost 40% of HCA patients, and half of all HCA remained stable after cessation of OCP intake. Only one HCA experienced growth during follow up imaging. Apart from being effective, this noninvasive therapy was safe as there were no HCA related complications during the follow-up period. Finally, we demonstrate that HCA diameter was significantly associated with the rate of HCA regression.

Up to now, there has been only one report describing HCA regression rate and the timing of HCA resection. Klompenhouwer *et al*. stated that 15% of HCA in their cohort showed regression to 50 mm or smaller after 6 months. This increased to 25% of patients after 1 year.[18] Also, they observed that larger HCA often require more than 6 months to regress to a diameter <50 mm.[18] Their sample size allowed them to exclude a correlation between HCA subtype and response. We were not able to reproduce this in our dataset because of a smaller sample size. Although the authors stated that patients were advised to halt OCP intake and lose weight, it is unclear when OCP intake was exactly stopped in their cohort. This could lead to an underestimation of the effect of OCP cessation and makes estimation of regression time inaccurate.

Apart from including few other HCA subtypes than I-HCA, our study has potential weaknesses. We cannot rule out any residual bias, which is inherent to the retrospective design of our study. We were unable to perform extensive subanalyses in the group with regression to <50 mm in size due to our sample size (n=49 at baseline). Our study focused on the relative change of HCA diameter. In the clinical setting however, absolute HCA size (≥50 mm) remains crucial for treatment. Hence, we are not able to recommend any specific prolongation of the current wait-and-see period Also, measurement errors could have been made during analyses of HCA diameter. OCP cessation date was obtained through either patient files or patient reporting – both may be subject to recall bias. Finally, we were not able to take a possible change in BMI through time into account as it turned out to be rarely reported more than once (at baseline) in the electronic patient files.

It is important to note that not all HCA responded to a reduction of circulating estrogen levels and that estrogen sensitivity may possibly vary across subtypes. It has previously been hypothesized that the estrogen (and general androgen) sensitivity of HCA is due to an increased expression of all androgen receptors, and estrogen receptors in specific. Unfortunately, studies which identified, characterized, and quantified these receptors, only analyzed small patient series (<20 cases). In addition, none of the authors performed any subtype analysis as these have been identified since 2008.[19–23] This might have resulted in unwittingly staining a mix of HCA subtypes. Future research will determine the definite role of estrogen receptors in the HCA (subtype) response.

We observed that HCA diameter at presentation was larger in obese patients. While one could argue this could be explained through a reduction of auto-sensation of any liver masses in obese patients compared to lean patients, age of diagnosis did not differ between the two groups. A possible mechanism is the additional growth stimulation through estrogen synthesis by the excessive adipose tissue. It is currently unclear to what extent obesity contributes to HCA formation and growth, and weight loss to HCA regression. Up to now there has only been one report on weight loss induced HCA regression and consists of three cases.[16] Future studies will need to be performed for more definite answers.

We found large HCA to regress at a relatively faster rate. This could be an indication for a stronger metabolic activity and dependency on estrogen (induced stimulants). Clinically, this observation is of importance as current guidelines do not take baseline HCA size into account for selection of patients suited for a wait-and-see period. We confirmed the observation of Klompenhouwer *et al.*: large HCA show significant regression, even at a faster rate than their smaller counterparts, and can reduce themselves to <50 mm size – but only when provided sufficient time. Extending the wait-and-see period, which was a safe strategy in our cohort, may potentially prevent surgical interventions in some patients. Although complication rates are low, the two major surgical complications we observed underscore the potential risk associated with surgery.

In conclusion, we found that the 98% of HCA remain either stable or show regression after OCP cessation. Large HCA showed faster regression than small HCA, but this

required a longer time than the currently advised 6-month period. No HCA induced complications were observed during follow-up. A conservative approach could lead to HCA regression below 50 mm and thereby potentially prevent unnecessary hepatic surgery in most patients.

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CHAPTER 6

A Nationwide Assessment of Hepatocellular Adenoma Resection: Indications and Pathological Discordance

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Abstract

Background

Hepatocellular adenomas (HCA) are benign liver tumors, associated with bleeding, or malignant transformation. Data on the indication for surgery are scarce. We analyzed indications and outcome of patients operated for HCA <5 cm, compared to HCA ≥5 cm. Changes in final postoperative diagnosis were assessed.

Methods

We performed a retrospective study including patients who underwent resection for (suspected) HCA in the Netherlands from 2014-2019. Indication for resection was analyzed and stratified for small (<5 cm) and large (≥5 cm) tumors. Logistic regression analysis was performed on factors influencing change in tumor diagnosis.

Results

Out of 222 patients who underwent surgery, 44 (20%) patients had a tumor <5 cm. Median (IQR) age was 46 (33-56) years in patients with small tumors and 37 (31-46) years in patients with large tumors (p=0.016). Patients with small tumors were more frequently male (21% vs. 5%, p=0.002). Main indications for resection in patients with small tumors were suspicion of (pre)malignancy (55%), (previous) bleeding (14%), and male sex (11%). Patients with large tumors were operated because of tumor size ≥5 cm (52%), suspicion of (pre)malignancy (28%), and (previous) bleeding (5.1%). No difference was observed in HCA-subtype distribution between small and large tumors. Ninety-six (43%) patients had a postoperative change in diagnosis. Independent risk factors for change in diagnosis were tumor size <5 cm (adjusted odds ratio [aOR] 3.4; p<0.01), male sex (aOR 3.7; p=0.03), and lack of hepatobiliary CE-MRI (aOR 1.8; p=0.04).

Conclusion

Resection for small (suspected) HCA was mainly indicated by suspicion of (pre) malignancy, whereas for large (suspected) HCA tumor size was the most prevalent indication. Male sex, tumor size <5 cm, and lack of hepatobiliary CE-MRI were independent risk factors for postoperative change in tumor diagnosis.

Introduction

Hepatocellular adenomas (HCA) are benign liver tumors which are frequently associated with chronic oral contraceptive pill (OCP) use and obesity.[1,2] Complications are associated with tumor size ≥5 cm. Large HCA (≥5 cm) are associated with hemorrhage (15-20%) and a small chance of malignant transformation to hepatocellular carcinoma (HCC; 1.6%), whereas both of these complications are very rare in HCA <5 cm.[3–6] According to current international guidelines, size >5 cm is an indication for resection.[7,8] The role of liver resection for the treatment of smaller HCA, however, remains unclear.[7]

The key to non-invasive HCA management is the HCA's ability to stabilize or regress in size after estrogen lowering and lifestyle advice (oral contraceptive pill cessation and weight loss).[2,9] Since 2016, European guidelines recommend lifestyle changes for six months prior to surgery in HCA ≥5 cm in females, after which HCA response is evaluated.[7] Invasive treatment is recommended if HCA size remains ≥5 cm, whereas a non-invasive approach is advocated in HCA <5 cm.[7] The 5 cm diameter cut off for invasive treatment is regardless of any significant response in terms of regression in size. International guidelines unequivocally recommend intervention for HCA in all male patients because of high rate of malignant transformation, regardless of any co-occurring metabolic disease.[7,8,10,11] HCA-related symptoms include nausea, fatigue, bloating, and pain.[12] These symptoms have been related to significant quality of life (QoL) impairment and surgical resection may be an effective treatment relief.[12]

Indications for resection of HCA are clear and concise in current European guidelines and discourage resection of HCA <5 cm in females. However, up to one third of all resected benign liver tumors, including HCA, are <5 cm. Data on indications for resection in this specific group remain scarce.[13–15] Evaluation of indications for resection of HCA, and especially HCA <5 cm, could assist clinicians and patients in future treatment decisions. In the current study we aimed to provide an evaluation of resection indications for small (suspected) HCA <5 cm, in comparison to larger HCA (≥5 cm) in a nationwide cohort. We also analyzed changes in final postoperative diagnosis.

Methods

A nationwide observational cohort study was performed in the Netherlands. Data were retrieved from the Dutch Hepato Biliary Audit; a mandatory nationwide registry in which all Dutch liver surgery centers record all liver resections performed. Data verification was performed by a trusted third-party to provide insight into data completeness and quality.[16] Additional data, including indications for resection, were collected from local electronic patient files. STROBE guidelines were adhered to in study design and manuscript preparation.[17] The Medical Ethical Committee of the University Medical Center Groningen confirmed that the Law on Medical Scientific Research involving human subjects did not apply (MEC 2020-004). All local ethical and scientific committees were consulted for study approval. The study was registered prior to initiation in the UMCG research registry (UMCG RR#201900849), and in all local research registries when obliged.

Patient selection

Included were patients who underwent liver resection in the Netherlands for (presumed) HCA (*i.e.* patients with suspected HCA but later proven alternate diagnosis (*e.g.* focal nodular hyperplasia [FNH] or malignancy) were also included). Inclusion period was defined patients operated between the 1st of January 2014 and 31st of December 2019 and registered in the mandatory audit before the 1st of April 2020. Patients were excluded when surgery was indicated by (suspicion of) hepatic malignancy but definitive postoperative pathological tumor diagnosis was HCA. Patients were also excluded if information regarding date of birth, date of surgery, or type of intervention was missing.

Outcomes

Primary outcome was the main indication for resection for presumed HCA as determined by the local (multidisciplinary tumor board) practitioner(s), stratified for small HCA (largest tumor diameter <5 cm) and large HCA (largest tumor diameter ≥5 cm). Indications were compared between regional hospital vs. tertiary referral hospitals. When multiple HCA were resected, the largest tumor diameter was registered.

Secondary outcomes included 30-day major morbidity, defined as a Clavien-Dindo grade IIIa or greater complication (*i.e.* requiring re-intervention, medium care or intensive care management, organ failure, or death) within 30 days of surgery, and 30-day mortality defined as death within 30 days of surgery.[18] Changes in preoperative diagnosis and diagnosis after final postoperative histopathological analysis were scored. Patients in whom there was doubt on preoperative diagnosis were also scored as such, *e.g.* preoperative doubt on HCA/FNH. In this analysis all (suspected) primary and secondary malignancies were characterized as "malignancy".

Variables

Patient characteristics included age, sex, American Society of Anesthesiologists classification, comorbidity score according the Charlson Comorbidity Index, previous medical history of liver disease, and a history of previous liver resection. Tumor characteristics included number of HCA and diameter of largest HCA prior to treatment, as well as subtype of HCA. Treatment characteristics included surgical approach (*i.e.* open or minimally invasive approach), major (≥3 adjacent Couinaud hepatic segments) or minor resection, and type of hospital (*i.e.* tertiary referral hospital or regional hospital) where treatment was performed. The conclusion on any (pre) malignant tumor were derived from the original radiology and histopathology reports. The indication "suspicion of (pre)malignancy" was only scored as such if the radiology and/or histopathology reports regarded the tumors as such. Imaging and/or pathology were not centrally re-reviewed.

Statistical Analyses

Dichotomous data were presented as proportions. Continuous variables were reported as median with interquartile range (IQR). Variable distribution was assessed by plotting histograms. Categorical variables were expressed as number (*n*) and percentage (%). Variables were analyzed using appropriate statistical tests for variable type and distribution. Multivariate analysis using logistic regression was performed, with reporting of odds ratio (OR), adjusted OR (aOR), and 95% confidence interval

(95% CI). Covariates were included if $p<0.10$ after univariate analysis and corrected for interaction when necessary. Parameters with two-tailed $p<0.05$ were considered statistically significant. All analyses were performed in R version 4.1.0.® (R Core Team (2021). R Foundation for Statistical Computing, Vienna, Austria). Study data were collected and managed using REDCap electronic data capture tools hosted at the University Medical Center Groningen.[19,20]

Results

Baseline characteristics

A total of 222 patients who underwent surgery for (suspected) HCA were included, of whom 44 (20%) patients with small tumors (<5 cm) and 178 (80%) patients with large tumors (≥5 cm) (**Table 1**). Patients with small tumors were older (46 years vs. 38 years, $p=0.016$) and more frequently male (20% vs 5.1%, $p=0.002$) than patients with large tumors. In both groups, 33% of patients had hepatic steatosis. Median tumor diameter was 30 (21-40) mm in patients with small tumors compared to 83 (64-110) mm in patients with large tumors (**Table 1**, $p<0.001$). Bilobar presence of tumors was approximately 35-40% in both groups. The number of tumors was comparable in both groups, with 60% of patients diagnosed with 1 tumor, and 20% with 2 tumors (**Table 1**).

Overall use of preoperative magnetic resonance imaging (MRI) was similar between the two groups (86% vs. 92%, $p=0.37$), although hepatobiliary contrast-enhanced MRI (CE-MRI) was less often used in patients with small tumors (58% vs. 71%, $p=0.008$). Preoperative histopathology was obtained in 5 (11%) patients with small tumors, compared to 42 (24%) patients with large tumors ($p=0.12$; **Table 1**). Discussion of the indication for surgery in a multidisciplinary team meeting occurred in 91% of patients with small tumors, and in 89% of patients with large tumors ($p=0.97$). A multidisciplinary team meeting, however, was more often consulted in tertiary referral centers (94%) than in regional hospitals (75%; $p<0.001$) prior to surgery.

Table 1. Baseline characteristics of (suspected) HCA patients, stratified for tumor diameter

Characteristic	Tumor <5 cm (*n*=44)		Tumor ≥5 cm (*n*=178)		*p*-value
Female sex (*n*, %)	35	(80)	169	(95)	**0.002**
Age at surgery (years)	46	(33-56)	38	(31-46)	**0.016**
Body mass index (kg/m^2)	27	(22-32)	28	(24-32)	0.68
Charlson Comorbidity Index (CCI)					0.70
CCI 0/1	43	(98)	169	(95)	
CCI ≥2	1	(2)	9	(5)	
American Society of Anesthesiology (ASA)					**0.013**
ASA I/II	33	(75)	162	(91)	
ASA ≥III	10	(23)	15	(8.4)	
Missing	1	(2.3)	1	(7.9)	
Preoperative MRI (*n*, %)	38	(86)	164	(92)	0.37
MRI contrast agent					**0.008**
Liver-specific contrast agent	7	(16)	36	(20)	
Extracellular contrast agent	22	(50)	115	(65)	
No contrast administered*	9	(21)	11	(6.2)	
Missing	6	(14)	16	(9.0)	
Number of tumors (*n*, %)					0.52
1 tumor	26	(59)	107	(60)	
2-5 tumors	9	(21)	36	(20)	
6-9 tumors	2	(4.5)	9	(5.1)	
≥10 tumors	2	(4.5)	2	(1.1)	
Missing	5	(11)	24	(14)	
Diameter of largest tumor (mm)	30	(21-40)	83	(64-110)	**<0.001**
Bilobar tumor occurrence (*n*, %)	15	(34)	74	(42)	0.43

Continuous values are provided as median & interquartile range.
Abbreviations: HCA, hepatocellular adenoma; MRI, magnetic resonance imaging; HCC, hepatocellular carcinoma; FNH, focal nodular hyperplasia.

Indications for surgery

Indications for resection differed between patients with small and large tumors and (p<0.001). In patients with small tumors <5 cm, the most common indication for resection (55%) was suspicion of (pre)malignancy (either on imaging or on histopathological analyses) (**Figure 1a**). Other indications for resection of small tumors were (previous) tumor hemorrhage (14%), male sex (11%), pregnancy wish (4.5%), tumor growth (4.5%), and patient uncertainty (4.5%). The main indication for

resection of large tumors ≥5 cm was because of tumor size (52%), followed by suspicion of (pre)malignancy (27%), histopathological features of beta-catenin mutated HCA (5.6%), and (previous) hemorrhage (5.1%) (**Figure 1b**). Other reasons were abdominal complaints (*i.e.* pain, bloating, or tiredness), exophytic tumor growth, HCA induced amyloidosis, and HCA induced anemia. In regional hospitals, more HCA were resected because of previous hemorrhage (12% vs. 5.3%), or male sex (12% vs. 1.2%), when compared to tertiary referral centers (p=0.004) (**Table 2**). All patients operated due to male sex received an MRI, and no difference in MR-contrast was observed (p=0.11).

Table 2. Grouped indications for surgery and postoperative diagnosis of HCA patients, stratified for hospital type.

Characteristic	Regional hospital (*n*=52)		Tertiary referral hospital (*n*=170)		*p*-value
Indication of surgery (*n,* %)					**0.004**
Hemorrhage (old or new)	6	(12)	9	(5.3)	
Abdominal complaints	1	(1.9)	7	(4.1)	
Size ≥5 cm	22	(42)	70	(41)	
Atypia tumor	15	(29)	67	(39)	
Male sex	6	(12)	2	(1.2)	
Other	2	(3.8)	15	(8.8)	

Abbreviations: HCA, hepatocellular adenoma.

Preoperative histopathological and imaging characteristics

A total of 47 patients (21%) had undergone preoperative biopsy, more often in large tumors (42/178) than in small tumors (5/44), albeit not significantly (p=0.12; **Table 1**). Eventually, 11 patients (23%) with a preoperative biopsy underwent resection because of cellular atypia. At final pathology, ten of those were diagnosed as HCA and one as focal nodular hyperplasia (FNH). Sixty-one out of 175 (35%) patients without preoperative biopsy were operated because of suspected (pre)malignancy on MRI. Of those, 34 patients (56%) had undergone a preoperative contrast-enhanced MRI with liver-specific contrast agent, 7/20 (44%) of patients with tumors <5 cm and 27/41 (66%) of patients with tumors ≥5 cm (p=0.22).

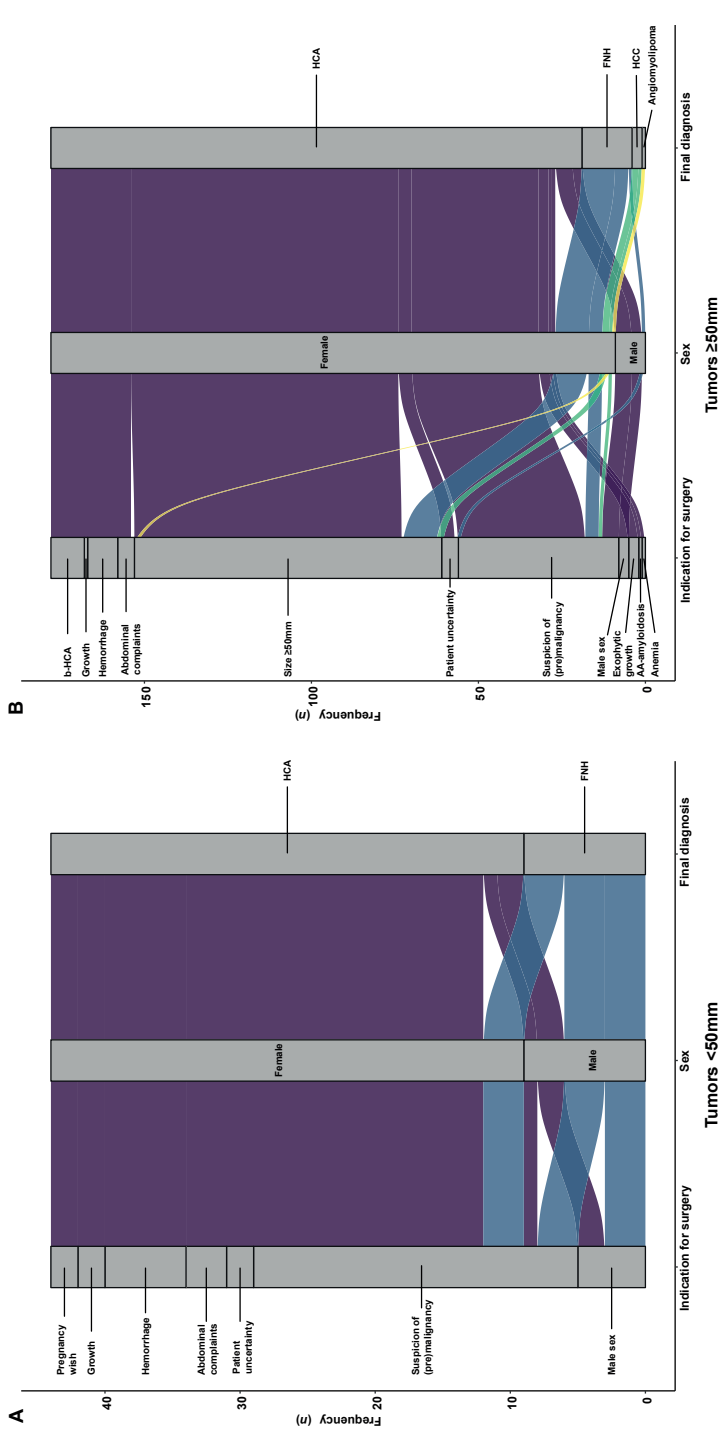

Figure. 1: Alluvial plots depicting the individual distribution of indication for resection in patients with tumors <5 cm (A) or ≥5 cm (B), grouped by sex, and final diagnosis. Abbreviations: HCA, hepatocellular adenoma; b-HCA, beta-catenin mutated HCA; FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; AA-amyloidosis, amyloid A amyloidosis.

Final histopathological outcomes and risk factors for change in diagnosis

At final pathology, no differences were observed for HCA subtypes between tumor size groups (**Table 3**). However, FNH was diagnosed in 24 patients comprised 21% of the smaller tumors, vs. 8.5% of the resected larger tumors (p=0.11). Of all 24 patients with FNH at final pathology, 22 patients (92%) had undergone MRI in the preoperative work-up, and in 14 patients (64%) a liver-specific contrast agent was administered. In the total cohort, use of hepatobiliary contrast-enhanced MRI was similar for male and female patients (p=0.10). In patients with tumors <5 cm, hepatobiliary contrast-enhanced MRI was used in the diagnostic workup of 3 males (33%) and in 19 females (54%) (p=0.46). At final pathology, 6/9 male patients were diagnosed with FNH, compared to 3/35 female patients; p<0.001). From the six male patients with resected FNH <5 cm, none had preoperative histopathology analyzed, and indications for resection were suspicion of (pre)malignancy on MRI (n=3), and because of male sex with HCA suspicion (n=3). Three resected tumors turned out to be HCC, all in females with tumors ≥5 cm (**Figure 1b**). Indication for resection of two HCC was because of tumor size ≥5 cm which with co-occurring tumor growth), and one HCC was resected because of suspicion of (pre)malignancy.

Analysis of significant changes in pre- and postoperative diagnosis revealed 96 (43%) changed diagnoses (**Figure 2**). A change in diagnosis was observed in 14 (78%) male patients compared to 82 (40%) of female patients (p<0.01), in 31 (70%) small tumors compared to 65 (37%) large tumors (p<0.001), and in 46 (54%) patients without preoperative hepatobiliary contrast-enhanced MRI compared to patients with hepatobiliary CE-MRI available (p<0.05). No differences were seen between patients with or without any MRI, or with or without percutaneous biopsy. These observations were similar in univariate logistic regression, which demonstrated an increased risk of diagnostic change in male patients (OR 5.2; 95% CI 1.8-18.9; p<0.01), in tumors <5 cm (OR 4.1; 95% CI 2.1-8.7; p<0.001), and in patients without hepatobiliary CE-MRI (OR 2.1; 95% CI 1.2-3.6; p<0.05). Use of MRI regardless of use of contrast (type) did not influence diagnostic change (p=0.44), and neither did use of percutaneous biopsy (p=0.27). A model was constructed including sex, tumor size category, use

of hepatobiliary contrast-enhanced MRI (**Figure 3**). All included variables proved independent risk factors for change in diagnosis: tumors <5 cm (aOR 3.4; 95% CI 1.7-7.4; p<0.01), male sex (aOR 3.7; 95% CI 1.2-13.8; p=0.03), and lack of hepatobiliary CE-MRI (aOR 1.8; 95% CI 1.0-3.3; p=0.04). Influence of a sex-tumor size category interaction was explored including the three aforementioned variables but did not improve the model (aOR 2.6; 95% CI 0.2-66.3; p=0.48).

Surgical outcomes

No difference in frequency of surgery was observed throughout the years. During the inclusion period, there was a trend towards more frequent laparoscopic resections in patients with smaller tumors (67% vs. 53%; p=0.13). Major resections (n=56) were more often performed in patients with large tumors. Sixteen (29%) major resections were performed through laparoscopy. Postoperative outcomes were similar for patients who underwent surgery for small or large tumors, with 30-day major morbidity <3%, and 30-day mortality <1% (**Table 3**).

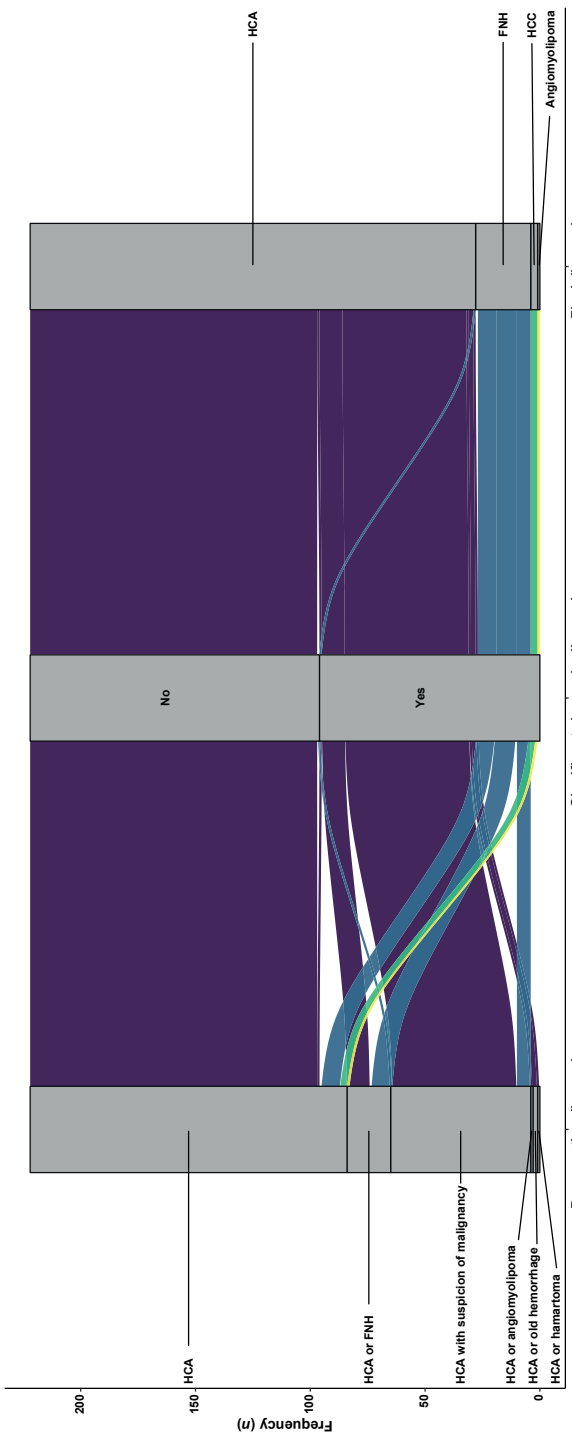

Figure 2: Alluvial plot depicting the change in tumor diagnosis before and after resection in the total cohort. Abbreviations: HCA, hepatocellular adenoma; FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma.

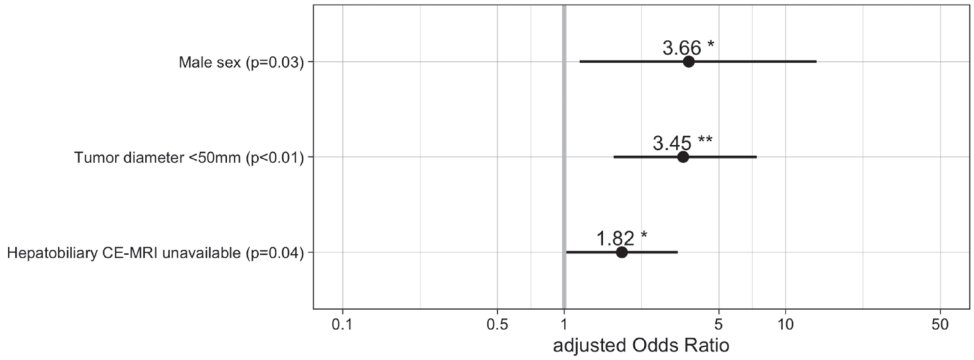

Figure 3: Forest plot of logistic regression analysis on risk factors for change in tumor diagnosis. Abbreviations: CE-MRI, contrast-enhanced magnetic resonance imaging.

Table 3. Operative characteristics and final histopathology of (suspected) HCA patients, stratified for tumor diameter

Characteristic	Tumors <5 cm (*n*=44)		Tumors ≥5 cm (*n*=178)		*p*-value
Final histopathology					
Tumor diagnosis					0.11
HCA	35	(80)	159	(89)	
FNH	9	(20)	15	(8.4)	
HCC	0	(-)	3	(1.7	
Angiomyolipoma	0	(-)	1	(0.6)	
Missing	0	(-)	1	(0.6)	
HCA subtype (*n,* %)					0.09
I-HCA	18	(41)	99	(56)	
H-HCA	5	(11)	14	(7.9)	
b-HCA / b-IHCA	0	(-)	12	(6.7)	
U-HCA	2	(4.5)	8	(4.5)	
No subtype analyses performed	10	(23)	28	(16)	
Alternate tumor than HCA	9	(21)	17	(9.6)	
Postoperative change of tumor diagnosis (*n,* %)	31	(71)	65	(37)	**<0.001**
Operative characteristics and outcomes					
Year of surgery (*n,* %)					0.20
2014	8	(18)	28	(16)	
2015	9	(21)	27	(15)	
2016	4	(9.1)	36	(20)	
2017	12	(27)	27	(15)	
2018	5	(11)	34	(19)	
2019	6	(14)	26	(15)	
Type of resection					**0.042**
Wedge resection	11	(25)	29	(16)	
Segment resection	28	(64)	99	(56)	
Left hemihepatectomy	0	(-)	6	(3.4)	
Right hemihepatectomy	1	(2.3)	38	(21)	
Extended left hemihepatectomy	0	(-)	1	(0.6)	
Extended right hemihepatectomy	0	(-)	1	(0.6)	
Missing	4	(9.1)	4	(2.2)	
Extensiveness of resection (*n,* %)[†]					**<0.001**
Minor resection	43	(98)	123	(69)	
Major resection	1	(2)	55	(31)	
Surgical approach					0.13
Open	14	(32)	83	(47)	
Laparoscopic	29	(66)	94	(53)	
Missing	1	(2.3)	1	(0.6)	

Table 3. Continued

Characteristic	Tumors <5 cm (*n*=44)		Tumors ≥5 cm (*n*=178)		*p*-value
30-day major morbidity (*n,* %)‡	1	(2)	3	(1.7)	1.00
30-day mortality (*n,* %)	0	(-)	1	(0.6)	1.00

Continuous values are provided as median & interquartile range.
† ≥3 adjacent Couinaud hepatic segments.
‡Defined as Clavien-Dindo score ≥3a.
Abbreviations: HCA, hepatocellular adenoma; FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; I-HCA, inflammatory HCA; H-HCA, hepatocyte nuclear factor 1A inactivated HCA; b-HCA, beta-catenin mutated HCA; b-IHCA, hybrid b-HCA and I-HCA; U-HCA, unclassified HCA.

Discussion

In this study, indications for resection of small (suspected) HCA, compared to large HCA were investigated in a nationwide cohort. The study included 222 patients, of whom 44 patients (20%) underwent surgery for small tumors (<5 cm). Half of patients with small tumors were operated because of suspicion of (pre)malignancy and the remaining patients mainly underwent surgery because of (previous) hemorrhage or male sex, whereas for patients with large tumors, the most prevalent indication was tumor size itself. A logistic regression model showed that male sex (aOR 3.7), small tumor size (aOR 3.4), and lack of hepatobiliary CE-MRI (aOR 1.8) were independent risk factors for a postoperative change in diagnostic.

The diagnostic process for benign liver tumors is complex because of the distinct clinical and risk-profiles between and within benign liver tumors in often relatively young and healthy patients. When it comes to decision-making to proceed to surgery, some indications are stronger because of a clear trade-off between the benefit and (potential) harm of surgery. Risk of malignant transformation is such an indication, which is reflected in the observed indications in our study cohort. In half of patients with small tumors, surgery was performed because of suspicion of (pre)malignancy on imaging or histopathology, and the same holds true for almost a third of patients with large tumors. All 18 male patients in our cohort were operated because of their sex in combination with (suspicion of) HCA diagnosis. Male sex is an independent risk factor for malignant transformation, and the premalignant beta-catenin mutated HCA (b-HCA) occur more often in males, which may justify the indication for resection.[3,4,6] Male patients with HCA due to metabolic disease like hepatocyte nuclear factor 1A

maturity-onset diabetes of the young (HNF1A-MODY) or glycogen storage disease might be exceptions but future research is needed for definite answers regarding oncologic safety.[21,22] HNF1A-MODY should especially be considered if multiple *HNF1A* inactivated HCA (H-HCA) are observed in a (male) patient, which can be preceded by diabetic symptoms.[21] Because H-HCA generally demonstrate very limited risk of bleeding or malignant transformation, a conservative approach with follow-up imaging may be warranted, also in male patients. Future research on oncologic safety is needed for definite conclusions as *HNF1A* mutations are rare and have been observed in 1.5% of resected HCC, and a family with HNF1A-MODY and H-HCA-induced primary hepatic malignancies has been reported.[23,24]

Relative indications such as abdominal complaints or patient uncertainty were observed in only 5 (11%) patients with small tumors, and in 10 (5.6%) patients with large tumors. It is assumed that the severity of symptoms led to the indication for resection, however, in the absence of well-developed QoL instruments for patients with benign liver tumors, it remains difficult to assess the burden of disease.

Prevention of hepatic hemorrhage by tumor rupture, which is size dependent and is low in tumors <5 cm, is another important indication for invasive tumor treatment.[5,6] Tumor size was the deciding factor in half of patients with large tumors ≥5 cm. Risk of HCA bleeding is especially increased in exophytic HCA.[5,25] In our series, exophytic growth was an indication for only 3 cases, whereas previous hemorrhage was an indication in 15 cases. European guidelines do not consider previous tumor hemorrhage as an absolute indication for surgery, although in rare cases such as bleeding in exophytic HCA, previous hemorrhage can be a relative indication for intervention. Before deciding upon HCA treatment after bleeding, HCA should first be observed for post-hemorrhagic necrosis-induced regression, which might remove the need for tumor resection.[25] Finally, current European guidelines recommend HCA resection if size remains ≥5 cm six months after lifestyle alterations (*i.e.* ceasing OCP and weight loss). However, six months might be a too short interval for large HCA to regress sufficiently, and data suggests that watchful waiting can be prolonged safely.[9,26]

The clinical decision process is dependent on the (suspected) preoperative tumor diagnosis. A postoperative change in tumor diagnosis was observed quite frequently

(43%). Although amounting for only a small number of total cases, preoperative diagnosis was altered from HCA or (pre)malignancy to FNH in 6 out of the 9 male patients with tumors <5 cm. A therapeutically defensive approach by resecting tumors not distinguishable between HCA or FNH in male patients is conceivable, however preoperative diagnostic work-up should be adequate. Our findings that especially male sex, small tumors, and lack of hepatobiliary contrast-enhanced MRI were independently associated with increased risk of change in diagnosis may highlight the need to improve the diagnostic process to prevent unnecessary hepatic surgery. We propose to perform a hepatobiliary contrast-enhanced MRI in all patients with (suspected) HCA, and to perform a percutaneous biopsy whenever there is doubt on tumor diagnosis after this imaging. Furthermore, all (suspected) HCA in male patients should be confirmed via percutaneous liver biopsy, preferably through histopathological molecular analysis due to higher diagnostic sensitivity.[27] A suspicion of malignant transformation after hepatobiliary contrast-enhanced MRI needs to be confirmed by liver biopsy, especially in tumors <5 cm, and in male patients. In our opinion, potential complications and morbidity following unnecessary surgery outweighed the limited risk of biopsy-induced bleeding. Molecular analysis better capable in diagnosing beta-catenin (*CTNNB1*) mutated HCA and should supplement immunohistochemistry whenever a beta catenin mutation is suspected.[27] Molecular analysis also allows for differentiation between exon 3 and exon 7/8 *CTNNB1* HCA mutations, the latter having less malignant potential, although exon 7/8 mutated HCA transforming into HCC have been observed.[6,28] Of note, percutaneous ablation is effective and safe in treating hepatic malignancies and HCA, and could be performed in the same session directly after the histological biopsy in tumors <5 cm.[29,30]

A limitation of the current study is the retrospective assessment of preoperative diagnostic workup, including imaging, as the radiologic analysis often contains many nuances open to varying interpretations. In addition, the current data does not allow for analysis of indications per HCA subtype, which may have been potentially insightful and could be analyzed in future studies. Another potential limitation is the accuracy and coverage of the included registry data. Third-party data verification has deemed 97% of the data accurate, yet not all specific information concerning operative outcomes could

be obtained.[16] Because the current study reflects the historical decision-making process from 2014-2019 in a nationwide cohort, substantial improvements in diagnostic workup have been made since, including identification of new HCA subtypes. For example, sonic hedgehog mutated HCA (sh-HCA) have been discovered in recent years, which represent 4% of HCA.[6,31] Sh-HCA are especially at increased risk of tumor bleeding.[6] Unfortunately, immunohistochemical staining of argininosuccinate synthetase 1 or molecular characterization of inhibin beta E chain with *GLI1* was not routine practice during the study period.[6,31,32]

Future studies on preoperative modality and final tumor diagnosis are needed to uncover potential areas of improvement of care. Although some extent of diagnostic uncertainty occurs in every modality, suboptimal use of imaging modalities or radiologic contrast agents might lead to unnecessary diagnostic ambiguity. Second, the 'relative' indications for resection of (suspected) HCA like impact on QoL by psychological burden or abdominal complaints should be further explored. This necessitates both development and validation of QoL tools or patient-related outcome instruments specifically for patients with benign liver tumors, as well as analysis of these potential consequences in a cohort.

In conclusion, surgery for small HCA was mainly indicated by suspicion of (pre) malignancy, whereas for large (suspected) HCA size was the most prevalent indication. Male sex, tumor size <5 cm, and lack of hepatobiliary CE-MRI were independent risk factors for postoperative change in tumor diagnosis. Future studies should focus on evaluation of preoperative diagnostics, as well as exploration of QoL related indications such as patient uncertainty or abdominal complaints.

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CHAPTER 7

High Childhood Serum Triglyceride Concentrations Associate with Hepatocellular Adenoma Development in Patients with Glycogen Storage Disease Type Ia

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Abstract

Background

Glycogen storage disease type Ia (GSDIa) is an inborn error of carbohydrate metabolism caused by pathogenic variants in the *G6PC1* gene and is associated with hepatocellular adenoma (HCA) formation. Data on risk factors for HCA occurrence in GSDIa are scarce. We investigated HCA development in relation to sex, *G6PC1* genotype, and serum triglyceride concentration (TG).

Methods

An observational study of genetically confirmed GSDIa patients ≥12 years was performed. Patients were categorized for sex, presence of 2, 1, or zero predicted severe *G6PC1* variants (PSV), and median TG during childhood (<12 years; stratified for above/below 5.65 mmol/L, *i.e.* 500 mg/dL).

Results

Fifty-three patients (23 females) were included, of which 26 patients developed HCA at a median (interquartile range) age of 21 (17-25) years. At the age of 25 years 48% of females and 30% of males had developed HCA (Log-Rank p=0.045). Two-thirds of GSDIa patients carried 2 PSV, 20% one, and 13% none. Neither the number of PSV, nor any specific *G6PC1* variants were associated with HCA occurrence. Childhood TG was 3.4 (3.0-4.2) mmol/L in males vs. 5.6 (4.0-7.9) mmol/L in females (p=0.026). Childhood TG >5.65 mmol/L was associated with HCA development at younger age, compared to patients with childhood TG <5.65 mmol/L (18 vs. 33 years; Log-Rank p=0.001). Cox-regression analysis including TG, sex, and TG-sex interaction correction revealed childhood TG >5.65 mmol/L as an independent risk factor for HCA development (HR 6.0, 95% CI 1.2-29.8; p=0.028).

Conclusions

In GSDIa patients, high childhood TG concentration was associated with an increased risk of HCA, and earlier onset of HCA development, independent of sex-associated hypertriglyceridemia, and *G6PC1* genotype.

Introduction

Glycogen storage disease type Ia (GSDIa; OMIM #232200) is a rare, inborn error of carbohydrate metabolism caused by pathogenic variants in the glucose-6-phosphatase catalytic subunit 1 (*G6PC1*) gene.[1,2] The GSDIa phenotype is characterized clinically with fasting intolerance, hepatomegaly, and failure to thrive and biochemically with non-ketotic hypoglycemia, and hypertriglyceridemia. Evolving dietary strategies have greatly improved the life expectancy of GSDIa patients, shifting the GSDIa paradigm from an acute and lethal disease to a chronic disorder. Long-term complications include hepatocellular adenoma (HCA) formation.[3–5]

HCA are rare, benign liver tumors, with size (>5 cm) dependent associated complications consisting of hepatic hemorrhage transformation to hepatocellular carcinoma.[6–9] Outside the context of GSDIa, HCA formation is strongly associated with female sex, as >90% of HCA occur in females, and circulating estrogen or androgen (*e.g.* oral contraceptives or anabolic steroids).[9–11] In GSDIa, however, about 30% of GSDIa patients with HCA are male. HCA incidence in GSDIa increases with age, with a median age of diagnosis at around 15 years and an incidence of 70-80% over the age of 25 years.[3,12–15]

G6PC1 is a single-copy gene, with five exons coding for 357 amino acids.[2] *G6PC1* expression is restricted to the liver, kidney, and intestine.[2] Genetic variants within the *G6PC1* catalytic domain (*i.e.* amino acids 83, 119, 170, and 176) have shown to completely abolish glucose-6-phosphatase (G6Pase) function, whilst truncating (nonsense) variants either abolish or greatly impair G6Pase function.[2] G6Pase dysfunction impairs hydrolysis of glucose-6-phosphate to glucose and phosphate which disrupts the final and common step of glycogenolysis and gluconeogenesis.[5,16] Although the *G6PC1* genotype has been linked to the severity of the metabolic phenotype of GSDIa, no specific *G6PC1* variants have definitively been associated with HCA formation.

Improved dietary management in GSDIa has resulted in improved metabolic control, which is commonly evaluated through serum triglyceride concentration (TG). Prolonged suboptimal metabolic control (hypertriglyceridemia >5.65 mmol/L or 500 mg/dL) has been associated with HCA development.[15] Recent studies on GSDIa patients demonstrate better clinical outcomes, including lower TG and lower HCA prevalence

compared to historical cohorts, which at least in part may be attributed to optimized dietary treatment strategies.[12]

Since longitudinal data on HCA incidence in GSDIa patients is scarce, the association and potential interaction of sex, *G6PC1* genotype, and metabolic control on HCA development is yet unknown. The aim of this study was to assess the association between sex, type of *G6PC1* variants, and TG in childhood, and HCA formation in a nationwide cohort of genetically confirmed GSDIa patients.

Methods

Study design

A nationwide, retrospective, observational, multi-center cohort study of GSDIa patients was performed between 1969 and September 2021. The metabolic expert centers of seven Dutch university medical centers provided information on patients followed-up. Inclusion criteria were current age ≥12 years, availability of diagnostic imaging, and GSDIa diagnosis based on *G6PC1* genetic analysis by traditional Sanger sequencing or next generation sequencing. Strengthening the Reporting of Observational Studies in Epidemiology guidelines were adhered to for study design and manuscript preparation.[17] The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The Law on Medical Scientific Research involving human beings (WMO) did not apply in an a priori approval by the Medical Ethical Committee of the University Medical Center Groningen (UMCG-MEC 2019-119). The study was registered prior to initiation in the UMCG research registry (UMCG-RR#202000465). All patient data was collected and processed in accordance with Dutch privacy laws.

Data collection and definitions

HCA was diagnosed by either MRI, histopathology, or both. Date of first HCA diagnosis was retrospectively adjusted to first tumor observation on ultrasound, in case of later diagnosis on MRI or histopathology. Largest HCA diameter was measured by ultrasound and/or magnetic resonance imaging (MRI) according to Response Evaluation Criteria in Solid Tumors (RECISTv1.1) criteria.[18]

G6PC1 variants were categorized according to both the molecular characteristics of the genetic variants as well as the G6Pase location. All *G6PC1* missense variants in the active site (*i.e.* amino acids 83, 119, 170, and 176) and all *G6PC1* nonsense variants (regardless of location) were categorized as predicted severe variant (PSV). Patients' *G6PC1* genotypes were categorized as 0, 1, or 2 PSV. *G6PC1* variants accounting for 50% or more of observed variants in the cohort (*i.e.* p.Arg83Cys, p.Gln347X, and p.Gln27ArgfsX9) were grouped and compared to all other variants.

Birth cohorts were defined as the older or current treatment era as previously reported.[12] The current treatment was defined as treatment that started in 1986, the year when large-scale clinical use of uncooked cornstarch therapy commenced.[12]

TG were measured at the local laboratories according to standard practice. TG data were expressed in mmol/L. Longitudinal childhood TG were calculated as median of measurements per six months per patient. Of the included patients, a single childhood TG was calculated per patient as the median of all measurements obtained and available before the age of 12 years. Childhood TG were categorized into low and high childhood TG, defined as those patients with median childhood TG above or below 5.65 mmol/L (500 mg/dL), according to previous definition.[15] To correct for metabolically dysregulated patients, and thereby with more frequent TG measurements, sensitivity analyses on childhood TG were performed by prior calculation of the median TG per six months, and then calculating a single median TG on those values. Sensitivity analyses on childhood TG stratification were also performed through categorization of childhood TG above or below 6.0 mmol/L, as recommended by the European Study on GSDIa management guideline.[3,4] A sensitivity analysis on childhood TG and development of HCA was performed for use of lipid-lowering drugs (including fibrates, statins, omega-3 fatty acid supplements, or ursodeoxycholic acid) at any given time prior to HCA diagnosis.

Data presentation and statistics

Patients were categorized in groups according to sex (male/female), number of PSV (0, 1, or 2, and 0/1 or 2), childhood TG (low/high), and birth cohort (older/current). Study data were collected from individual patient records and managed using REDCap electronic data capture tools (Vanderbilt University, Nashville, Tennessee, United States

of America) hosted at the University Medical Center Groningen.[19,20] The data that support the findings of this study are available from the corresponding author, VEDM, upon reasonable request. Genetic variants were presented according to Human Genome Variation Society recommendations.[21] Figures were composed using R and GraphPad Prism version 9.0 for Mac (GraphPad Software, La Jolla, CA, USA, www.graphpad.com). Dichotomous data were presented as proportions. Continuous variables were reported as median with interquartile range (IQR). Categorical variables were expressed as number (*n*) and percentage (%). Statistical analysis was performed using R version 4.1.0 (R Foundation for Statical Computing, Vienna, Austria), including the "survival" and "survminer" packages. Univariate survival analyses were performed using Kaplan-Meier analyses and the Log-Rank test. Multivariate survival analysis was performed using a Cox proportional-hazards model. Parameters with two-tailed $p<0.05$ were considered statistically significant.

Results

Seventy-seven GSDIa patients from 66 families were diagnosed at the outpatient clinic of the seven participating centers. Twenty-four patients were excluded because of current age <12 years (*n*=8), no imaging performed (*n*=6), or no *G6PC1* variant analysis available (*n*=10). Fifty-three patients from 46 families were included for data analysis, with a median follow-up time of 32 (22-43) years (**Figure 1**). Most patients (56%) were diagnosed within their first year of life, and the median age of GSDIa diagnosis was 10 months (5-30), (**Table 1**).

GSDIa and HCA formation

HCA was diagnosed in 26 of 53 GSDIa patients (49%), at a median age of 21 (17-25) years. The lowest age of HCA diagnosis was 13 years (**Figure 2a**). No difference was observed in age of GSDIa diagnosis between patients who did or did not develop HCA (*p*=0.98) (**Table 1**). Kaplan-Meier survival analysis demonstrated no significant difference in time to HCA development between birth cohorts before and after the introduction of uncooked corn starch diet in 1986 (**Figure 2b**). Eight patients were

diagnosed with hepatic adenomatosis (diagnosis of >10 HCA). Median number of HCA in non-adenomatosis patients was 3 (1-6) HCA. The median diameter of all HCA was 35 (18-65) mm.

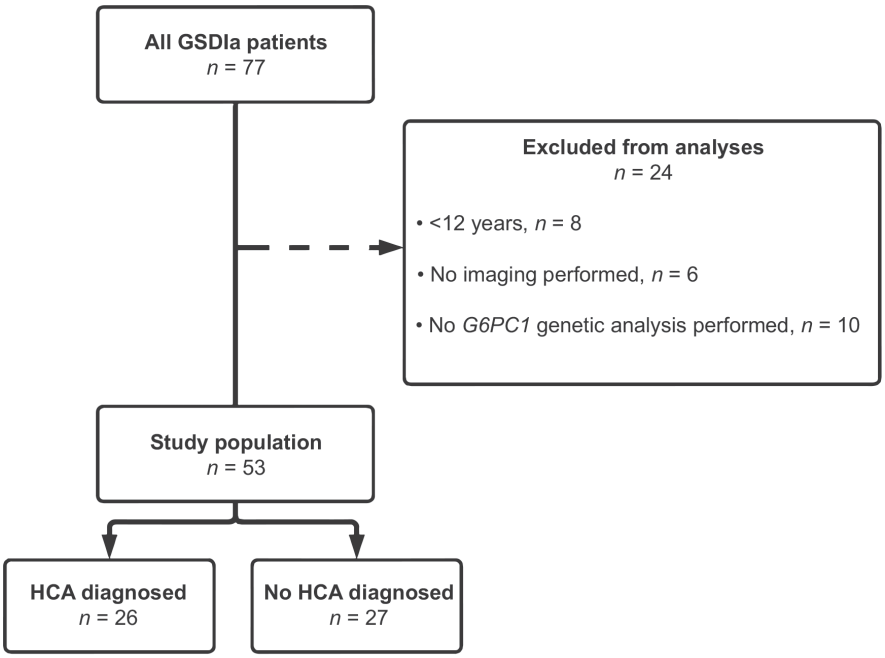

Figure 1. Flowchart of inclusion of the study population.
Abbreviations: GSDIa; glycogen storage disease type Ia; HCA, hepatocellular adenoma.

HCA formation and sex

HCA formation was more common in female than in male GSDIa patients (at age 25 years, 48% and 30%, respectively, Log-Rank p=0.045; **Figure 2c** & **Table 1**). HCA formation also occurred earlier in female patients; the age at which 50% of the women had developed HCA was 23 years, compared to 30 years in males (**Figure 2c**). Adenomatosis was diagnosed in 3/13 male patients, and 5/10 female patients (p=0.69). Among non-adenomatosis patients, male patients had median 6 (2-7) HCA, compared to 3 (1-5) for females (p=0.22). Largest median HCA size was 41 (15-104) mm in males, and 28 (19-47) mm in females (p=0.64).

Table 1. Baseline characteristics of GSDIa patients

Characteristic	Total cohort (*n* = 53)	Patients with HCA (*n* = 26)	Patients without HCA (*n* = 27)	*p*-value
Current age (years)	34 (24-45)	37 (28-45)	25 (22-42)	0.07
Sex (n of female patients, %)	23 (43)	15 (58)	8 (30)	**0.039**
Age of GSDIa diagnosis (months)	10 (5.0-30)	11 (4-48)	11 (5.0-23)	0.98
Birth cohort				
Born before 1986 (*n,* %)	21 (40)	12 (46)	9 (33)	0.34
Born after 1986 (*n,* %)	32 (60)	14 (54)	18 (67)	
Childhood TG concentration (mmol/L)*	3.95 (3.18-5.79)	4.60 (4.03-7.84)	3.16 (2.33-3.37)	**<0.001**
Type of *G6PC1* variant†				
No predicted severe variants (*n,* %)	7 (13)	3 (12)	4 (15)	0.88
1 predicted severe variant (*n,* %)	11 (21)	6 (23)	5 (19)	
2 predicted severe variants (*n,* %)	35 (66)	17 (65)	18 (67)	

Continuous values are provided as median & interquartile range.
*Median of serum triglyceride concentration up to and including 12 years of age.
†Predicted severe variants are any nonsense *G6PC1* variants and all missense variants within the *G6PC1* active site. Abbreviations: HCA, hepatocellular adenoma; GSDIa, glycogen storage disease type Ia; TG, serum triglyceride concentration (mmol/L); *G6PC1*, glucose-6-phosphatase catalytic subunit 1; PSV, predicted severe variant.

HCA formation and G6PC1 gene variants

Two-thirds of GSDIa patients carried 2 PSV, 20% had 1 PSV, and 13% had no PSV. The number of PSV within a GSDIa patient was not associated with the diagnosis of HCA (p=0.88; **Table 1**). The most frequently observed *G6PC1* variants were p.Arg83Cys (26%), p.Gln347X (17%), and p.Gln27ArgfsX9 (9%) (**Table 2**). No specific *G6PC1* variant hotspot was associated with HCA formation (**Figure 3**). In total, 23 out of 53 (44%) GSDIa patients carried homozygous *G6PC1* variants. Twenty-seven unique genetic variant combinations were observed (**Table 2**).

The number of PSV was not associated with time to HCA formation (**Figure 2d**), neither when comparing 0 PSV or 1 PSV, to 2 PSV. Analyses of the three most frequently observed variants (p.Arg83Cys, p.Gln347X, and p.Gln27ArgfsX9) did not reveal any significant association with HCA occurrence, for mono-allelic, bi-allelic, and homozygous variants compared to other genetic variants in the cohort.

HCA formation and childhood serum triglyceride concentration

Childhood TG data was available in 23 GSDIa patients (10 females, 43%), with a median childhood TG of 3.9 (3.2-5.8) mmol/L. In total, 14 of the 23 patients

developed HCA during follow up. Male GSDIa patients had a significantly lower median childhood TG than female GSDIa patients (3.4 (3.0-4.2) mmol/L vs. 5.6 (4.0-7.9) mmol/L, respectively; p=0.026; **Figure 4a**). Median childhood TG was 3.9 (3.3-4.2) mmol/L for GSDIa patients with 0 PSV, 3.7 (3.4-3.9) mmol/L for 1 PSV, and 4.4 (3.2-7.8) mmol/L for 2 PSV (0 vs. 1 PSV p=0.79, 1 vs. 2 PSV p=0.65, 0 vs. 2 PSV p=0.38). GSDIa patients who developed HCA had a median childhood TG of 4.6 (4.0-7.8) mmol/L, compared to 3.2 (2.3-3.4) mmol/L for GSDIa patients without HCA diagnosis (p<0.001; **Figure 4b**). Seventeen GSDIa patients (74%) had a median childhood TG <5.65 mmol/L (500 mg/dL).[15] A sensitivity analysis with stratification of patients according to an alternative cutoff value of 6.0 mmol/L (proposed by Rake *et al.*[4]), yielded the same patient distribution and similar outcome.

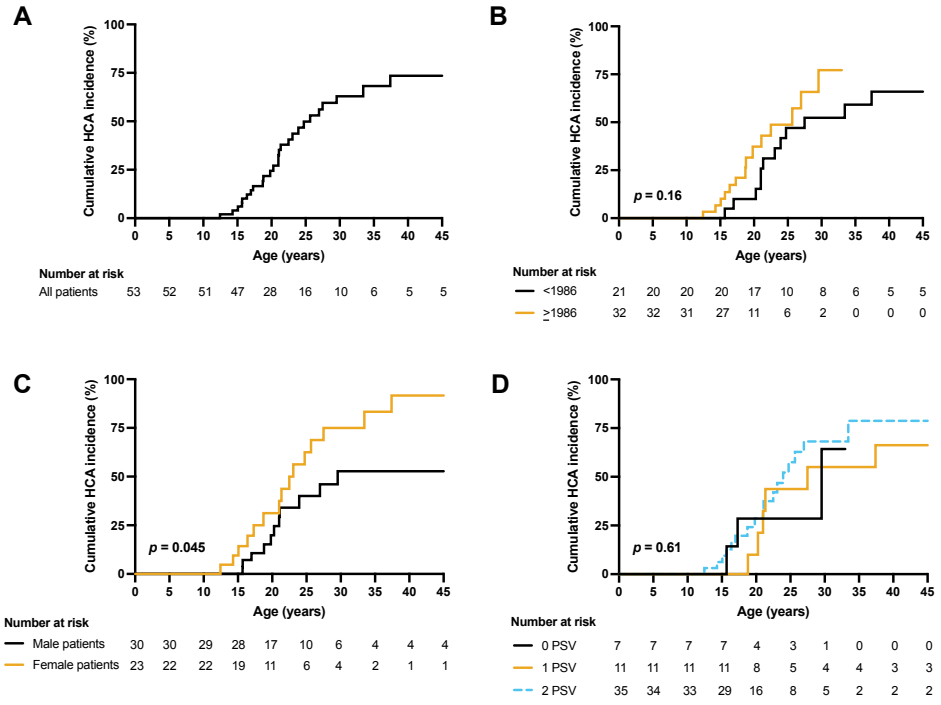

Figure 2. Kaplan-Meier survival analysis for time to HCA occurrence in GSDIa patients. (A) Total cohort. (B) Stratified by treatment era. (C) Stratified by sex. (D) Stratified by *G6PC1* variant severity. Levels of significance: p-values noted (Log-Rank test). Abbreviations: HCA, hepatocellular adenoma; GSDIa, glycogen storage disease type Ia; *G6PC1*; glucose-6-phosphatase catalytic subunit 1; PSV, predicted severe variant.

Table 2. Frequency of *G6PC1* variants in relation to female sex and HCA formation in GSDIa patients

Genetic variant	*G6PC1* variant	Type of variant*	Frequency (*n*, %)		Female sex (*n*, %)		HCA formation (*n*, %)	
c.247C>T c.326C>T	p.Arg83Cys	PSV	28	(26)	14	(50)	14	(50)
c.1039C>T	p.Gln347X	PSV	18	(17)	11	(61)	11	(61)
c.79delC	p.Gln27ArgfsX9	PSV	9	(8.5)	4	(44)	6	(67)
c.189G>A	p.Trp63X	PSV	8	(7.6)	4	(50)	1	(13)
c.467G>T	p.Trp156Leu	Non-PSV	8	(7.6)	0	(-)	2	(25)
c.809G>T c.1039C>T	p.Gly270Val	Non-PSV	6	(5.7)	1	(17)	3	(50)
c.979_981delTTC c.980_982delTCT c.1058delTTC	p.Phe327del	PSV	5	(4.7)	2	(40)	3	(60)
c.248G>A	p.Arg83His	PSV	4	(3.8)		(50)	2	(50)
c.563G>C	p.Gly188Arg	Non-PSV	4	(3.8)	1	(25)	2	(09)
c.508C>T	p.Arg170X	PSV	3	(2.8)	2	(67)	2	(67)
c.209G>A	p.Trp70X	PSV	2	(1.9)	1	(50)	0	(-)
c.797G>T	p.Gly266Val	Non-PSV	2	(1.9)	1	(50)	2	(100)
c.IVS4+1G>A (c.562+10G>A, intron)	Unknown	PSV	2	(1.9)	1	(50)	0	(-)
2bp deletion exon 1	p.Ile59X	PSV	1	(0.9)	1	(100)	1	(100)
c.648G>T	p.Leu216Leu	PSV	1	(0.9)	1	(100)	1	(100)
c.788delA	p.Lys263ArgfsX38	PSV	1	(0.9)	0	(-)	0	(-)
c.866G>A	p.Ser289Asn	Non-PSV	1	(0.9)	0	(-)	0	(-)
c.884G>A	p.Arg295His	Non-PSV	1	(0.9)	1	(100)	1	(100)
c.1091G>T	p.Val338Phe	Non-PSV	1	(0.9)	1	(100)	1	(100)
Unknown	p.Arg380His	Non-PSV	1	(0.9)	0	(-)	0	(-)

*Predicted severe variants are any nonsense *G6PC1* variants and all missense variants within the *G6PC1* active site. Abbreviations: *G6PC1*, glucose-6-phosphatase catalytic subunit 1; HCA, hepatocellular adenoma; GSDIa, glycogen storage disease type Ia; PSV, predicted severe variant.

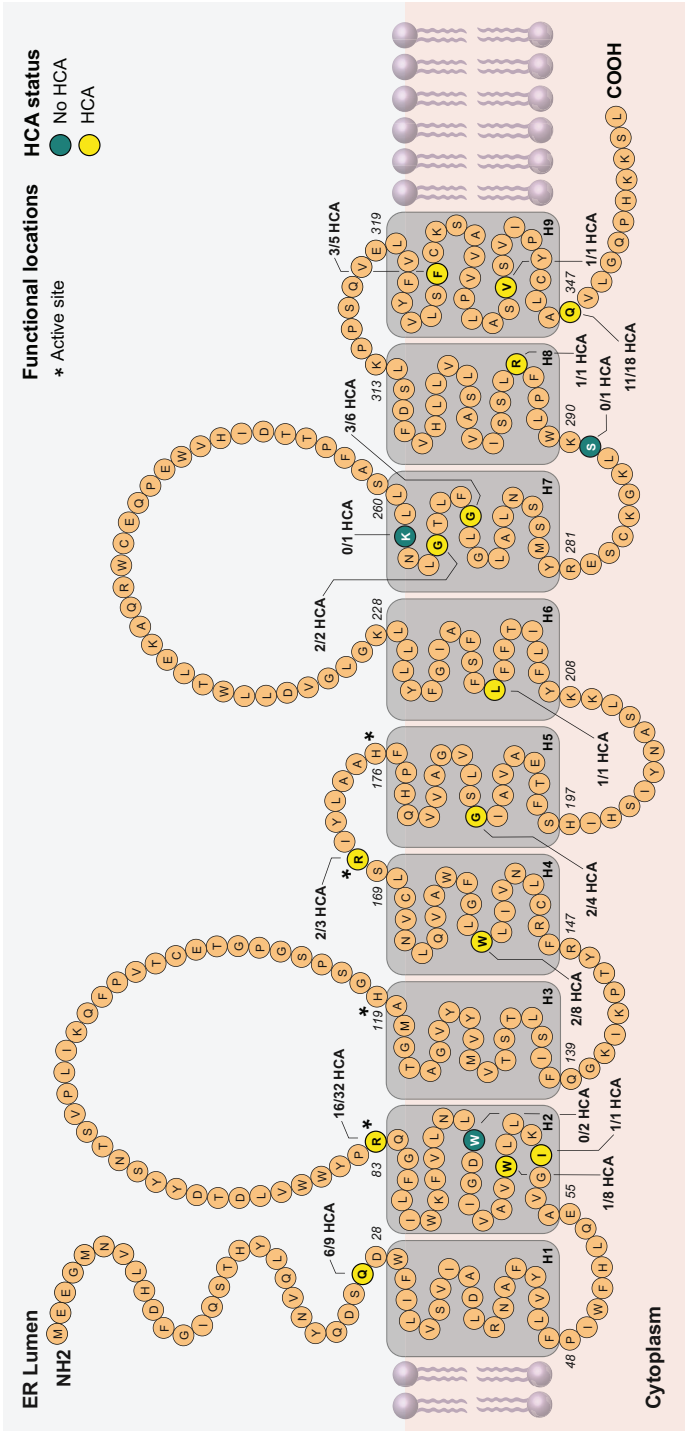

Figure 3. Schematic overview of *G6PC1* with observed variants and occurrence of HCA. No specific *G6PC1* variant was associated with HCA formation. The *G6PC1* active site is defined as amino acids 83, 119, 170, and 176. Abbreviations: *G6PC1*; glucose-6-phosphatase catalytic subunit 1; HCA; hepatocellular adenoma; ER lumen, endoplasmatic reticulum lumen.

In a separate sensitivity analysis on the historical use of lipid-lowering drugs or not, median childhood TG was 3.7 (3.0-4.3) mmol/L vs. 3.9 (3.2-7.3) mmol/L for patients with or without history of lipid-lowering drug use, respectively (p=0.56). Kaplan-Meier survival analysis did not reveal a significant difference in time to HCA diagnosis between patients with or without historical use of lipid-lowering drugs (Log-Rank p=0.18).

Fifty percent cumulative HCA incidence was 18 years for GSDIa patients with median childhood TG >5.65 mmol/L, compared to 33 years for GSDIa patients with a median childhood TG <5.65 mmol/L (Log-Rank p=0.001, **Figure 5a**). A multivariate Cox-regression model was performed, after testing the proportional-hazard assumption using Schoenfeld residuals. A model 1 including sex and categorized median childhood TG (above/below 5.65 mmol/L) was constructed (**Figure 5b**). Male sex was associated with a hazard ratio (HR) of 0.4 (95% CI 0.1-1.4; p=0.15). In this model, GSDIa patients with a median childhood TG >5.65 mmol/L had a HR of 4.6 (95%CI 1.3-16.3) for life-time HCA development (p=0.018). Because females had a higher median childhood TG compared to males (**Figure 4a**), an interaction term was included in model 2 (**Figure 5c**). In model 2, GSDIa patients with median a childhood TG >5.65 mmol/L had a HR of 6.0 (95% CI 1.2-29.8) for formation of HCA (p=0.028).

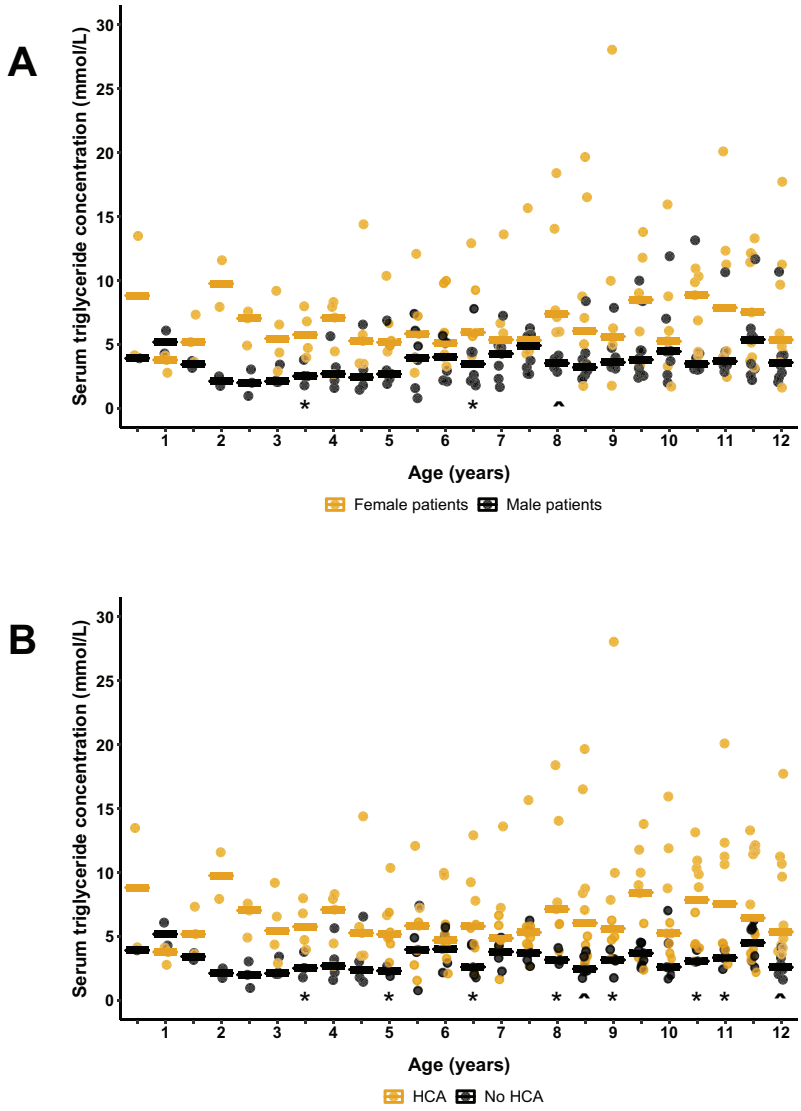

Figure 4. Longitudinal median childhood serum triglyceride concentration in GSDIa patients per patient per six months. (A) Stratified for sex. (B) Stratified for diagnosis of HCA. Horizontal lines represent median TG concentrations per moment of measurement. Levels of significance: *p<0.05; ^p<0.01 (Mann-Whitney U test). Abbreviations: GSDIa, glycogen storage disease type Ia; HCA, hepatocellular adenoma.

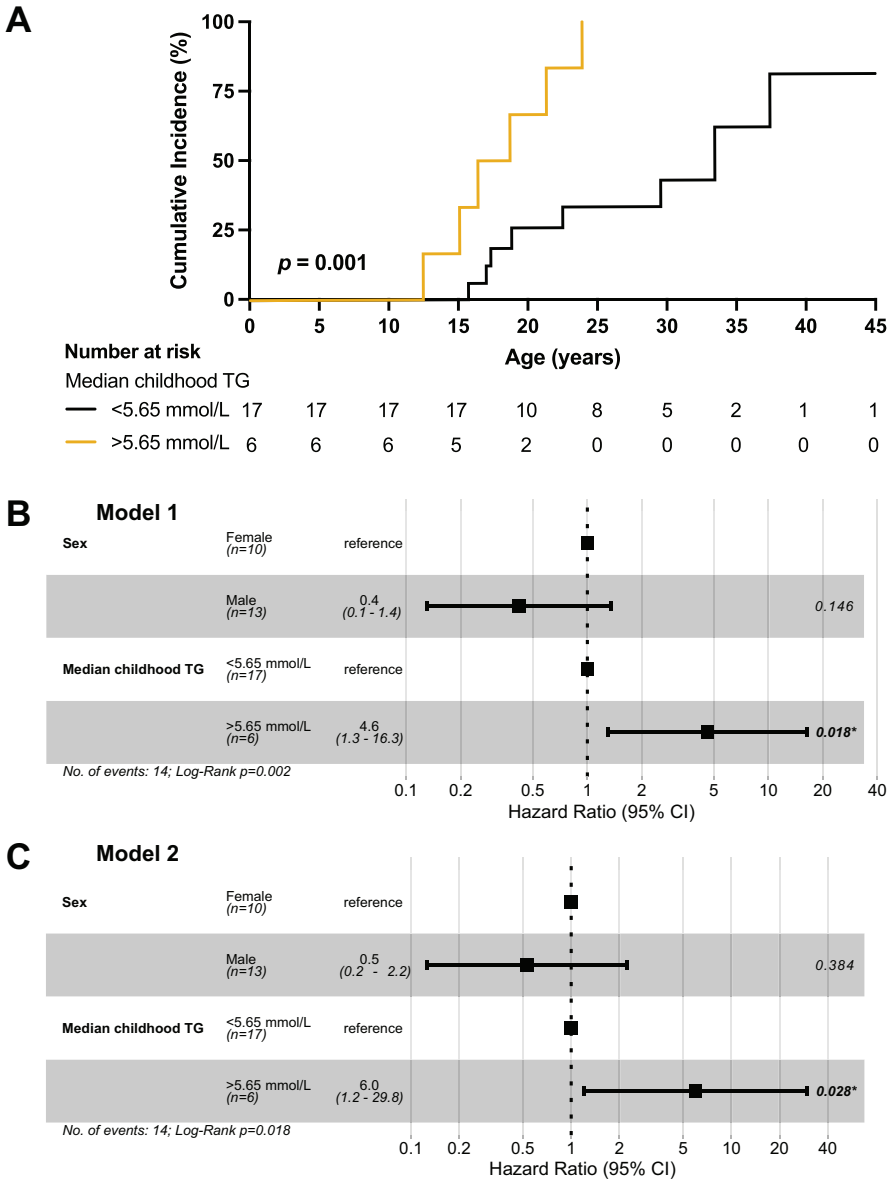

Figure 5. Influence of median childhood serum triglyceride concentration on HCA occurrence in GSDIa patients, patients clustered according to childhood serum triglyceride concentration (TG) above or below 5.65 mmol/L (500mg/dL). (A) Kaplan-Meier survival analysis for time to HCA occurrence, stratified by median childhood TG above/below 5.65 mmol/L. Levels of significance: *p*-values noted (Log-Rank test). (B) Cox-regression analysis including sex and median childhood TG (model 1). Levels of significance: *p*-values noted (Cox-regression analysis). (C) Cox-regression analysis including sex, median childhood TG, and interaction term for sex and median childhood TG (model 2). Levels of significance: *p*-values noted (Cox-regression analysis). Abbreviations: GSDIa, glycogen storage disease type Ia; HCA, hepatocellular adenoma; TG, serum triglyceride concentration.

Discussion

We investigated potential risk factors for the development of HCA in GSDIa patients, using a retrospective, nationwide, observational cohort. During a median follow-up time of 32 years, HCA developed in 26/53 patients. High childhood serum TG concentration was observed more frequently in female patients and was an independent risk factor for HCA development. We did not identify a clear *G6PC1* genotype association with HCA development.

Previous studies have shown that HCA formation in GSDIa occurs during adolescence, which is consistent with our current results.[3,15] In our cohort of GSDIa patients, by the age of 40 years 65% of female patients and 37% of male patients had developed HCA, which is similar to previous reports.[9,14,22] The higher frequency of HCA in male GSDIa patients than HCA in male non-GSDIa patients suggests an alternative, additional pathway to HCA genesis in addition to the exposure to high circulating estrogen/androgen concentration caused by either increased endogenous production (in overweight patients), or supplementation (oral contraceptives or anabolic steroids).[11,23,24] The observed lower childhood TG observed in male patients, compared to female patients suggests that there may be an intricate relationship between sex-associated TG metabolism, and HCA formation (**Figure 4a**).

In our study, as well as in previous reports, HCA in GSDIa has especially been reported in patients with metabolic dysregulation (either by severe G6Pase dysfunction or therapy incompliance) while HCA regression has been observed after strict dietary management.[12,25] It has been suggested that a Warburg-like metabolic switch in hepatocytes resulting from metabolic imbalance contributes to tumor development in GSDIa. The consequent hyperactivation of specific pathways inducing cell growth and mitotic activity may promote hepatic tumorigenesis in GSDIa patients.[26] For instance, enhanced fatty acid synthase activity in GSDIa may provide a beneficial environment for neoplastic progression, as many malignant tumors, including hepatocellular malignancies, display increased fatty acid synthase activity, while fatty acid synthesis inhibition has antitumoral effects.[27–29] However, whether cellular adaptations in metabolic and/or signal transducation pathways explain the increased risk for (advanced)

HCA development in patients with severe G6Pase dysfunction or therapy incompliance, remains to be established in future mechanistic studies.

There is only limited research on genotype–phenotype correlations for GSDIa.[1–3,15,30] A thorough investigation of *G6PC1* genotype in relation to HCA development, however, has not been reported thus far. In our study, *G6PC1* variants and G6Pase impairment, indirectly quantified through the number of PSV, were not significantly associated with HCA development. We also did not identify a "hotspot" for pathogenic *G6PC1* variants that was associated with HCA development. No novel genetic variations were identified in this cohort, and more than half of patients were diagnosed with 2 PSV.[31–33] PSV load, analyzed individually (0, vs. 1 vs. 2 PSV) or grouped (0/1 vs. 2 PSV) did not reveal as a particular risk factor for HCA diagnosis.

Our cohort consists of 27 unique *G6PC1* variant combinations including 23 subjects with homozygous *G6PC1* variants. Although many patients in our study display unique combinations of *G6PC1* variants and despite a relatively low number of inclusions, lessons can be learned from patients with homozygosity for specific *G6PC1* variants. For example, median age of HCA diagnosis was 16 (15-17) years for p.Arg83Cys homozygotes (n=10), as compared to 27 (26-27) years for p.Gln347X homozygotes (n=3). GSDIa patients exhibiting attenuated hypoglycemic phenotypes may explain clinical GSDIa diagnosis at adult ages. We previously reported milder fasting intolerance in GSDIa patients homozygous for c.467G>T (p.Trp156Leu) and c.1039C>T (p.Gln347X), *G6PC1* variants that are associated with retained G6Pase activity *in vitro*.[34] On the other hand, GSDIa patients with compound heterozygosity, for c.508C>T (p.Arg170X) and c.575C>T (p.Ala192Val), homozygosity for c.1039C>T (p.Gln347X), and compound heterozygosity for c.648G>T (p.Leu216Leu) and c.986A>T (p.Lys329Met), resulting in reduced G6Pase activity *in vitro*, have presented clinically with hepatocellular carcinoma, HCA, or acute pancreatitis, respectively.[35–37] Similarly, patients homozygous for the common Japanese c.648G>T (p.Leu216Leu) *G6PC1* pathogenic splice variant are at increased risk of hepatocellular carcinoma.[30,38,39] In summary, we hypothesize that the complex human GSDIa phenotype including HCA susceptibility is at least partially explained by the impact of the *G6PC1* genotype and the duration of the untreated,

highly perturbed metabolic state, with subsequent late diagnosis, start of dietary treatment, and compliance.[40]

Dietary management strategies are the cornerstone of GSDIa treatment. Continuous glucose infusion, continuous nocturnal drip, and uncooked cornstarch have greatly improved GSDIa outcomes. Serum TG concentration is considered an important longitudinal outcome parameter for biomedical control in GSDIa.[3,4,12] The 2002 European Study on GSDIa management guideline recommends TG <6.0 mmol/L as biomedical target, after performing a large multicenter observational cohort study evaluating GSDIa clinical course and outcomes.[3,4] The 2010 Association for Glycogen Storage Disease Conference consensus panel discussion defined a TG target at 500 mg/dL (5.65 mmol/L), and were used as a stratification by Wang *et al.*[15] In our study, childhood TG levels >5.65 mmol/L were associated with increased risk of HCA development as well as earlier HCA diagnosis. Stratification of the cohort at 6.0 mmol/L, as defined by the European guidelines, yielded similar results.[4] Our observations confirm the results from Wang *et al.* that high serum TG precedes HCA diagnosis in GSDIa patients, which should re-emphasize the importance of strict metabolic management to prevent (or delay) HCA formation.[15] In the aforementioned paper, a 5-year mean TG prior to HCA diagnosis or censoring was calculated. Our current results, however, show that HCA formation may already be predicted during childhood, although our dataset does not allow to differentiate between metabolic control and controllability (because of genotype, or sex) of patients. Our observation of comparable median childhood TG's between 0, 1, and 2 PSV suggests mainly female sex as non-therapeutic risk factor for hypertriglyceridemia.

Several limitations may have influenced the outcomes of this study. First, (availability of) treatment strategies, including dietary therapy, have evolved over time. Increased treatment efficacy influenced both metabolic control as well as overall survival of patients, including those with more severe metabolic phenotypes. However, stratification by birth cohort did not reveal any significant differences in HCA occurrence. Second, patient-specific heterogeneity in environmental and/or genetic factors may have resulted in residual confounding that could not be accounted for due to the retrospective nature

of this study. Third, serum TG analysis is likely more often performed in patients with metabolic dysregulation, as this parameter is measured frequently during hospital admissions or outpatient department evaluations. We have mitigated this aspect by calculating medians for all childhood TG data, and a median per six months for longitudinal measurements, yielding similar results.

The data in this study may assist in patient centered (dietary) management and follow-up, as we have identified subgroups of patients especially vulnerable for HCA development. This study illustrates the importance of correlating the multifactorial processes that define the complex human GSDIa phenotype, including the *G6PC1* genotype, parameters of biomedical control, and sex to long-term complications. We have analyzed a subset of those traits, and more investigations are needed on the alternate complications such as nephropathy and biomedical outcome markers such as lactate, uric acid, and continuous glucose monitoring parameters. These are urgently warranted to compose a set of person-centered outcomes for GSD Ia patients, to standardize future data collections, to identify important endpoints for clinical trials, and to evaluate novel treatments in the future.[41–43]

In conclusion, in GSDIa patients, high childhood TG concentration was associated with an increased risk of HCA, and earlier onset of HCA development, independent of sex-associated hypertriglyceridemia, and *G6PC1* genotype. Recognition of these risk factors may assist in further development of individual monitoring strategies for GSDIa.

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CHAPTER 8

Surgical Outcomes of Laparoscopic and Open Resection of Benign Liver Tumors in the Netherlands: A Nationwide Analysis

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Abstract

Introduction

Data on surgical outcomes of laparoscopic liver resection (LLR) versus open liver resection (OLR) of benign liver tumor (BLT) are scarce. This study aimed to provide a nationwide overview of postoperative outcomes after LLR and OLR of BLT.

Methods

This was a nationwide retrospective study including all patients who underwent liver resection for hepatocellular adenoma, hemangioma, and focal nodular hyperplasia in the Netherlands from 2014 to 2019. Propensity score matching (PSM) was applied to compare 30-day overall and major morbidity and 30-day mortality after OLR and LLR.

Results

In total, 415 patients underwent BLT resection of whom 230 (55.4%) underwent LLR. PSM for OLR and LLR resulted in 250 matched patients. Median (IQR) length of stay was shorter after LLR than OLR (4 vs. 6 days, 5.0–8.0, $p<0.001$). Postoperative 30-day overall morbidity was lower after LLR than OLR (12.0% vs. 22.4%, $p=0.043$). LLR was associated with reduced 30-day overall morbidity in multivariable analysis (aOR:0.46, CI:0.22–0.95, $p=0.043$). Both 30-day major morbidity and 30-day mortality were not different.

Discussion

LLR for BLT is associated with shorter hospital stay and reduced overall morbidity and is preferred if technically feasible.

Introduction

The role of liver resection in the treatment of benign liver tumors (BLT) remains challenging.[1,2] Indications for resection differ per tumor type as clinical implications across BLT (sub)types vary significantly.[2] The majority of BLT are comprised of hepatocellular adenoma (HCA), hemangioma, and focal nodular hyperplasia (FNH).[3] The majority of these tumors occur mainly in middle-aged women and are most accurately radiologically characterized through hepatobiliary contrast-enhanced magnetic resonance imaging (CE-MRI).[4]

HCAs are associated with long term oral contraceptive pill use and obesity.[5,6] Tumors of ≥5 cm diameter are associated with hemorrhage (15-20%) and malignant transformation to hepatocellular carcinoma has been described.[7,8] Conservative treatment, by estrogen lowering lifestyle advices including oral contraceptive pill cessation and weight loss, can lead to HCA regression.[9,10] Current European guidelines recommend a wait-and-see period of six months after commencing lifestyle advices. Current guidelines advocate surgery if tumor size remains ≥5 cm.[2] This period, though, may be too short for large HCAs to regress to sub-5 cm size.[11]

Indications for resection in FNH or hemangioma are less distinct, as risk of hemorrhage in hemangiomas and FNHs is very rare in the former, and non-existent in the latter.[12,13] However, both hemangioma and FNHs are known to cause abdominal complaints such as pain, nausea or bloatedness by compression.[14] A rare complication associated with large hemangiomas (≥5 cm) is Kasabach-Merritt syndrome - a consumptive coagulopathy.[15] These consequences could warrant surgical intervention in selected patients as the FNH or hemangioma burden could outweigh the risk of adverse events associated with liver resection.[2]

As indications for BLT surgery are ambiguous, therapeutic strategies are often drafted through shared decision-making by patient and clinician. This process necessitates availability of accurate and elaborate information with regards to surgical outcomes as surgical burden should outweigh risks of postoperative morbidity. Up to now limited series on outcomes after surgery for benign liver tumors have been performed and evidence is scarce. Additionally, potential strategies to decrease adverse events remain

controversial.[16–19] As for malignant tumors, laparoscopic liver resection (LLR) may have potential benefits over open liver resection (OLR) by decreasing blood loss, length of hospital stay (LOS), and postoperative morbidity.[16,20,21] However, the role of laparoscopy in BLT surgery has been scientifically underexposed too.

The current study aimed to provide an evaluation of postoperative surgical outcomes after liver resection for BLT, to assess laparoscopy influence on postoperative outcomes, and to identify predisposing factors for post-operative complications using a multivariable analysis in a nationwide, population-based design.

Methods

A nationwide population-based study was performed in the Netherlands. Data were retrieved from the Dutch Hepato Biliary Audit (DHBA), a nationwide registry in which all Dutch hospitals eligible for liver surgery are obliged to record all liver resections performed. Data verification was performed by a trusted third-party to provide insight into DHBA data completeness and quality.[22] No ethical approval to perform this study was needed under Dutch law as the DHBA is part of the Dutch inspectorate of health care and research is carried out with an anonymized dataset.

Patient selection

Included were patients who underwent liver resection for HCA, hemangioma or FNH in the Netherlands between the 1st of January 2014 and December 31st 2019 and were registered in the DHBA before the 1st of April 2020. Patients were excluded if information regarding date of birth, date of surgery, or type of intervention was missing. Patients who underwent liver resection for unspecified type of BLT were excluded.

Definitions and outcomes

Major liver resection was defined as resection of three or more adjacent segments as per Couinaud classification.[23] Outcomes were stratified for type of BLT and for surgical approach. Surgical approach was categorized for OLR and LLR, converted procedures were included as LLR in the intention to treat analysis.

Postoperative outcomes included 30-day overall morbidity (*i.e.* any complication within 30-days of surgery), and LOS calculated as time between date of surgery and the date of discharge. Furthermore, 30-day major morbidity, defined as a Clavien-Dindo grade IIIa or higher complication (*i.e.* requiring re-intervention, medium care or intensive care management or death) within 30 days of surgery, and 30-day mortality defined as death within 30 days of surgery or during initial hospitalization were assessed.[24]

Other postoperative outcomes included specific complication rates such as bile leakage, postoperative hemorrhage requiring reintervention, postoperative liver failure according to the International Study Group of Liver Surgery, deep surgical site infection (*i.e.* biloma or abscess), incisional surgical site infection, pneumonia, myocardial complication, or a thrombo-embolic complication.[25]

Variables

Patient characteristics included age, sex, American Society of Anesthesiologists (ASA) classification, comorbidity score according the Charlson Comorbidity Index (CCI), history of liver disease and a history of liver resection. Tumor characteristics included type of BLT, number of BLT and diameter of largest BLT prior to treatment. Treatment characteristics included surgical approach, extensiveness of liver resection (major or minor), and type of hospital (*i.e.* tertiary referral hospital or regional hospital) where treatment took place.

Statistical Analysis

Baseline characteristics and postoperative outcomes were compared between groups using the Chi-square test or Fisher exact test as appropriate for categorical variables. The independent two-sample t-test was used for continuous outcomes which were presented as medians with interquartile ranges (IQR).

Funnel plots were plotted for evaluation of hospitals performance relative to mean outcome rates in the Netherlands to address hospital variation concerning 30-day overall and major morbidity after resection.

Univariable and multivariable logistic regression was performed to assess risk factors for adverse events in the complete population. The association of risk factors with adverse events were reported as adjusted odds ratio (aOR) with 95% confidence interval (CI). Variables were entered into multivariable analysis after univariable testing with the outcome as dependent variable. Variables were included in multivariable analysis if $p<0.20$ after univariable analysis. Statistical significance was defined as a two-sided $p<0.05$ in the multivariable model. To assess the influence of annual overall and BLT resection volume on postoperative outcomes in the complete BLT population, both variables were included in these logistic regression models. Annual overall volume and BLT resection volume were calculated as total number of liver resections and BLT indicated liver resections performed per hospital per year, respectively. Overall volume was categorized for <20, 20-39, 40-59, 60-79, and ≥80 procedures, with the first two categories merged for analysis due two low inclusions. Annual hospital volume for BLT resection was categorized <5, 5-15, and ≥15 procedures.

Multicollinearity was assessed in all logistic regression models and indicated if the calculated variance inflation factor was higher than 2.5.

Differences in postoperative outcomes between OLR and LLR were assessed after propensity score matching (PSM). As a first step in PSM, a multivariable logistic regression was used to estimate propensity scores per patient. Hereafter, PSM was performed with a 1:1 ratio using the nearest neighbor method with a caliper of 0.01. Covariates for PSM were, ASA score, type of BLT, history of liver resection, number of BLT, diameter of largest BLT, bilobar disease, and major liver resection. To assess the quality of the matching process standardized mean differences (smd) were used. Standard mean differences below 0.1 for baseline characteristics between the two groups indicate negligible differences between the OLR and LLR groups after PSM. Differences in tumor and operative techniques needed to be negligible to decrease possible selection bias. After PSM, baseline characteristics and outcomes were compared between the groups using the Chi-square test or Fisher exact test for categorical variables. Continuous outcomes were presented as medians with interquartile ranges (IQR). A multivariable logistic regression model was performed using backward selection to identify which variables were associated with 30-day overall morbidity and 30-day major morbidity corrected for possible confounders in the PSM population.

All analyses were performed in R version 3.2.2® (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 415 patients were included of whom 246 (59.0%) underwent resection for HCA, 87 (20.7%) for hemangioma, and 85 (20.3%) for FNH. Laparoscopic resection was performed in 230 (55.4%) patients (**Table 1**).

Patients who underwent resection because of HCA or FNH were more often female, were younger, had lower CCI, and had lower ASA scores versus patients who underwent resection because of hemangioma (**Table 2**). Resection of HCA was more frequently performed for a higher number of tumors, and for a larger tumor diameter compared to hemangioma or FNH, resulting in more frequent major liver resections. Likewise, resection of HCA was performed more often in tertiary referral centers.

The total number of BLT resection did not increase during the study period. Laparoscopic liver resection was performed more frequently over the years as 16 LLR were performed in 2014, 56 in 2018 and 29 in 2019 (p<0.001). Laparoscopic resection was less often applied in case of bilobar disease or when a major liver resection was performed (**Table 1**).

Postoperative outcomes and hospital variation

After BLT resection, 30-day overall morbidity after BLT resection occurred in 73 patients (17.5%), and 30-day major morbidity occurred in 24 patients (5.7%). Thirty-day mortality did not occur (0%). Overall 30-day morbidity rates ranged from 8.3% to 50% between hospitals. None of the hospitals performing liver surgery for BLT had a significantly higher 30-day overall morbidity rate compared to the mean 30-day overall morbidity. Six hospitals had a significantly lower 30-day overall morbidity compared to the mean 30-day overall morbidity. Major morbidity rates between hospitals ranged from 3.5% to 19.4%. None of the hospitals performing liver surgery for BLT had a significantly higher 30-day major morbidity rate compared to the mean 30-day major

morbidity rate. Five hospitals had a significantly lower 30-day major morbidity compared to the mean 30-day major morbidity.

Table 1. Baseline characteristics for patients diagnosed with a benign liver tumor (BLT) between 2014 and 2019 in the Netherlands who underwent liver resection stratified for surgical approach.

Factor		Open Liver Resection	Laparoscopic Liver Resection	*p*-value
		n (%)	*n* (%)	
Total		**185**	**220**	
Patient characteristics				
Sex				0.371
	Male	18 (10)	30 (13)	
	Female	167 (90)	200 (87)	
Age (years)				0.101
	<50	118 (64)	160 (70)	
	50-64	51 (28)	42 (18)	
	65-79	16 (9)	27 (12)	
	≥80	0 (0)	1 (0)	
Charlson Comorbidity Index (CCI)				0.543
	0/1	156 (84)	200 (87)	
	2 +	29 (16)	30 (13)	
Body Mass Index (BMI, kg/m^2)	Mean (SD)	27.5 (5.7)	27.3 (6.0)	0.723
American Society of Anesthesiology (ASA) classification				0.097
	ASA I/II	168 (92)	198 (86)	
	ASA III+	15 (8)	32 (14)	
	Missing	2	0	
History of liver resection				**0.017**
	No	172 (97)	228 (100)	
	Yes	6 (3)	0 (0)	
	Missing	7	2	
History of liver disease§				0.728
	No	177 (97)	220 (98)	
	Yes	6 (3)	5 (2)	
	Missing	2	5	
Histopathological liver disease				
	Normal liver	121 (70)	140 (68)	0.362
	Steatosis	36 (21)	55 (27)	
	Steato-hepatitis	7 (4)	7 (3)	
	Cirrhosis	3 (2)	3 (1)	
	Sinusoidal dilatation	6 (3)	2 (1)	
	Missing	12	23	
Tumor- and operative characteristics				

Table 1. Continued

Factor		Open Liver Resection	Laparoscopic Liver Resection	*p*-value
		n (%)	*n* (%)	
Number of BLT				0.835
	1	119 (73)	161 (75)	
	2	17 (10)	17 (8)	
	3	9 (6)	14 (7)	
	≥4	18 (11)	23 (10)	
	Missing	22	15	
Maximum diameter of largest BLT (mm*)				0.770
	≥50	40 (27)	56 (29)	
	≥50	109 (73)	138 (71)	
	Missing	36	36	
Bilobar disease				**0.011**
	No	107 (58)	161 (71)	
	Yes	77 (42)	67 (29)	
	Missing	1	2	
Major liver resection				**<0.001**
	No	117 (63)	208 (90)	
	Yes	68 (37)	22 (10)	
Type of BLT				0.513
	Hepatocellular adenoma	114 (62)	131 (57)	
	Hemangioma	38 (21)	48 (21)	
	Focal nodular hyperplasia	33 (18)	51 (22)	
Type of hospital∞				0.223
	Regional hospital	50 (27)	76 (33)	
	Tertiary referral hospital	135 (73)	154 (67)	

Bold *p*-values indicate statistical significance of $p<0.05$.
§ History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis.
*Millimeter.
∞ Type of hospital: tertiary referral centers are defined as hospitals with highest expertise on oncologic surgery.

Table 2. Baseline characteristics for patients diagnosed with a benign liver tumor (BLT) between 2014 and 2019 in the Netherlands who underwent liver resection stratified per type of BLT.

Factor		Hepatocellular adenoma	Hemangioma	Focal nodular hyperplasia	*p*-value
		n **(%)**	***n*** **(%)**	***n*** **(%)**	
Total		245	86	84	
Patient characteristics					
Sex					**<0.001**
	Male	16 (7)	23 (27)	9 (11)	
	Female	229 (93)	63 (73)	75 (89)	
	Missing				
Age in years					**<0.001**
	<50	193 (79)	22 (26)	63 (75)	
	50-64	38 (16)	30 (47)	15 (18)	
	65-79	13 (5)	24 (27)	6 (7)	
	>80	1 (0)	0 (0)	0 (0)	
Charlson Comorbidity Index (CCI)					
	0/1	214 (87)	65 (76)	77 (92)	**0.006**
	2 +	31 (13)	21 (24)	7 (8)	
Body Mass Index (BMI)	Mean (Sd)	28.2 (5.8)	26.2 (5.1)	26.0 (6.4)	
American Society of Anesthesiology (ASA) classification					**0.002**
	ASA I/II	218 (89)	71 (84)	77 (92)	0.214
	ASA III+	26 (11)	14 (16)	7 (8)	
	Missing	1	1	0	
History of liver resection					0.386
	No	235 (98)	81 (99)	84 (100)	
	Yes	5 (2)	1 (1)	0 (0)	
	Missing	5	4	0	
History of liver disease§					0.947
	No	233 (97)	83 (98)	81 (98)	
	Yes	7 (3)	2 (2)	2 (2)	
	Missing	5	1	1	
Histopathological liver disease					**<0.001**
	Normal liver	129 (56)	65 (88)	67 (87)	
	Steatosis	79 (36	5 (8)	7 (10)	
	Steato-hepatitis	12 (5)	1 (1)	1 (1)	
	Cirrhosis	3 (1)	2 (2)	1 (1)	
	Sinusoidal dilatation	6 (2)	1 (1)	1 (1)	
	Missing	16	12	7	

Table 2. Continued

Factor		Hepatocellular adenoma	Hemangioma	Focal nodular hyperplasia	*p*-value
		n **(%)**	***n*** **(%)**	***n*** **(%)**	
Tumor- and operative characteristics					
Number of BLT	1	149 (69)	64 (77)	68 (84)	
	2	21 (10)	10 (12)	3 (4)	
	3	12 (6)	5 (6)	6 (7)	
	≥4	33 (15)	4 (5)	4 (5)	
	Missing	30	4	3	
Maximum diameter of largest BLT (mm*)					**0.030**
	<50	47 (23)	27 (40)	22 (30)	
	≥50	155 (77)	41 (60)	51 (70)	
	Missing	43	18	11	
Bilobar disease					0.268
	No	151 (62)	60 (70)	57 (70)	
	Yes	93 (38)	26 (30)	25 (30)	
	Missing	1	0	2	
Major liver resection					0.051
	No	182 (74)	71 (83)	72 (86)	
	Yes	63 (26)	15 (17)	12 (14)	
Type of liver resection					**0.036**
	Right hemihepatectomy	39 (15)	10 (12)	9 (11)	
	Left hemihepatectomy	12 (5)	2 (2)	1 (1)	
	Extended right hemihepatectomy	1 (0)	3 (4)	0 (0)	
	Extended left hemihepatectomy	1 (0)	0 (0)	0 (0)	
	Segment resection	143 (59)	43 (51)	57 (69)	
	Wedge resection	45 (19)	26 (31)	16 (19)	
	Missing	4	2	1	
Surgical approach					0.820
	OLR	114 (47)	38 (44)	33 (39)	
	LLR	131 (53)	48 (56)	51 (61)	
Type of hospital∞					**0.003**
	Regional hospital	64 (26)	39 (45)	23 (27)	
	Tertiary referral hospital	181 (74)	47 (55)	61 (73)	

Table 2. Continued

Factor		Hepatocellular adenoma	Hemangioma	Focal nodular hyperplasia	*p*-value
		n **(%)**	***n*** **(%)**	***n*** **(%)**	
Year of procedure					0.852
	2014	36 (15)	14 (16)	13 (16)	
	2015	37 (15)	19 (32)	14 (16)	
	2016	52 (21)	13 (15)	14 (16)	
	2017	51 (21)	20 (23)	19 (23)	
	2018	40 (16)	12 (14)	15 (18)	
	2019	29 (12)	8 (9)	9 (11)	

§ History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis. Abbreviations: OLR: Open liver resection; LLR: Laparoscopic liver resection. *Millimeter. ∞ Type of hospital: tertiary referral centers are defined as hospitals with highest expertise on oncologic surgery.

Risk factors for adverse events and influence of hospital volume

In univariable logistic regression and multivariable logistic regression, several risk factors for adverse events were observed. Age above 65 (aOR 2.65, CI 1.17 – 5.80, p=0.016), history of liver disease (aOR 4.20, CI 1.01 – 16.0, p=0.037) and major liver resection (aOR 1.94, CI 1.04 – 3.61, p=0.037) were independently associated with higher 30-day overall morbidity (**Table 3a**). Laparoscopic liver resection (aOR 0.55, CI 0.41 – 0.98, p=0.044) was associated with lower 30-day overall morbidity. No influence of type of BLT or hospital volume was observed for 30-day overall morbidity.

Also, CCI higher than 2 (aOR 3.20, CI 1.06 – 8.81, p=0.029) and major liver resection (aOR 3.48, CI 1.32 – 9.14, p=0.011) were associated with higher 30-day major morbidity (**Table 3b**). No influence of surgical approach, type of BLT or hospital volume was observed for 30-day major morbidity.

Propensity Score Matching: baseline- and surgical characteristics

PSM was performed to minimize baseline differences in the OLR and LLR groups (**Table 4**). Matching resulted in balanced covariates as the standard mean difference was 0.100 or lower for all variables except for histological diagnosis as more patients

with parenchymal liver disease were included in the LLR group. This minor imbalance proved insignificant as no significant differences in baseline characteristics were observed between both resection groups. For analysis of postoperative outcomes, 125 patients (50%) who underwent OLR and 125 patients (50%) who underwent LLR were included.

Postoperative outcomes

Median LOS was shorter after LLR compared to OLR (4 days (3 – 6) vs. 6 days (5 – 8), $p<0.001$). Thirty-day overall morbidity occurred in 15 patients after LLR 12.0% which was lower compared to the 28 patients (22.4%, $p=0.043$) in which a complication occurred after OLR (**Figure 1a**). The 30-day major morbidity rate was not different between LLR and OLR. Six patients (4.8%) and 8 patients (6.4%) experienced 30-day major morbidity after LLR and OLR respectively ($p=0.783$).

Postoperative outcomes stratified for LLR and OLR did not show differences in specific liver-related complication rates (**Figure 1b**). Similarly, no differences were observed in other complication rates (*i.e.* pneumonia, cardiac, thrombo-embolic, or infectious) between LLR and OLR (data not shown).

Associated factors with 30-day overall morbidity and 30-day major morbidity after PSM

Multivariable logistic regression in the PSM population showed that bilobar disease (aOR 2.11, CI 1.04 – 4.28, $p=0.037$) was associated with higher 30-day overall morbidity (**Table 5**). Performing LLR was independently associated with lower 30-day overall morbidity (aOR 0.46, CI 0.22 – 0.95, $p=0.043$). No variables were independently associated with 30-day major morbidity.

Table 3a. Univariable and multivariable logistic regression model to assess the association of patient-, tumor- and surgical characteristics with 30-day overall morbidity after benign liver tumor (BLT) resection in the Netherlands between 2014-2019.

			Univariable analysis			Multivariable analysis		
Factor		***n***	**OR**	**CI (95%)**	***p*-value**	**aOR**	**CI (95%)**	***p*-value**
Sex					0.556			
	Male	48	1					
	Female	367	1.29	0.59 – 3.25				
Age (years)					0.080			**0.016**
	<65	371	1			1		
	>65	44	1.90	0.90 – 3.81		2.65	1.17 – 5.80	
	Missing*							
Charlson Comorbidity Index (CCI)					0.340			
	0/1	356	1					
	2+	59	1.39	0.68 – 2.67				
Body Mass Index			0.99	0.94 – 1.03	0.569			
American Society of Anesthesiology (ASA) classification					0.742			
	I/II	366	1					
	III +	47	1.14	0.50 – 2.38				
	Missing*	2						
History of liver disease§					0.020			**0.037**
	No	397	1			1		
	Yes	11	4.26	1.20 – 14.5		4.20	1.01 – 16.0	
	Missing*	7						
Histopathological liver disease¥					0.344			
	No	261	1					
	Yes	119	1.18	0.66 – 2.07	0.563			
	Missing	35	1.88	0.78 – 4.19	0.137			
Number of BLT					0.808			
	1	280	1					
	2	34	0.83	0.27 – 2.09	0.720			
	3	23	0.73	0.17 – 2.22	0.615			
	≥4	41	1.36	0.58 – 2.93	0.453			
	Missing	37	1.38	0.56 – 3.09	0.454			
Maximum diameter largest BLT (mm)*					0.287			
	<50	96	1					
	≥50	247	0.74	0.40 – 1.40	0.342			
	Missing	72	1.58	0.76 – 3.32	0.220			

Table 3a. Continued

			Univariable analysis			Multivariable analysis		
Factor		***n***	**OR**	**CI (95%)**	***p*-value**	**aOR**	**CI (95%)**	***p*-value**
Bilobar disease					0.195			0.160
	No	268	1			1		
	Yes	144	1.41	0.83 – 2.36		1.48	0.85 – 2.57	
	Missing*	3						
Type of benign liver tumor					0.841			0.951
	Hepatocellular adenoma	245	1			1		
	Hemangioma	86	1.18	0.62 – 2.19	0.595	1.04	0.51 – 2.06	0.905
	Focal nodular hyperplasia	84	0.96	0.48 – 1.83	0.909	1.12	0.53 – 2.25	0.753
Major liver resection					0.005			**0.037**
	No	325	1			1		
	Yes	90	2.21	1.26 – 3.83		1.94	1.04 – 3.61	
Surgical approach					0.003			**0.044**
	OLR	185	1			1		
	LLR	230	0.46	0.27 – 0.77		0.55	0.41 – 0.98	
Type of hospital∞					0.535			
	Regional hospital	126	1					
	Tertiary referral hospital	289	1.20	0.69 – 2.14				
Annual hospital volume of BLT resection					0.457			
	<5	150	1					
	5-15	163	1.14	0.62 – 2.09	0.678			
	>15	102	1.51	0.79 – 2.89	0.215			
Overall annual hospital volume					0.827			
	0-39	58	1					
	40-59	31	0.57	0.15 – 1.82	0.366			
	60-79	55	0.85	0.33 – 2.17	0.737			
	>80	271	0.81	0.41 – 1.70	0.555			

Bold *p*-values indicate statistical significance of $p<0.05$.
* Missing not included in analyses based on relatively small group.
§ History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis.
Abbreviatons: Mm = millimeter. OLR: Open liver resection; LLR: Laparoscopic liver resection.
∞ Type of hospital: tertiary referral centers are defined as hospitals with highest expertise on oncologic surgery.
¥ All patients with a nonnormal histological diagnosis of liver tissue are placed under 'Yes'.

Table 3b. Univariable and multivariable logistic regression model to assess the association of patient and tumor characteristics with 30-day major morbidity after benign liver tumor (BLT) resection in the Netherlands between 2014-2019.

			Univariable analysis			Multivariable analysis		
Factor		***n***	**OR**	**CI (95%)**	***p*-value**	**aOR**	**CI (95%)**	***p*-value**
Sex					0.612			
	Male	48	1					
	Female	367	1.47	0.41 – 9.35				
Age (years)					0.756			
	≤65	371	1					
	>65	44	1.22	0.28- 3.74				
Charlson Comorbidity Index (CCI)					0.127			**0.029**
	0/1	356	1			1		
	2+	59	2.213	0.74 – 5.33	0.315	3.20	1.06 – 8.81	
Body Mass Index			0.96	0.89 – 1.03				
American Society of Anesthesiology (ASA) classification					0.859			
	I / II	366	1					
	III +	47	1.12	0.26 – 3.42				
	Missing*	2						
History of liver disease§					0.619			
	No	397	1					
	Yes	11	1.70	0.09 – 9.52				
	Missing*	7						
Histopathological liver disease¥					0.327			
	No	261	1					
	Yes	119	0.72	0.23 – 1.91	0.533			
	Missing*	35	2.12	0.58 – 6.27	0.207			
Number of BLT					0.314			
	1	280	1					
	2	34	0.13	0.01 – 36.8	0.989			
	3	23	0.61	0.04 – 3.45	0.694			
	≥4	41	0.75	0.12 – 2.72	0.702			
	Missing	37	1.28	0.29 – 4.05	0.700			
Maximum diameter largest BLT (mm)*					0.526			
	<50	96	1					
	>50	247	1.38	0.48 – 4.97	0.577			
	Missing	72	2.09	0.57 – 8.45	0.268			
Bilobar disease					0.864			
	No	268	1					
	Yes	144	0.92	0.37 – 2.16				
	Missing*	3						

Table 3b. Continued

			Univariable analysis			Multivariable analysis		
Factor		***n***	**OR**	**CI (95%)**	***p*-value**	**aOR**	**CI (95%)**	***p*-value**
Type of benign liver tumor					0.236			0.099
	Hepatocellular adenoma	245	1			1		
	Hemangioma	86	0.71	0.15 – 2.06	0.502	0.61	0.13 – 2.01	0.457
	Focal nodular hyperplasia	84	1.06	0.72 – 4.63	0.178	2.41	0.90 – 6.22	0.071
Major liver resection					0.018			**0.011**
	No	325	1			1		
	Yes	90	2.78	1.16 – 6.44		3.48	1.32 – 9.14	
Surgical approach					0.333			0.934
	OLR	185	1					
	LLR	230	0.66	0.29 – 1.52		0.96	0.39 – 2.41	
Type of hospital∞					0.896			
	Regional hospital	126	1					
	Tertiary referral hospital	289	1.06	0.45 – 2.81				
Annual hospital volume of BLT resection					0.983			
	<5	150	1					
	5-15	163	0.92	0.35 – 2.41	0.856			
	>15	102	0.98	0.32 – 2.80	0.969			
Overall annual hospital volume					0.269			
	0-39	58	1					
	40-59	31	1.57	0.36 – 6.41	0.526			
	60-79	55	0.61	0.12 – 2.62	0.515			
	>80	271	0.50	0.17 – 1.60	0.199			

Bold *p*-values indicate statistical significance of $p<0.05$.
* Missing not included in analyses based on relatively small group.
§ History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis.
Mm = millimeter.
OLR: Open liver resection; LLR: Laparoscopic liver resection.
∞ Type of hospital: tertiary referral centers are defined as hospitals with highest expertise on oncologic surgery.
¥ All patients with a nonnormal histological diagnosis of liver tissue are placed under 'Yes'.

Table 4. Baseline characteristics after propensity score matching for patients diagnosed with a benign liver tumor (BLT) between 2014 and 2019 in the Netherlands who underwent liver resection stratified for surgical approach.

Factor		Open Liver Resection	Laparoscopic Liver Resection	*p*-value	smd
		n **(%)**	***n*** **(%)**		
Total		**125**	**125**		
Patient characteristics					
Sex				0.570	0.096
	Male	14 (11)	18 (14)		
	Female	111 (89)	107 (86)		
Age (years)				0.684	0.077
	<65	113 (90)	110 (88)		
	>65	12 (10)	15 (12)		
Charlson Comorbidity Index (CCI)				0.487	0.098
	0 / 1	102 (82)	109 (87)		
	2+	23 (18)	16 (13)		
Body Mass Index (BMI, kg/m^2)	Mean (SD)	27.2 (6.0)	27.3 (5.6)	0.652	0.081
American Society of Anesthesiology (ASA) classification				0.342	0.100
	ASA I / II	115 (92)	109 (87)		
	ASA III+	10 (8)	16 (13)		
History of liver resection				1.000	<0.001
	No	124 (99)	124 (99)		
	Yes	1 (1)	1 (1)		
	Missing*	1	1		
History of liver disease§				1.000	0.045
	No	121 (97)	119 (98)		
	Yes	4 (3)	3 (99)		
	Missing*	0	3		
Histopathological liver disease				0.342	0.104
	Normal liver	83 (80)	73 (72)		
	Abnormal liver parenchyma^	21 (20)	29 (28)		
	Missing*	21	23		
Tumor- and operative characteristics					
Number of BLT				1.000	<0.001
	≤3	102 (82)	102 (82)		
	≥4	13 (18)	13 (18)		
	Missing*	10	10		
Maximum diameter of largest BLT (mm*)				0.911	0.035
	<50	35 (32)	32 (30)		
	≥50	75 (68)	74 (70)		
	Missing*	15	19		

Table 4. Continued

Factor		Open Liver Resection	Laparoscopic Liver Resection	*p*-value	smd
		n **(%)**	***n*** **(%)**		
Bilobar disease				1.000	<0.001
	No	81 (65)	81 (65)		
	Yes	43 (34)	43 (34)		
	Missing*	1	1		
Major liver resection				1.000	<0.001
	No	105 (84)	105 (84)		
	Yes	20 (16)	20 (16)		
Type of BLT				0.951	0.040
	Hepatocellular adenoma	70 (56)	72 (58)		
	Hemangioma	26 (21)	26 (21)		
	Focal nodular hyperplasia	29 (23)	27 (22)		
Type of hospital∞				0.893	0.034
	Regional hospital	42 (34)	40 (32)		
	Tertiary referral hospital	84 (66)	85 (68)		

Bold *p*-values indicate statistical significance of $p<0.05$.
Smd = standard mean difference. § History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis. ^ Abnormal liver parenchyma includes steatosis, sinusoidal dilatation, cirrhosis, and steatohepatitis. *Millimeter. ∞ Type of hospital: tertiary referral centers are defined as hospitals with highest expertise on oncologic surgery.

Table 5. Results of stepwise multivariable logistic regression model after propensity score matching for patients diagnosed with a benign liver tumor (BLT) between 2014 and 2019 in the Netherlands who underwent liver resection

			Multivariable analysis		
30-day overall morbidity					
Factor		***n***	**OR**	**CI (95%)**	***p*-value**
Charlson Comorbidity Index (CCI)					0.786
	0/1	211	1		
	2+	39	1.14	0.43 – 2.78	
American Society of Anesthesiology (ASA) classification					0.820
	I / II	224	1		
	III+	26	1.15	0.33 – 3.47	
Histopathological liver disease					0.911
	Normal liver	156	1		
	Abnormal liver parenchyma	50	1.19	0.51 – 2.74	0.684
	Missing	44	1.16	0.29 – 3.74	0.817
Maximum diameter of largest BLT (mm)					0.240
	<50	67	1		
	≥50	149	0.58	0.25 – 1.35	0.197
	Missing	34	1.23	0.42 – 3.44	0.691
Bilobar disease					**0.037**
	No	162	1		
	Yes	86	2.11	1.04 – 4.28	
	Missing*	2			
Type of BLT					0.805
	Hepatocellular adenoma	142	1		
	Hemangioma	52	1.21	0.47 – 3.04	0.685
	Focal nodular hyperplasia	56	0.85	0.32 – 2.11	0.727
Major liver resection					0.171
	No	210	1		
	Yes	40	1.85	0.74 – 4.38	
Surgical approach					**0.038**
	OLR	125	1		
	LLR	125	0.46	0.22 – 0.95	
Charlson Comorbidity Index (CCI)					0.253
	0/1	211	1		
	2+	39	3.44	0.85 – 12.1	

Table 5. Continued

			Multivariable analysis		
30-day overall morbidity					
Factor		***n***	**OR**	**CI (95%)**	***p*-value**
American Society of Anesthesiology (ASA) classification					0.072
	I/II	224	1		
	III+	26	2.48	0.45 – 10.6	
Histopathological liver disease					0.889
	Normal liver	156	1		
	Abnormal liver parenchyma	50	0.97	0.22 – 3.78	0.966
	Missing	44	1.34	0.20 – 7.58	0.632
Type of BLT					0.275
	Hepatocellular adenoma	142	1		
	Hemangioma	52	0.53	0.07 – 2.73	0.488
	Focal nodular hyperplasia	56	2.10	0.55 – 7.70	0.259
Major liver resection					0.145
	No	210	1		
	Yes	40	2.72	0.68 – 9.37	
Surgical approach					0.600
	OLR	125	1		
	LLR	125	0.73	0.21 – 2.40	

* Bold *p*-values indicate statistical significance of $p<0.05$.
Missing not included in analyses based on relatively small group.

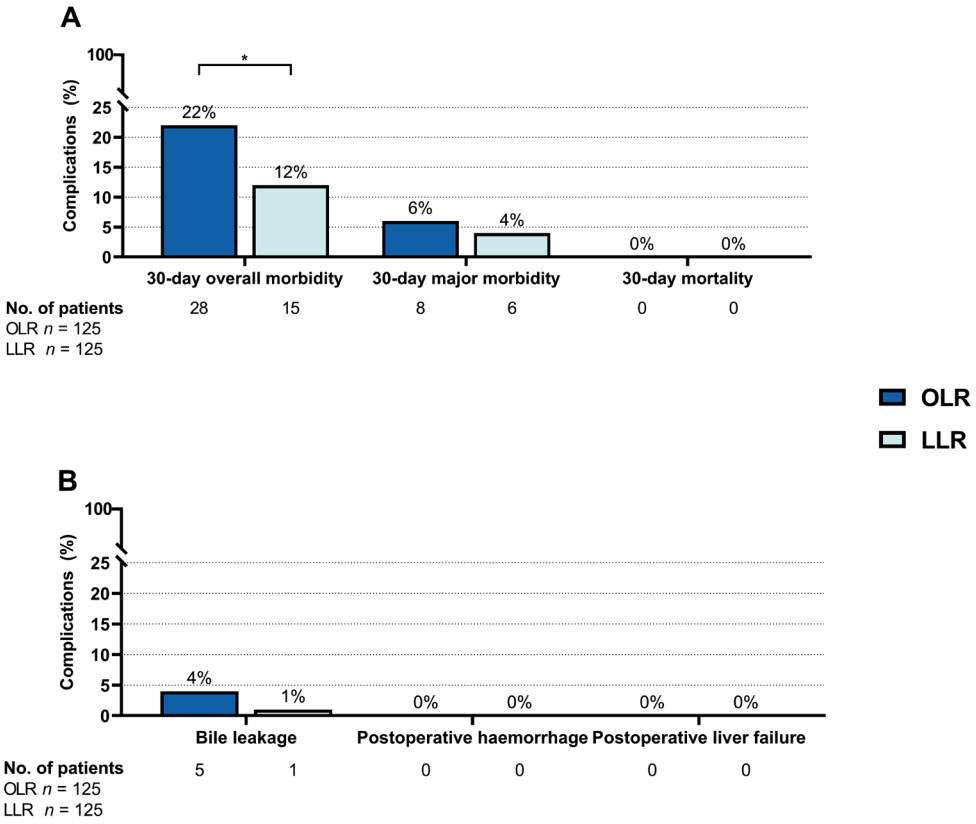

Figure 1. Overview of percentage of patients included after propensity score matching with main outcomes and liver-specific outcomes after benign liver tumor resection in the Netherlands stratified for open liver resection (OLR) and laparoscopic liver resection (LLR). (A) 30-day outcomes. (B) Specific complications. * $p<0.05$

Discussion

This population-based, propensity score matched, study comprises a nationwide study on surgical outcomes for BLT and encompasses one of the largest series up to date. Overall 30-day morbidity was 17.5%, and 30-day major morbidity was 5.7% without mortality. Minimal hospital variation for postoperative outcomes was present. Several hospitals demonstrated better than average performance. Risk factors for 30-day overall morbidity included age above 65, history of liver disease and major liver resection, while risk factors for 30-day major morbidity were CCI above 2 and major liver resection. No influence of hospital volume or type of BLT was observed. PSM was performed and resulted in 250 matched patients who underwent OLR and LLR. LLR proved beneficial with regards to postoperative outcomes such as LOS and 30-day overall morbidity. A more favorable outcome regarding 30-day overall morbidity was also observed for LLR after adjusting for confounding factors, as LLR was associated with lower 30-day overall morbidity. This could indicate that use of LLR may assist in postoperative morbidity reduction when performing BLT indicated liver resection.

Historically, limited series on surgical outcomes of BLT have been reported. Previous studies show overall morbidity rates of 10-20% and major morbidity rates around 10% after resection of BLT. [13,20,21,26–28] Previously reported surgical outcomes after BLT resection range 10-35% and 5-15% for overall and major morbidity, respectively. Hence, the current observations are concordant and indicate resection of hemangioma and FNH in the Netherlands to be comparable to earlier studies.[29–31]

Several risk factors were observed in all resected BLT patients for adverse events. Higher age, higher comorbidity scores and factors associated with the extent of the liver resection were associated with 30-day overall morbidity and 30-day major morbidity. These risk factors are comparable with earlier described risk factors in liver resection for malignant indications.[32,33] Hospital variation concerning postoperative outcomes of BLT resection is present in the Netherlands without any hospitals performing significantly worse than the nationwide average. Most BLT resections were performed in higher volume centers. Some high-volume centers performed better than average (no statistical significance). Overall annual hospital volume for all liver resections and annual hospital

of BLT resection, though, were not correlated with postoperative outcomes, similar to prior observations.[34] This observation, alongside the aforementioned results equal to malignant liver resection indicates safety of BLT resection in all hospital qualifying for malignant liver resection by sufficient case load.

LLR was associated with reduced postoperative morbidity compared to OLR and similar to outcomes of LLR for liver malignancies in general.[35–37] The current results are similar to previous reports on minimally invasive liver surgery. A nationwide study from the Netherlands showed similar results as the current study (30% vs. 42% of complications after LLR and OLR respectively, p=0.040).[38] Previous results regarding laparoscopic BLT resection showed postoperative morbidity incidence of 13.9%; similar to 13% overall 30-day morbidity.[39] his study confirms that if technically feasible, LLR is preferred over OLR concerning resection of BLT.

Potential limitations of this study are registry data associated problems regarding accuracy and coverage. Although third-party data verification deemed 97% of the data accurate, not all specific information concerning operative outcomes could be obtained.[22] Another potential limitation is the lack of information regarding preoperative decision-making process, specific tumor location and preoperative indication for surgery. These were not registered in the DHBA This could have influenced the decision to perform resection of BLT and could be a possible explanation for the surgical intervention in the hemangioma and FNH patients as the European Guideline advocates a wait-and-see policy.[2] Lack of information regarding the preoperative specific tumor location and indication for surgery could thereby lead to confounding by indication despite correction for patient and tumor characteristics. Also, specific tumor location could have been a reason to perform LLR or OLR and this may reflect in the differences in postoperative outcomes. However, this information is not registered in the DHBA and could not be obtained. Another limitation is lack of perioperative details such as perioperative outcomes which can be attributed to the audit nature of this cohort.

Future studies will have to be conducted on improving outcomes after BLT resection. Resection of BLT is often performed in young and healthy patients and therefore major complications of any sort should be avoided. BLT resection should be used only in a

highly selected group of patients after a weighted shared decision-making process by patient and surgeon. Outcomes such as morbidity and mortality are very important in this process. However, possible influence of BLT resection on quality of life should be part of the evaluation of these patients to further assess which patients benefit from BLT resection.[16,40] The role of a composite outcome measure such as Textbook Outcome, which has been described in other fields, is therefore even more relevant for BLT patients.[41] The authors propose surgeons and treating physicians to aspire results comparable to *i.e.* donors participating in living liver transplantation. The authors will therefore initiate drafting of an international Textbook Outcome in BLT patients.[42]

In conclusion, 30-day postoperative outcomes after resection of BLT in this nationwide population-based study are good. BLT resection is safe and can be performed when indicated. LLR is preferred over OLR in appropriately selected patients because of short-term benefits. Although the current study encompasses observations in the Netherlands, the nationwide design and inclusion size provides insights for shared decision-making as well as an international benchmark for quality evaluation.

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CHAPTER 9

Study Protocol for a Multicenter Nationwide Prospective Cohort Study to Investigate the Natural Course and Clinical Outcome in Benign Liver Tumors and Cysts in the Netherlands: The BELIVER Study

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Abstract

Introduction

Benign liver tumors and cysts (BLTCs) comprise a heterogeneous group of cystic and solid lesions, including hepatic hemangioma, focal nodular hyperplasia, and hepatocellular adenoma. Some BLTCs, for example (large) hepatocellular adenoma, are at risk of complications. Incidence of malignant degeneration or hemorrhage is low in most other BLTCs. Nevertheless, the diagnosis BLTC may carry a substantial burden and patients may be symptomatic, necessitating treatment. The indications for interventions remain matter of debate. The primary study aim is to investigate patient reported outcomes (PROs) of patients with BLTCs, with special regard to the influence of invasive treatment as compared to the natural course of the disease.

Methods

A nationwide observational cohort study of BLTC patients will be performed between October 2021 and October 2026, the minimal follow-up will be two years. During surveillance, a questionnaire regarding symptoms and their impact will be sent to participants on a biannual basis and more often in case of invasive intervention. The questionnaire was previously developed based on patient reported outcomes (PROs) considered relevant to patients with BLTCs and their caregivers. Most questionnaires will be administered by computerized adaptive testing through the Patient-Reported Outcomes Measurement Information System (PROMIS). Data, such as treatment outcomes, will be extracted from electronic patient files. Multivariable analysis will be performed to identify patient and tumor characteristics associated with significant improvement in PROs or a complicated postoperative course.

Ethics & dissemination

The study was assessed by the Medical Ethics Committee of the University Medical Center Groningen and the Amsterdam UMC. Local consultants will provide information and informed consent will be asked of all patients. Results will be published in a peer-reviewed journal.

Study registration

Netherlands Trial Register - NL8231 - 10-12-2019.

Introduction

Benign liver tumors and cysts (BLTCs) comprise a heterogeneous groups of cystic and solid lesions.[1] Although extensive research has been performed in the field of BLTCs, their natural course including their influence on patient reported outcomes (PROs) has been underexposed. The most common and relevant cystic lesions are simple non-parasitic liver cysts (estimated incidence of 18%) and "cystadenomas" (1-5% of all liver cysts),[2] now referred to as mucinous cystic lesions of the liver and biliary system and intraductal papillary neoplasms of the liver and bile ducts, MCNs and IPNBs). Solid lesions include hepatic hemangioma (0.4-20%), focal nodular hyperplasia (FNH, 0.4-3%), and hepatocellular adenoma (HCA, 0.001-0.004%).[3–6]

Many BLTCs are found incidentally on routine imaging for unrelated pathology.[3,7] The rising incidence of those so called incidentalomas is at least partly attributable to the increasing use of non-invasive imaging modalities.[2] Main complications of BLTCs are bleeding and malignant transformation - both of which rarely occur.[8,9] Of the five most common and relevant solid and cystic lesions, only (large) HCAs and "cystadenomas" have a known risk of malignant transformation.[9] Treatment indications remain an important matter of debate. In general, treatment of BLTCs is only recommended when they either have a risk of complications or cause severe complaints often with associated impairment of quality of life. When little or no risk of complications is present, the latter is often the sole indication for treatment.[3]

However, this recommendation has various nuances which hampers shared decision and makes the management of BLTCs exceptionally prone to undesirable practice variation.[10,11] Firstly, the influence of treatment on PROs is important but rarely reported.[12] Secondly, in current literature, PROs after treatment by surgery or interventional radiology are rarely compared with conservative management.[12,13] Finally, variations in diagnostic methods may be present, for example FNH is easily misdiagnosed as HCA when inadequate diagnostics are applied.[3,14,15]

Therefore, this observational cohort study aims to investigate the PROs of patients with BLTCs during their natural courses as well as after treatment. These data will enable patients and professionals to make well-informed treatment decisions together to optimize value-based outcomes. In addition, the study will provide an overview of the clinical practice in the Netherlands.

Methods

Study design

The BELIVER study (Natural Course and Clinical Outcome in BEnign LIVER Tumors and Cysts) is an investigator-initiated, nationwide, multicenter observational cohort study. All Dutch medical centers treating patients with BLTCs are eligible for participation, facilitated and coordinated through the Dutch Benign Liver Tumor Group (DBLTG) network. The study was registered in the Netherlands Trial Register (NTR NL8231). Reporting of the study protocol and, eventually, of the full study is done according to the STROBE statement.

Study population

Adult patients (≥18 years old) presenting with a common and/or clinically relevant BLTC at participating centers are eligible for inclusion. Clinically relevant BLTCs are defined as all BLTCs potentially eligible for either surgical intervention or follow-up. Strict cut-off values regarding BLTC size will not be defined and are assessed on a per patient basis by treating professionals.

The study will be conducted from October 2021 till October 2026. The minimal follow-up will be two years. Patients diagnosed with an uncommon BLTC, unwilling or unable to provide written informed consent or to fill in the questionnaire and patients with another disease substantially affecting PROs will be excluded. Uncommon BLTCs and clinically less relevant are excluded. These include choledochal cysts, hepatic angiomyolipoma and biliary hamartoma/Von Meyenburg complexes.[16] Additionally, patients with polycystic liver disease are excluded as they form a circumscriptive group of patients with very typical symptoms and treatments, including liver transplantation and they are currently already included in another international study.[17]

Study objectives and outcomes

The primary study objective is to systematically record the PROs during the natural course and after (minimally) invasive treatment of patients with BLTCs. Secondary study objectives are to evaluate changes in tumor/cyst diameter and the occurrence

of any mortality and complications, related to either the natural course of the disease (malignant transformation or hemorrhage) or related to tumor or cyst treatment. The study will also provide an overview of potential variation in management and outcomes of Dutch patients with BLTCs.

The primary study outcome measure is change in PROs including severity of symptoms from the start compared to the end of the follow-up period. Symptoms are measured by a questionnaire, focusing on PROs relevant to patients with BLTCs and their caregivers and partly administered through the Patient-Reported Outcomes Measurement Information System (PROMIS).

The questionnaire is administered biannually. Although a multiplicity would have enabled a more accurate longitudinal study with correction for confounding events, increasing questionnaire frequency will also probably lead to a reduction of study adherence and result in an increased patient burden. Moreover, one might argue that continuing surveys even after cessation of medical follow-up may introduce disease burden that remind patients of their diagnosis. However, the biannual questionnaires may just as well be a confirmation of wellbeing for patients. In addition, currently some patients might be subjected to extended periods of follow-up even in the absence of this study because of practice variation.

Secondary outcomes related to interventions include postoperative complications according to Clavien-Dindo Classification, the Comprehensive Complication Index, 30 and 90-day mortality, and the Society of Interventional Radiology classification for adverse events.[18–20] Treatment effects will be evaluated with additional questions regarding intervention indication, the effectiveness of the treatment on symptoms, and the likeliness of patients to choose the treatment again. If surgical intervention is applied, questions on incisional herniation are added to the questionnaire after intervention. Supplementary questionnaires will be sent after interventions at three, six, and twelve months, thereafter resuming to biannual questionnaires. An example of two cases and their follow-up with questionnaires is shown in **Figure 1**.

In addition to data collected from questionnaires, data will be extracted from local electronic patient files. This includes the following data: 1) baseline patient characteristics (age, gender, comorbidity); 2) tumor or cyst characteristics (among which diameter, imaging, and histopathological examination), 3) certain data specific for the type of BLTC the patient was

diagnosed with, and 4) details on the intervention performed. **Table 1** summarizes collected variables. All tumor and cyst diameters will be measured according to RECISTv1.1 criteria.[21]

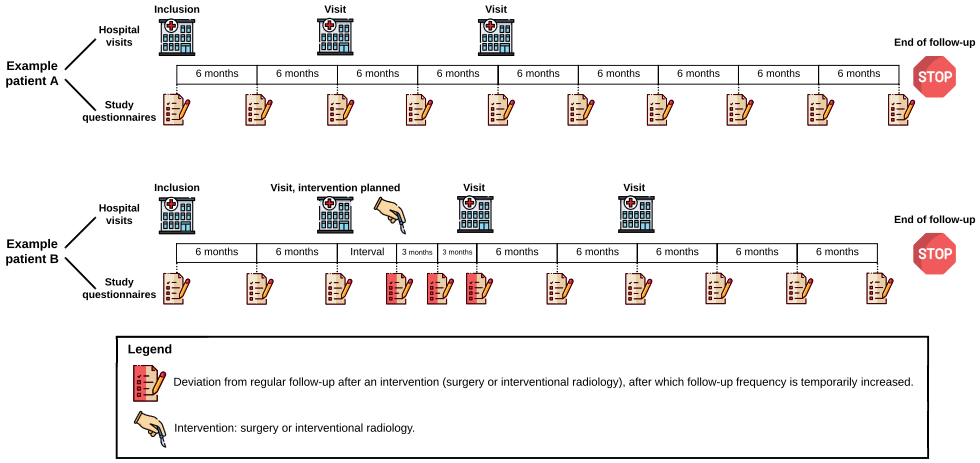

Figure 1. An overview of the hospital visits and study questionnaires of two fictional patients included in the study. In general, patients receive a questionnaire every six months. Deviations from this normal course of follow-up caused by patients undergoing an intervention are indicated by red questionnaires. Please note that these two patients were included around similar dates, but total follow-up durations might differ between patients depending on the date of inclusion.

Patient involvement and questionnaire selection

Various questionnaires have been used to evaluate PROs of patients with BLTCs. However, these questionnaires were not developed for the evaluation of outcomes of BLTC patients and therefore most likely do not appropriately measure outcomes relevant to patients with BLTCs. Based on literature and focus groups with patients with BLTCs and their caregivers, we selected relevant patient-reported outcomes (PROs). These were: insecurity/anxiety, pain, fatigue and limitations in daily life. The domains anxiety, fatigue, ability to participate and pain interference will be evaluated in the current study using computerized adaptive testing through the Dutch-Flemish Patient-Reported Outcomes Measurement Information System (PROMIS).[22–24] PROMIS instruments have recently succesfully been used in research on various patient groups.[25,26] Additionally, numerical rating scales for pain (current and most, least, and average pain over a week) and two general health and quality of life questions will be assessed.

Table 1. Overview of recorded variables

Baseline information		**Tumor or cyst specific questions**		**Treatment characteristics**		
Patient characteristics	**Tumor/cyst characteristics***	**Solid lesions**	**Cystic lesions**	**Intervention**	**Surgery**	**Interventional radiology**
Age	Total number of lesions at baseline	Focal nodular hyperplasia	Simple hepatic cysts	Date of intervention	Type of approach (open, laparoscopic, robot)	Type of procedure (aspiration sclerotherapy, TAE, RFA/MWA)
Sex	Location of lesion (left hemiliver, right hemiliver, bilobar)	Hemangioma	Mucinous cystic neoplasms	Duration of hospital stay	Occurrence and reason for conversion	Sclerotherapy (volume of aspiration, length of sclerosing, type of sclerosing agent)
Mortality If yes, reason	Type of lesion	Hepatocellular adenoma	Intraductal papillary neoplasms	Operation or procedure time	Type of procedure (fenestration, wedge resection, segmental resection, hemihepatectomy, transplantation)	TAE (volume and type of embolization agent [simple embolization, chemoembolization or lipiodolization])
Comorbidity (ASA score and Elixhauser comorbidity index)	Diameter, date and modality of diagnosis			30-day and 90-day mortality	Specification of resected segments	
	Diameter, date and modality of follow-up				Amount of blood loss	
	Occurrence of misdiagnosis If so, revised diagnosis and diagnostic modality				Additional procedures (*e.g.* argon beam coagulation, omental transposition, concurring cholecystectomy)	
	Histopathological diagnosis with immunohistochemistry if available				Complications (type, CD, CCI & SIR)	

Abbreviations: ASA: American society of anesthesiologists; TAE, transarterial embolization; RFA, radiofrequency ablation; MWA, microwave ablation; CD, Clavien-Dindo; CCI, comprehensive complication index; SIR, society of interventional radiologists classification for adverse events.* According to RECISTv1.1 criteria, lesions will only be measured on CT or MRI (longest diameter), measured on the transversal plane on post-contrast series. Maximum of two lesions. If the target lesion is not visible on follow-up imaging (index imaging is imaging shortest before inclusion), then the diameter of the next largest tumor will be measured.

Data collection

Data will be collected using electronic case report forms using an online based platform which automatically generates patient identifiers consisting of the hospital code and a number. A subject identification log will be kept in each center by the principal investigator or local coordinating investigator. This subject identification log will contain the personal details which can be used to send questionnaires to patients. Only this dedicated person has the key for decoding patient data. At completion of the follow-up period, the database will be exported from the online platform. The database will be hosted on a secure server with the infrastructure, configuration, and licenses that are consistent with current norms and laws to ensure safe and secure data storage and processing.

Sample size and statistical analysis

No sample size calculation was conducted as this is an observational cohort study. A previous single center prospective cohort study on the (conservative and surgical) treatment of HCAs and FNHs included 110 patients in 4.5 years.[27] This current study has a broader scope as it spans across at least seven medical centers, includes more BLTC types, and includes patients treated by interventional radiological procedures. Therefore, the aim is to include at least 450 patients.

Statistical analyses will be performed using SPSS statistics for Windows version 24.0 (SPSS Inc., Chicago, IL, USA) and R for Windows version 3.6.3 (R Core Team, Vienna, Austria). Categorical data will be presented as proportions. Continuous data will be presented as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables will be compared using the Fisher exact test or the Chi-square test. Continuous variables will be compared using the Mann-Whitney U test or the Student's t-test. Cox proportional-hazardsmodel will be used when appropriate. A two-tailed $p<0.05$ will be considered statistically significant.

Scores for each patient-reported outcome measure at the start and end of follow-up will be compared using a paired t-test, and factors associated with significant gain in these measures will be evaluated. Patients will be stratified according to treatment

strategy (conservative, surgical, transarterial (chemo-)embolization and lipiodolization, aspiration and sclerotherapy, or radiofrequency or microwave ablation). Sensitivity analyses will be performed for the type of BLTC, and for the time between questionnaires and hospital visits, as hospital visits and imaging may increase the extent of the emotional burden experienced by patients. For surgically treated patients, predictors of a complicated course (Clavien Dindo 3b) will also be evaluated.

Trial sites

Initiating centers are Amsterdam UMC and University Medical Center Groningen. At least all other centers participating in the DBLTG will be included. Participating centers will at least include:

1. Amsterdam University Medical Centers, Amsterdam, the Netherlands
2. University Medical Center Groningen, Groningen, the Netherlands
3. Erasmus Medical Center, Rotterdam, the Netherlands
4. Maastricht University Medical Center+, Maastricht, the Netherlands
5. Radboud University Medical Center, Nijmegen, the Netherlands
6. Leiden University Medical Center, Leiden, the Netherlands

To identify and/or avoid selection bias, non-DBLTG and non-academic centers will also be enabled to join during the study.

Ethics and dissemination

Ethical considerations

This trial will be conducted in accordance with the principles of the Declaration of Helsinki and as stated in the laws governing human research and Good Clinical Practice. The study does not interfere or change the process of treatment of the BLTCs in the included patients. The study was determined to be beyond the scope of the Dutch law on research on human subjects (WMO) according to the Medical Ethics Committee (MEC) of the Amsterdam UMC, location AMC (MEC AMC W19_134 # 19.167) and the MEC of the University Medical Center Groningen (MEC UMCG 201900292). The study will be evaluated by MECs of all participating centers. Moreover, the study

will also be reviewed according to local requirements of each center. Finally, the study proposal was reviewed by the scientific committee of the DBLTG. All substantial amendments will be notified to these committees and organizations. Data will be kept for at least fifteen years after study completion.

Informed consent and withdrawal of consent

Informed consent for use of the questionnaires and the data collected from the electronic patient files will be obtained from all patients by the treating professional in participating centers. Information will be provided to patients by physicians. This will consist of both printed folders and links to digital information. A dedicated website has been created (URL: https://www.DBLTG.nl/BELIVER/). Also, dedicated e-mailboxes have been constructed.

Patients can withdraw from study participation at any time and without consequences or reason. With each questionnaire that is sent, it is noted that if patients wish to withdraw, they can do so at any time. In case of withdrawal, patients will be contacted and asked for allowance of data analysis until that point. There is no specific replacement of individual subjects after withdrawal. Patients who have chosen to withdraw from the study will receive follow-up and treatment according to current standard of care by their treating physician. If participants do not respond to questionnaires, a reminder will be sent after one month. If there is no reaction to this reminder, patients will be contacted by telephone to verify if they still wish to participate or not.

Additional burden and risk associated with study participation

The proposed study does not interfere with standard patient care. No additional blood samples, increase in number of hospital visits, physical examination or other tests are indicated. However, in case of cessation of medical follow-up, patients included in the study will still receive questionnaires.

There are no direct benefits for patients participating in this study. There are no risks involved with participating in this study. The additional burden of the study is minimal. Completion of the questionnaire will take approximately 15 minutes. The

questionnaires might remind patients of their BLTC diagnosis. Some of the questions might be confronting (*i.e.* questions regarding the impact of complaints on daily life and work).

Administrative aspects, monitoring and publication

All results, either positive or negative, will be published in a peer-reviewed journal. All results will be reported suiting reporting guidelines provided by the EQUATOR-network (URL: https://www.equator-network.org/). All Dutch centers collaborating in the DBLTG will be invited to participate in this study. All results originating from this study will be published on behalf of the DBLTG. Co-authorship is available for one physician at each center supplying at least five cases and for two physicians at each center supplying at least ten cases. In each center it may be decided individually which one or two physicians will be mentioned as co-authors. Co-authorships may also be offered to persons who contributed substantially to the conceptualization and execution of the study. All co-authorships will have to fulfill the international committee of medical journal editors (ICMJE) regulations.[28]

In addition to these co-authorships, others involved may be listed as collaborator and the journal will be asked to list them as such also in MEDLINE/PubMed. For each center supplying at least thirty cases, one collaborator may be included; for centers supplying at least forty cases, two collaborators; for centers supplying fifty or more cases, three collaborators.

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CHAPTER 10

Summary, Discussion, and Future Perspectives

Summary

In this thesis I have investigated multiple aspects of benign liver tumors (BLT), and more specifically hepatocellular adenoma (HCA) management, beyond the current guidelines. This encompassed an analysis of current guidelines, management of BLT by European experts, conservative treatment, HCA during pregnancy, surgical indications and outcomes for HCA, HCA in the context of glycogen storage disease type Ia (GSDIa), and the influence of BLT on quality of life (QoL).

In **Chapter 1**, a general introduction on all BLT and in particular on HCA was provided, followed by a description of the thesis outline. To obtain more insight into current availability and content of international clinical guidelines on BLT, we performed a scoping review in **Chapter 2**. After a systematic literature review of 367 unique papers, three guidelines were included and analyzed, originating from the American College of Gastroenterology (ACG), Brazilian Hepatology Society (SBH), and the European Association for the Study of the Liver (EASL). Several differences between guideline recommendations regarding HCA, focal nodular hyperplasia (FNH), and hepatic hemangioma were observed. These were mainly: (1) indications for percutaneous biopsy in all three tumors, (2) advice on the use of oral contraceptive pills (OCP) in FNH and HCA, (3) recommendations on follow-up for FNH and HCA, (4) the lack of recommendations for HCA in male patients in some guidelines, and (5) approaches to HCA subtype diagnosis on magnetic resonance imaging (MRI). Recognition of the limited availability of practice guidelines, and differences in guideline recommendations can help to harmonize international practice standards and aids in identifying unmet needs in research, thereby potentially improving patient care.

Although one singular European guideline has been published, there is no insight into actual current European approaches to BLT patients. **Chapter 3** describes the results of a pan-European electronic survey study on the diagnostics and treatment of FNH and HCA. European BLT experts, including dedicated hepatologists/gastroenterologists, hepatobiliary surgeons, radiologists, and pathologists, were consulted with a two-part survey. Part one focused on local practices, logistics, and approaches to treat BLT both in general and in more specific clinical situations. Part two consisted of eight fictive clinical

vignettes focusing on three distinct domains: (1) FNH, (2) HCA and pregnancy, and (3) HCA ≥5 cm. After submission of 294 invitations, 95 experts responded, of which 61 responses were included. Respondents included surgeons (38%), gastroenterologists/hepatologists (25%), radiologists (8%), and pathologists (1.6%) from ten European countries. Practice variation regarding lifestyle modification and imaging follow up in patients with FNH was observed. Also, variation in the management of larger HCA (>5 cm) after lifestyle modification, and before/during pregnancy was observed.

Although pregnancy-associated estrogen increase may lead to HCA growth and potentially (lethal) hemorrhage, HCA <5 cm are generally considered as safe during and after pregnancy. Data on HCA ≥5 cm during pregnancy, however, are scarce. Hence, we performed a systematic literature review on the behavior of HCA during and after pregnancy, as well as a description of a new cohort consisting of 11 patients, described in **Chapter 4**. The systematic literature review included 33 studies, including 90 patients with 99 pregnancies. Seventy-three (74%) pregnancies featured HCA without prior invasive treatment. In half of these pregnancies HCA remained stable, 15% showed regression, and 31% demonstrated growth. Fifteen HCA-related bleedings occurred, in HCA measuring 6.5-17 cm, eight during pregnancy, two during labor, and five postpartum. The postpartum period is currently not specifically considered as risky; however, increased clinical awareness and close surveillance in patients with larger HCA during the postpartum period might be warranted. As follow-up study, an observational study was proposed of HCA ≥5 cm during and after pregnancy to acquire more data on the behavior of large HCA, as well as on safety and effectiveness of (minimally) invasive treatments during and after pregnancy.

Because HCA growth and regression is associated with estrogen levels, the cornerstone in conservative treatment of HCA ≥5 cm in female patients is cessation of OCP use. No data, however, was available on the safety and outcomes of stopping OCP intake. **Chapter 5** includes an observational cohort study investigating the safety and effect of OCP cessation. Seventy-eight patients were included, with HCA diameters ranging between 1.0 cm and 16.7 cm. Median HCA diameter was 3.7 cm in patients with a body mass index (BMI) <30 kg/m^2, compared to 5.8 cm in patients with a BMI >30

kg/m^2. Age of diagnosis was similar between the two BMI categories. After a median of 1.3 years following OCP cessation, 5% of HCA demonstrated complete regression, 37% partial regression, 56% stability, and 1.3% growth. Thirty-nine HCA ≥5 cm were included, with a median diameter of 8.6 cm, regressing to 5.5 cm after a median period of 1 year. There were 14 HCA (36%) which regressed from an initial ≥5 cm diameter to sub-5 cm diameter during a median follow-up period of 1.3 years. HCA size emerged as an independent predictor of ≥30% tumor regression; hazard ratio (HR) for HCA size 5-10 cm was 2.4, and for HCA size ≥10 cm was 8.4. We observed 98% of HCA to remain either stable or regress after OCP cessation, without any complications. These findings confirm the safety and importance of awaiting HCA response after OCP cessation, even beyond the currently advised six-month period of wait-and-see, and especially in low-risk HCA.

Resection for small (<5 cm) HCA can usually be avoided. Specific, real-world data on indications for resection of HCA, however, is scarce. **Chapter 6** investigates the indications for resection of (suspected) HCA in a nationwide observational cohort study, stratifying results for tumors <5 cm and ≥5 cm. Data from the nationwide Dutch Hepatobiliary Audit were used, supplemented with a local data collection, including all patients operated in the Netherlands between 2014 and 2019. This resulted in an analysis of 222 operated patients. Forty-four (20%) underwent surgery for tumors <5 cm. Median tumor sizes were 3.0 cm for small tumors, compared to 8.3 cm for large tumors. Patients with small tumors were more frequently male (21% vs. 5%). Indications differed between small and large tumors. Patients with small tumors underwent surgery because of suspicion of (pre)malignancy (55%), (previous) tumor hemorrhage (14%), and male sex (11%). Patients with large tumors were operated on because of tumor size (52%), suspicion of (pre)malignancy (28%), and (previous) hemorrhage (5.1%). FNH was more often diagnosed at final histopathology diagnosis in patients with small tumors. In the Netherlands, up to 20% of patients who underwent resection for HCA had small (<5 cm) tumors, usually to treat or rule out (pre)malignancy.

As very limited data on HCA in context of GSDIa was available, **Chapter 7** is dedicated to investigation of risk factors for GSDIa related HCA formation. GSDIa is

characterized by a dysfunctional carbohydrate metabolism caused by genetic variants in the glucose-6-phosphatase catalytic subunit (*G6PC1*). A nationwide observational cohort study was performed including genetically confirmed GSD Ia patients currently aged ≥12 years and with available imaging studies. Of the included patients, median childhood (<12 years) serum triglyceride concentrations ('childhood TG') were used as proxy for metabolic control and stratified to a previously published target of 5.65 mmol/L (500 mg/dL). Genetic variants were classified according to predicted severe variations (PSV) defined by all *G6PC1* nonsense and active site missense variations. Fifty-three patients (23 females) were included, of whom 26 (49%) developed HCA during a median follow-up time of 32 years. HCA occurred more often and at a younger age, and more frequently in female patients than in male patients. Neither PSV category nor specific *G6PC1* variants were associated with HCA development. Median childhood TG was 4.6 mmol/L. Patients with childhood TG >5.65 mmol/L developed HCA 15 years earlier, compared to patients with childhood TG <5.65 mmol/L (18 vs. 33 years). Multivariate analysis using cox-regression was performed, including sex, childhood TG, and an interaction between sex and median childhood TG because of higher TG values in female patients. The model revealed TG >5.65 as an independent risk factor (HR 6.0) for HCA development. **Chapter 7** concludes that HCA development in GSDIa patients can be predicted by childhood TG concentrations >5.65 mmol/L. Female patients are more at risk of HCA development. Knowledge of these risk factors might assist in further development of individual monitoring strategies in GSDIa.

Minimally invasive, laparoscopic liver resection (LLR) is associated with decreased morbidity, when compared to open liver resection (OLR). Most of the data, however, comes from studies including patients who underwent surgery because of malignancy. Such patients typically have a poorer baseline condition and more often comorbidities, when compared to BLT patients. **Chapter 8** investigates surgical outcomes after OLR and LLR for BLT. All patients who underwent hepatic surgery for FNH, HCA, and hepatic hemangioma during 2014-2019 in the Netherlands were included. Propensity score matching (PSM) was applied to compare 30-day overall and major morbidity, and 30-day mortality, stratified for OLR and LLR. After a total inclusion of 415 patients, of

whom 230 (55%) underwent LLR, PSM resulted in 250 matched patients. Length of hospital admission was significantly shorter after LLR than OLR (4 days vs. 6 days). LLR also resulted in lower 30-day morbidity than OLR (12% vs. 22%; p=0.043). Univariate analysis showed LLR (adjusted odds ratio [aOR] 0.55), age >65 (aOR 2.65), history of liver disease (aOR 4.20), and major hepatic resection (aOR 1.94) were associated with 30-day overall morbidity. Finally, multivariate analysis revealed LLR to be associated with lower 30-day overall morbidity (aOR 0.46). Major morbidity within 30 days as well as 30-day mortality were similar. Hence, it was concluded that LLR should be preferred for BLT resection, if feasible.

The BELIVER prospective cohort study described in **Chapter 9**, is currently being performed. This nationwide multicenter study includes all patients with clinically relevant BLT. QoL is measured using both conventional instruments such as a visual analogue scale (VAS) for pain, as well as a newly developed patient-reported outcome measures instrument (PROM). The PROM has recently been developed using patient focus groups and were evaluated using computer adaptive testing (CAT), resulting in shorter and more accurate patient questionnaires. An example of CAT is refraining to ask if a patient can run if he/she has stated inability to walk. The study will provide semiannual questionnaires to patients, and if patients undergo any invasive treatment, additional questionnaires will be provided 3, 6, and 12 months after the intervention. Inclusion will be open for 4 years (until 2024), and the study will run until 2025 to guarantee minimally 12 months of follow-up.

Discussion

The chapters in the current thesis have focused on outcomes of the recommendations as well as potential lacunae in the current European clinical practice guideline on the management of BLT.[1] Therewithal, several uninvestigated relevant areas remain which deserve future studies. This chapter will describe the contemporary landscape of BLT research, examine and interpret the results of the included studies, and formulate a vista for the coming years of BLT research.

The (relatively) low incidence of clinically relevant BLT necessitate the need for nationwide collaboration. Although some individual Dutch medical centers already performed BLT research prior to 2016, no official collaborative network was present. Ease of performing research was increased by the foundation of the Dutch Benign Liver Tumor Group (DBLTG) in 2018 by researchers from the Amsterdam University Medical Center (AUMC; Belle V. van Rosmalen) and UMC Groningen (UMCG; Vincent E. de Meijer and Martijn P.D. Haring).[2] The DBLTG represents all medical specialties involved in BLT management (hepatology, radiology, pathology, and surgery). The DBLTG aims to improve BLT patient care by stimulating and coordinating BLT research. DBLTG participation is open for any medical center if all of the aforementioned specialties are represented. Submitted study proposals are reviewed by a scientific committee, and nationwide data can be consulted if the center's own data is shared *pro quo*. Current participating DLBTG centers are the AUMC, Leiden UMC, UMCG, Maastricht UMC+, and Radboudumc. The DBLTG is officially recognized as public benefit organization (ANBI) and is endorsed by the Dutch Society of Radiology (NVvR), the Dutch Society of Gastroenterology (NVGE), the Dutch Society of Hepatology (NvH), and the Dutch Liver Patient Society (NLV). The DBLTG will cease as an autonomous society after integration in the Dutch Society of Hepatology as official workgroup in from 2022 onwards, which will secure future activities.

BLT are a fascinating field of pathologies which carry confluence with many disease types and aspects of the medical practice. First, management of patients with BLT confronts medical doctors with their upmost central ethos: Hippocrates' *primum non nocere* (first, do no harm). The consideration on the adequate treatment for patients with

BLT, weighing therapeutic benefits to complication risks is complex, because treatment of BLT is mainly indicated by what the tumor could cause, instead of what the tumor already is or will be causing. This contrasts with *e.g.* untreated hepatic or pancreatic malignancy, which carries a certainty of lethality by invasive growth or metastasizing behavior.

Although only a small selection of BLT are clinically relevant with regards to complications, they may still cause alteration in QoL due to patient uncertainty. Patients and practitioners are confronted by the inherent flip side of diagnostic modalities, as 100% diagnostic certainty can seldomly be achieved. Patients and practitioners face hard decisions when a particular diagnosis implies severely differing management, such as FNH (no treatment or follow-up) versus HCA (invasive treatment) in male patients, whilst these two tumor types are notorious for having similar characteristics on imaging or histopathology. Fortunately, BLT resection by laparoscopy over conventional open resection, and development of even more minimally invasive techniques such as percutaneous tumor ablation or transarterial embolization have expanded treatment flexibility for patients and practitioners, whilst being effective and safe.[3,4] This therapeutic progression with reduced burden and risk of complications eases the decisional burden shared by patients and practitioners.

The critical appraisal and comparison of available BLT management guidelines in **Chapter 2** resulted in several relevant observations. The inclusion of only three guidelines after a global literature query may on itself indicate that BLT need additional concise treatment frameworks in Africa, Asia, the Americas, and Oceania. Also, multiple distinct differences between guideline recommendations were observed. Some differences could be explained by new evidence published after guideline drafting, or alternate interpretation of the moderate quality of available (observational) evidence, albeit one could argue they could also result from medico-cultural differences. For example, FNH have been unequivocally proven unresponsive to OCP use prior to publication of all guidelines.[5] The ACG guideline recommends ceasing of OCP, whereas the EASL guideline mentions safety of continuation. Recommendations on safety of percutaneous biopsy in hepatic hemangiomas also differed; the EASL guideline states it

as safe, whereas the other two guidelines mention risk of hemorrhage. Lastly, the ACG guideline describes clear imaging characteristics of beta catenin mutated HCA (b-HCA) diagnosis on MRI obviating the need for biopsy referring to a study including 2 b-HCA. All guidelines implemented different recommendation frameworks and had different scores on the AGREE-II appraisal. An important observation is the current unavailability of one uniform clinical practice guideline. Consensus between international hepatology/gastroenterology institutions could be increased through Delphi meetings focusing both on current controversial management recommendations, as well as the future research agenda.

Several relevant disagreements between European experts were observed in the results of the survey study in **Chapter 3**. Moreover, the patterns of agreement differed between the three vignette categories. Follow-up of FNH was controversial in the results from current practices (part I) as well as the clinical vignettes (part II). Although FNH was described as pathognomonic on imaging in our survey, lingering uncertainty on potential HCA occurrence instead of FNH might explain reluctance to discharge patients from follow-up. For example, 38% of respondents would start follow-up of the male patients, and 74% of respondents would start follow-up if FNH growth was observed in a female patient using OCP. In addition, 40% of respondents would cease OCP intake in female FNH patients when tumor growth was reported, whilst OCP has been proven to have no influence on FNH number or size, and FNH might grow and reduce in size on themselves.[5] Regarding HCA subtype identification on MRI, about a third of respondents accepted b-HCA/b-IHCA diagnosis on CE-MRI, whilst conclusive data is currently lacking and clinical practice guidelines discourage non-invasive b-HCA/b-IHCA diagnosis.[1,6,7] Regarding HCA, 85% of respondents would continue conservative management of HCA >5 cm after the advised six-month period, illustrating progression to a more conservative stance. Half of respondents, however, would advise to continue follow-up of postmenopausal patients with HCA <5 cm, although there is some evidence for safety and good prognosis of HCA after menopausal onset, which has been argued to allow for safe discontinuation of follow-up.[8] Weight loss was advised by >70% of respondents in HCA >5 cm, which demonstrates awareness

of EASL guideline recommendations and potential treatment efficacy, even though only anecdotal evidence is available.[9–11] Results from the survey comprehend the first objectification of substantial variability in European FNH and HCA management. The results of **Chapter 2** and **Chapter 3** are very usable in future Delphi meetings to increase consensus on current debated topics, as well as the future research agenda.

Management of HCA during pregnancy has been increasingly characterized by a more conservative stance in the recent years. Historically, women have been discouraged to become pregnant when HCA were present or were urged surgical treatment prior to or during pregnancy. The landmark study from Gaspersz *et al*. definitely objectified the safety of HCA <5 cm during and after pregnancy.[12] Safety of HCA ≥5 cm remained unclear though. In the combined retrospective cohort study and systematic review in **Chapter 4**, HCA growth was observed in about a quarter of HCA, of which 7 exceeded 5 cm. Bleeding episodes were observed in 15 patients, with HCA 6.5-17 cm. An important limitation of the included complications is the inherent publication bias of bleeding HCA. No data is available on the frequency of uncomplicated pregnancies with HCA ≥5 cm. Several of the included studies published before 1990 described casuistry with large HCA (>8 cm) diagnosed only after (often catastrophic) tumor hemorrhage during pregnancy, labor, or puerperium. Publications of these de novo peri-gestational HCA diagnoses have been greatly reduced in recent years due to the increased use of medical imaging in general, and standard use of gestational ultrasound (US) screenings.

Chapter 5 described that stable disease or tumor regression was seen in 96% of included HCA, without any bleeding complications after stopping OCP. One of the most important observations concerns the 39 included HCA ≥5 cm. Fourteen HCA (39%) with a median starting diameter of 6.5 cm regressed to sub-5 cm diameter after a median time of 1.3 years. This observation demonstrates the significant regression potential of large HCA, as well as the interval in which the regression occurred, being longer than the currently advised six-month period. Beyond investigation of safety and behavior, our study explored factors influencing HCA regression. Initial tumor diameter, stratified for ≥5 cm or ≥10 cm, revealed to be the only significant factor, whilst neither

duration of OCP use nor patient BMI were of influence. Our findings confirm the report by Klompenhouwer *et al.,* which observed regression to <5 cm in 38 of 44 HCA initially <7 cm after a median period of 63 weeks, and 6 out of 23 HCA ≥10 cm after a median period of 208 weeks. These, and our findings provide considerable evidence to regard the currently advised six-month period to be too short for sufficient regression, especially in case of large HCA. The absence of bleeding or oncological complications in our report is potentially biased because of the observational, retrospective nature of the study. HCA at risk of bleeding or with signs of (pre)malignancy on imaging received intervention instead of being managed conservatively. Hence, our results seem to be applicable for HCA eligible for conservative therapy, and not for all HCA. In addition to the HCA behavior, we observed obese patients (≥30 kg/m^2) to be diagnosed with larger HCA, whilst time to diagnosis between BMI-groups was similar. Using this data, practitioners can consider to follow-up HCA >5 cm (demonstrating regression and in absence of pre-malignant characteristics) 'beyond current guidelines' – longer than the advised six-month period, which some professionals already do according to **Chapter 4**.

Investigation of indications for HCA resection revealed distinct indications for HCA ≥5 cm and <5 cm in **Chapter 6**. Half of patients with small tumors were mainly operated on because of suspicion of (pre)malignancy, followed by about 10% because of either bleeding, or male sex. Half of the patients with large tumors, on the other hand, underwent resection because of tumor size ≥5 cm, followed by malignancy suspicion (30%). There were several findings which could motivate further studies. First, some patients were explicitly operated on because of uncertainty or abdominal complaints. Second, there were more male patients treated for tumors <5 cm, and there were more patients with ultimately proven FNH <5 cm at final histopathogical analysis. A limitation of the study is the retrospective assessment of preoperative diagnostic workup, including imaging, as the radiologic analysis often contains many nuances open to varying interpretations. No previous data on indications for resection was available before this study. The preoperative decisional process is often complex, individualized, and multifactorial. Our analytic method using one main indication for surgery could oversimplify the actual treatment indication, which potentially goes with softer secondary

arguments such as abdominal complaints. The frequency and impact of such symptoms have scarcely been investigated. They stress the relevance for the upcoming BELIVER study, which includes QoL outcomes using patient-reported outcome measures PROM.

Chapter 7 resulted in three important findings regarding HCA formation in GSDIa patients: HCA development was not associated with PSV or specific *G6PC1* variants, female sex was associated with earlier and more HCA development, as well as significantly higher childhood TG, and high childhood TG was independently associated with earlier and more HCA development. We concluded that high childhood TG (>5.65 mmol/L) was, independent from sex-associated hypertriglyceridemia, predictive for HCA diagnosis later in life, which can be considered a novelty. These findings may assist in further development of general and individual patient monitoring strategies as we have identified subgroups of patients especially vulnerable for HCA diagnosis. These findings suggest an intricate relationship between both carbohydrate metabolic environment, sex, and HCA development. Previously published reports have especially reported HCA in GSDIa patients with metabolic dysregulation (either by severe glucose 6-phosphatase [G6Pase] dysfunction or therapy incompliance), while HCA regression has been observed after strict dietary management.[13,14] A Warburg-like metabolic switch in hepatocytes resulting from metabolic imbalance potentially contributes to tumor development in GSDIa, which results in activation of tumorigenesis inducing pathways by stimulating cell growth and mitotic activity.[15] For instance, enhanced fatty acid synthase activity in GSDIa may provide a beneficial environment for neoplastic progression, as many malignant tumors, including hepatocellular malignancies, display increased fatty acid synthase activity, while fatty acid synthesis inhibition has antitumoral effects.[16–18] However, whether cellular adaptations in metabolic and/or signal transducation pathways explain the increased risk for (advanced) HCA development in patients with severe G6Pase dysfunction or therapy incompliance, remains to be established.

Knowledge of surgical outcomes is vital when patient and practitioner are collectively deciding upon surgery. Data on surgical outcomes of BLT patients are scarce but needed, as case-mix differs significantly from patients with hepatic malignancies. Surgical outcomes proved good in **Chapter 8**.

Risk factors for 30-day overall morbidity included age above 65, history of liver disease and major liver resection (≥3 hepatic segments), while risk factors for 30-day major morbidity were Charlson comorbidity index ≥2 and major liver resection. Only laparoscopic approach proved significantly associated with improved short-term outcomes after PSM and multivariate analysis. These risk factors were comparable with earlier described risk factors in liver resection for malignant indications.[19,20] Previous studies showed overall morbidity rates of 10-20% and major morbidity rates around 10% after BLT resection, which is in line with our observations.[21–29] This study underscored the importance of using laparoscopy whenever feasible in BLT patient.

In the field of BLT, a structural and standardized assessment of BLT-induced QoL impairment by, for example, anxiety for complications or abdominal complaints, is not implemented yet. Until now, no studies on QoL of BLT patients without invasive treatment have been performed. One systematic review on the impact of (minimally) invasive treatment reported symptom relieve in 82% of symptomatic patients.[30] Validated QoL tools were used in eight studies (visual analog scale, MQ Gill, SF36, EORTC, and EQ-5D).[30] Two of those studies reported significant better QoL scores following laparoscopic compared to open surgery. Whilst all of these aforementioned QoL instruments are validated, none of these are specific for BLT patients. PROM have been developed through BLT patient discussion panels, which encompasses the first step in exploring BLT-related QoL (unpublished data). **Chapter 9**, describing the prospective BELIVER study protocol, includes the first implementation of these BLT-PROM. The PROM will also be available for any researcher to use, which could be a catalyst for increased future research on BLT-associated QoL outcomes and treatment recommendations.

Future perspectives

The results observed in **Chapter 2** and **Chapter 3** provide material to commence an inter-continental discussion. By using the Delphi consensus method, international experts could formulate future guideline recommendations and a research agenda, aiming to reduce practice variations and to improve patient care.[31] Continuing on the observations of the HCA during and after pregnancy in **Chapter 4**, a retrospective cohort study should be performed in the Netherlands (or Europe) to further establish the outcomes of HCA ≥5 cm, and ≥10 cm during and after pregnancy.

Although **Chapter 5** identified clear factors influencing HCA regression, further research could be done on potential differences of estrogen environment in HCA patients with and without obesity. The abundance of biologically available estrogen is influenced by the estrogen-gut microbiome axis – the so called estrobolome.[32,33] Some gut microbiota express beta-glucuronidase, which increases biologically available estrogen both by deconjugation of estrogen and phytoestrogens.[33] Current research on the estrogen-gut axis is in a relatively early stage, although signs of relevance for (estrogen-sensitive) breast and endometrial cancer as well as endometriosis and infertility have been reported.[34–38] Future studies could focus on mapping of microbiome diversity of HCA patients, which might lead to insights into (risk factors for) HCA etiology, as well as providing therapeutic targets for estrogen reduction (and HCA regression).

In addition to stopping any OCP, obese females with HCA ≥5 cm are recommended to lose weight to stimulate HCA regression. Limited studies are available on weight loss-induced HCA regression.[9–11] Weight loss without adequate guidance has proven largely ineffective. A large, randomized trial of infertile women due to obesity observed 43% of patients included in a supervised weight loss program to achieve ≥5% body weight reduction, compared to only 11% in the control group.[39] Indications of similar results have been observed for HCA patients. A questionnaire sent in 2016 to 157 female HCA patients treated in the UMCG, revealed a self-reported median BMI of 29 kg/m^2, with 71% of patients having BMI ≥25 kg/m^2. Half of patients reported to attempt weight loss after HCA diagnosis, and those patients lost a median 11 kg in 6 months, of which 7 kg was gained again in the 12 months thereafter (unpublished results). Effectiveness of

weight-loss on HCA diameter could therefore be investigated through a trial using the "BeweegKuur". The "BeweegKuur" is a multidisciplinary program, which was developed by funding from Dutch Ministry of Health, aiming for durable weight loss by improving physical activity as well as dietary behavior. The intervention has been estimated cost-effective by the National Institute for Public Health and the Environment (RIVM).[40,41]

Indications for HCA resection were identified in **Chapter 6**. Surprisingly, some patients were operated on because of uncertainty (impairing QoL). The BELIVER study should provide more information on the extent to which BLT influence QoL. Another observation was a relatively high incidence of FNH being diagnosed in male patients. More research could be dedicated to the preoperative workup of patients with FNH, to prevent unnecessary invasive treatment due to incomplete diagnostic information. Additionally, investigation of indications for (minimally) invasive treatment of FNH and hepatic hemangiomas can provide more insight into real-life application of current clinical practice guidelines and uncover areas relevant for future updates.

Chapter 7 describes the first multivariate analysis of risk factors for HCA formation in GSDIa patients. Future mechanistic studies are needed for definite etiologic conclusions, and oncological safety of HCA in GSDIa. Also, current guidelines do not differentiate HCA etiology in male patients. Invasive treatment is recommended regardless of underlying metabolic disorders, even though these HCA demonstrate a significantly differing incidence and complication profile. HCA development due to (undiagnosed) metabolic disease should always be considered. Cases have been described with HCA preceding HNF1A-MODY diabetic symptoms.[42] As these HNF1A-MODY associated H-HCA are FDG-PET avid, they might be misinterpreted as malignancy.[42,43] Risk of H-HCA regression to HCC is extremely rare but not impossible; about 1.5% of all HCC carry a somatic *HNF1A* mutation and HCC in a HNF1A-MODY family have been described.[44,45] Future research should focus on oncological safety of GSDIa and HNF1A-MODY associated HCA in male patients, to provide ground for a potential future exemption of invasive treatment regardless of metabolic comorbidity.

Finally, future studies could be dedicated to HCA subtype identification on CE-MRI, as well as HCA subtype distribution. Non-invasive b-HCA/b-IHCA diagnosis is

relevant, as percutaneous biopsy is not always feasible or effective. Gadoxetic acid (Gd-EOB-DTPA) enhanced MRI has the highest sensitivity and specificity of non-invasive diagnostic modalities for HCA (subtype) diagnosis.[46–48] Current studies have included a limited number of b-HCA/b-IHCA patients, and often without molecular subtype confirmation.[6,7,49–55] Evaluation of MR characteristics of solely molecularly diagnosed b-HCA/b-IHCA as well as I-HCA is crucial, because beta-catenin (*CTNNB1*) exon 7/8 mutated HCA are known to have negative results on immunohistochemistry analysis.[56] Acquisition of histopathological material via percutaneous biopsy brings a small (1.6%) risk of severe bleeding.[57] Additionally, anatomical difficulties by tumor location or small size could hinder acquiring representative histopathology. Furthermore there is a risk of sampling error, as multiple HCA subtypes co-occurring within an individual patient, or multiple mutations co-occurring within a single HCA have been reported.[58] These limitations warrant further research on HCA subtype identification through CE-MRI, and in particular of b-HCA/b-IHCA. Present knowledge on HCA subtype identification, and molecular classification is predominantly the result of numerous French research initiatives resulting in significant and impactful data on HCA etiology, subclassifications, and outcomes.[58–72] The currently established relative distribution of HCA subtypes largely stems from their published results and is used globally in clinical and scientific practice. Yet, two important limitations should be recognized. First, their histopathological data originates from biopsies and resections, which may lead to a case-mix bias in the reported HCA subtype distribution. Second, HCA subtype distribution might be different in an alternate population, as their demographics, habitus, and characteristics differs from the French population. Therefore, a histopathological study in the Netherlands, in Europe, and in the United States of America should be performed for confirmation of HCA subtype distribution in alternate populations.

In conclusion, the current thesis has explored the management of BLT beyond the recommendations of current clinical practice guidelines – an endeavor relevant to BLT patients, clinicians involved in treating BLT patients, and BLT researchers. The included observations provide the information needed for an evidence-based improvement of BLT patient care. Furthermore, the thesis may provide ground for various future research opportunities to continue the current trend of individualization of BLT patient management.

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CHAPTER 11

Nederlandse Samenvatting

Introductie

Het veelvoudige gebruik van medische beeldvorming (echografie, computer tomografie en magnetische resonantie beeldvorming [MRI] in de hedendaagse kliniek leidt regelmatig tot toevalsbevindingen (incidentalomen). Incidentalomen van de lever komen voor bij 30-40% van de bevolking ouder dan 40 jaar en bestaan uit levercysten, focale vetophopingen en goedaardige levertumoren. Het overgrote deel van deze toevalsbevindingen in de lever zijn ongevaarlijk en hebben geen klinische gevolgen. In tegenstelling tot kwaadaardige levertumoren (leverkanker) zaait een goedaardige levertumor zich niet uit door de lymfe- of bloedbaan en groeit het niet de naastgelegen organen in. De meest voorkomende goedaardige levertumoren zijn leverhemangioom, focaal nodulaire hyperplasie (FNH) en leverceladenoom ofwel hepatocellular adenoom (HCA).

Leverhemangioom en FNH hebben zeer beperkte klinische consequenties. Beide tumorsoorten hebben geen potentieel om zich tot leverkanker te ontwikkelen en zijn ongevoelig voor geslachtshormonen zoals testosteron of oestrogeen. In zeer zeldzame gevallen kan een groot leverhemangioom (>10 cm) leiden tot verminderde beschikbaarheid van bloedplaatjes of tot een ernstige leverbloeding na stomp buiktrauma (bijvoorbeeld een fietsstuur). FNH heeft geen bloedingsneiging en dient niet (minimaal) invasief behandeld te worden, behalve in zeldzame gevallen waarbij forse grootte van de tumor tumorgrootte vanwege druk op andere de buikorganen zoals de maag of darmen leidt tot ongemak.

De meest klinisch relevante goedaardige levertumoren zijn HCA. Ongeveer 90% van alle HCA wordt gediagnosticeerd in vrouwen, veelal 20 tot 30 jaar oud. De belangrijkste risicofactor voor de ontwikkeling van HCA is (langdurige) blootstelling aan verhoogde geslachtshormonen. De bron van deze verhoogde geslachtshormonen kan zowel extern als intern zijn. Voorbeelden van externe bronnen zijn het gebruik van testosteron door body builders of het gebruik van oestrogeen in de orale anticonceptiepil (OAC) door vrouwen. Intern kan de oestrogeenproductie verhoogd zijn door de aanwezigheid van overmatig vetweefsel bij (ernstig) overgewicht. Zeer belangrijk voor de non-invasieve HCA-behandeling is dat HCA zich niet alleen vormen en groeien bij verhoogde

geslachtshormoonspiegels, maar ook kunnen krimpen en zelfs verdwijnen na verlaging van de geslachtshormoonspiegels. Een verlaging kan worden bereikt door het staken van de hormooninname of door gewichtsverlies (indien er sprake is van overgewicht). Indien een HCA-patiënt zwanger wordt, en hormoonspiegels dus stijgen, kan dit ook invloed hebben op de HCA-diameter. Een grote Nederlandse studie heeft aangetoond dat HCA <5 cm tijdens de zwangerschap ongevaarlijk zijn.

HCA kunnen twee complicaties veroorzaken: leverbloeding en ontaarding tot leverkanker. Beide complicaties zijn zeldzaam en komen nagenoeg alleen voor bij HCA >5 cm. Er zijn verschillende HCA-subtypen gekenmerkt door elk een onderscheidend klinisch profiel met specifieke genetische mutaties, risicofactoren voor vorming, kans op bloeding, kans op ontaarding tot kanker, en gevoeligheid voor geslachtshormonen. De gouden standaard voor het vaststellen van het HCA-subtype is analyse van weefsel (histopathologie) verkregen via (naald)biopsie. Van oudsher wordt dit gedaan met immunohistochemische kleuringen, alhoewel deze tegenwoordig ook worden aangevuld met moleculair tumoronderzoek. Het voordeel van moleculair onderzoek is een harde vaststelling van de aan- of afwezigheid van specifieke genetische mutaties, waar de kleuringen vals-negatieve resultaten kunnen opleveren. In recente jaren zijn er grote stappen gezet in de non-invasieve identificatie van HCA-subtypes op MRI met leverspecifiek contrast. Alhoewel zeldzaam, komen HCA ook voor bij mannelijke patiënten. Ongeveer 10% van alle HCA zijn beta-catenine gemuteerde HCA (b-HCA). B-HCA hebben de sterkste neiging van alle HCA-subtypes om kwaadaardig te ontaarden. B-HCA komen relatief vaker voor bij mannelijke patiënten, en daarnaast is mannelijk geslacht is een op zichzelf staande risicofactor voor kwaadaardige ontaarding van HCA – los van HCA-subtype.

Soms is het moeilijk om FNH en HCA te onderscheiden bij een MRI-onderzoek, zelfs als er leverspecifiek contrast wordt gebruikt. Het maken van een goed onderscheid is belangrijk: FNH en HCA worden sterk verschillend behandeld. Een FNH bij een mannelijke patiënt hoeft niet persé invasief behandeld te worden, OAC kan probleemloos worden gebruikt, invasieve behandeling dient alleen bij buikklachten te worden overwogen en is poliklinische follow-up (vervolgen) is niet nodig. Er zijn

verschillende invasieve behandelingen voor HCA. Kleine tumoren (<3 cm) kunnen worden weggebrand met een naald via de huid (geableerd). Indien er duidelijk voedende slagaders worden geobserveerd, kunnen deze worden afgesloten met een kunstmatig bloedpropje (embolisatie). Het kunstmatige bloedpropje wordt achtergelaten met een slangetje (katheter). De katheter wordt ingebracht via een kleine snee in de lies welke toegang geeft tot de liesslagader. Tot slot kan een deel van de lever worden weggesneden (resectie) via een kijkoperatie of via open buikchirurgie.

Om een gelijke behandeling te waarborgen worden klinische richtlijnen gebruikt, gebaseerd op wetenschappelijke literatuur. Er is momenteel één Europese richtlijn voor de behandeling van alle goedaardige levertumoren. Onderstaand is een selectie van de belangrijkste behandeladviezen voor goedaardige levertumoren.

Algemene diagnostiek en behandeling van goedaardige levertumoren

- Gebruik een MRI met leverspecifiek contrast voor de identificatie van het (sub) type levertumor
- Gebruik een multidisciplinair team met voldoende ervaring, bestaande uit: een maag-, darm, leverarts, leverradioloog, interventieradioloog, leverchirurg en leverpatholoog

FNH

- Diagnose van FNH is geen reden tot staken van OAC
- Overweeg alleen invasieve FNH-behandeling bij (ernstige) buikklachten, bij zowel mannelijke als vrouwelijke patiënten

HCA

- Maak bij een verdenking op HCA ten minste een MRI met leverspecifiek contrast, en eventueel een aanvullende leverbiopsie
- Mannelijke patiënten
- Alle bewezen HCA bij mannelijke patiënten dienen (minimaal) invasief behandeld te worden
- Vrouwelijke patiënten

1. Adviseer leefstijladviezen bij alle vrouwelijke patiënten met een vastgesteld HCA: staken met eventueel gebruik van OAC en gewichtsverlies bij overgewicht

2. Herhaal een MRI zes maanden na de leefstijladviezen
   2.1 Na zes maanden: indien de tumor <5 cm en stabiel of gekrompen in grootte → herhaal MRI na 1 jaar

Na 1 jaar: tumor stabiel of gekrompen → jaarlijkse follow-up

2.1.1 Na 1 jaar: tumor significante groei >20% → (minimaal) invasieve behandeling

2.2 Na zes maanden: indien tumor >5 cm of significante groei (>20%)→ (minimaal) invasieve behandeling

De huidige Europese richtlijn kenmerkt zich door specifieke en persoonlijke behandeladviezen, en poogt zo onder- en overbehandeling te voorkomen. De behandeling van HCA blijft echter complex vanwege: de verschillende HCA-subtypen, specifieke adviezen voor mannelijke en vrouwelijke patiënten, de goedaardige natuur met een kwaadaardig randje van HCA, de relatief jonge patiëntenpopulatie, het wisselende gedrag van HCA na leefstijladviezen en het gelijken van HCA en FNH op MRI. Daarnaast zijn er verschillende aspecten waar de huidige richtlijn geen of beperkt advies over geeft. Dit zijn onder andere: de veiligheid van OAC-staking voor HCA, HCA tijdens de zwangerschap, HCA ten gevolge van een stofwisselingsziekte en uitkomsten na HCA-resectie. In het huidige proefschrift is meer data verkregen over zowel de huidige aanbevelingen als de eerdergenoemde lacunes. Deze data kan helpen om behandeladviezen en informatie in de toekomstige richtlijnen verder te ontwikkelen, en zo de patiëntenzorg te verbeteren.

Samenvatting

Hoofdstuk 1 omvat een introductie tot goedaardige levertumoren en in het bijzonder HCA. Om een beter beeld te krijgen van de huidige internationale praktijk bestaat **Hoofdstuk 2** uit een beschrijvend literatuuronderzoek (review) van de huidige internationale richtlijnen voor goedaardige levertumoren. Er werden 3 richtlijnen afkomstig uit Brazilië, de Verenigde Staten en Europa gevonden en geanalyseerd. Meerdere verschillen werden geobserveerd tussen de aanbevelingen voor de behandeling van leverhemangioom, FNH en HCA. Deze waren voornamelijk: 1) indicaties voor biopsie in alle drie de tumoren, 2) adviezen voor pilgebruik in FNH en HCA, 3) aanbevelingen voor de follow-up van FNH en HCA, 4) missende aanbevelingen voor HCA bij mannelijke patiënten en 5) benadering van HCA-subtypering op MRI. Erkenning van de verschillende aanbevelingen kan helpen bij het internationaal gelijktrekken van de behandeling van goedaardige levertumoren, en zo de patiëntenzorg worden verbeterd. Daarnaast helpen de geobserveerde discussiepunten onderzoekers om de toekomstige onderzoeksagenda gericht op te stellen.

Alhoewel er één Europese richtlijn is, overkoepelend over zowel landen als medische specialismen, ontbreekt er momenteel data over de daadwerkelijke dagelijkse Europese klinische benadering van goedaardige levertumoren. **Hoofdstuk 3** onderzoekt deze dagelijkse praktijk middels een vragenlijstonderzoek. De vragenlijst werd verstuurd naar 295 Europese experts op het gebied van goedaardige levertumoren uit de maag-, darm- en leverkunde, chirurgie, buikradiologie en interventieradiologie, waarvan er 95 antwoordden. De vragenlijst bestond uit twee delen. Het eerste deel richtte zich op de dagelijkse gebruiken en mogelijkheden met betrekking tot diagnostiek en behandeling. Het tweede deel beschreef acht fictieve patiënten in drie categorieën: 1) FNH, 2) HCA tijdens de zwangerschap en 3) HCA >5 cm. Deelnemende experts (n=95) werden verzocht hun beleid ten aanzien van aanvullende diagnostiek, behandeling en follow-up te beschrijven. De meest opvallende praktijkvariatie werd geobserveerd op adviezen rondom OAC en follow-up van FNH-patiënten en behandeling van HCA-patiënten vóór en tijdens zwangerschap. Daarnaast weken respondenten af van de richtlijnadviezen bij vrouwelijke HCA patiënten. De voorkeur werd gegeven aan langer afwachten bij

een krimpend maar nog te groot (>5 cm) HCA na 6 maanden in plaats van de dan geadviseerde invasieve behandeling. De in dit hoofdstuk beschreven gegevens bieden handvatten voor herziening van de huidige richtlijnen. We stelden daarnaast voor om vergaderingen te organiseren om nieuwe onderzoeksgebieden te prioriteren en de beschreven discussiepunten gezamenlijk te verhelpen.

HCA vóór of tijdens de zwangerschap vormen een complexe klinische situatie. Recente data toonde aan dat patiënten met HCA <5 cm veilig zwanger kunnen worden. Data over HCA >5 cm was tot nog toe anekdotisch. **Hoofdstuk 4** beschrijft een gecombineerde methode: een observationele studie met 11 geanalyseerde patiënten en een literatuuronderzoek met 99 zwangerschappen van 90 patiënten uit 33 publicaties. Stabiele tumoren werden gezien bij 50% van de patiënten, 15% toonde regressie (krimp), en 31% groei. Vijftien HCA-veroorzaakte bloedingen werden geobserveerd in HCA 6,5-17 cm, waarvan 8 tijdens de zwangerschap, 2 tijdens de bevalling en 5 tijdens het kraambed. Het kraambed (postpartum periode) is momenteel nog niet aangemerkt als potentieel riskante periode, maar verdient deze erkenning. De studie concludeert dat er indicaties zijn dat HCA <10 cm mogelijk nauw gevolgd kunnen worden en tumoren alleen bij groei behandeld dienen te worden. Wij suggereerden om bevestigende data te verkrijgen middels een grote Europese dossierstudie naar HCA >5 cm tijdens en na de zwangerschap.

Oestrogeenverlagende leefstijladviezen (stoppen met OAC en gewichtsverlies bij overgewicht) vormen de hoeksteen van HCA-behandeling bij vrouwen. **Hoofdstuk 5** beschrijft een dossierstudie naar de veiligheid en het tumorgedrag van HCA na het staken van OAC. Achtenzeventig patiënten met HCA 1-16,7 cm werden geanalyseerd. Patiënten met overgewicht (body mass index; BMI >30 kg/m^2) hadden significant grotere HCA in vergelijking met de patiënten met BMI <30 kg/m^2 (respectievelijk 5,8 cm en 3,7 cm). Na mediaan 1,3 jaar na OAC-staking toonden 5% van HCA volledige regressie, 56% stabiliteit en 1,3% groei. De subgroep van 39 HCA >5 cm (mediaan 8,6 cm) kromp na mediaan 1 jaar tot 5,5 cm. Veertien van deze HCA (36%) krompen tot <5 cm diameter na mediaan 1,3 jaar. Beïnvloedende factoren tot significante (>30%) krimp werden multivariaat (meervoudig) onderzocht middels een Cox-proportional-

hazardsmodel. HCA-diameter 5-10 cm met hazard ratio (HR) 2,4 en HCA >10 cm met HR 8,4 bleken voorspellend. De studie observeerde 98% van de HCA stabiel of krimpend, zonder bloedingscomplicaties. Deze bevindingen benadrukken de veiligheid en het belang van het afwachten van de reactie van HCA na het stoppen van OAC, ook voorbij de momenteel geadviseerde periode van 6 maanden, zeker in laagrisico HCA**.**

De Europese richtlijn adviseert om HCA <5 cm bij vrouwen niet invasief te behandelen, vanwege het zeldzame voorkomen van complicaties bij die grootte. Toch vinden deze operaties plaats, bijvoorbeeld omdat (een voorstadium van) leverkanker niet uitgesloten kan worden. Data over de reden (indicatie) tot de resectie ontbreekt tot nog toe. **Hoofdstuk 6** onderzoekt de indicaties voor resectie van (verdachte) HCA en vergelijkt deze tussen patiënten met een kleine tumor (HCA <5 cm) en grote tumor (HCA >5 cm) in een nationale dossierstudie. Alle Nederlandse patiënten die een leveroperatie ondergingen vanwege (verdenking op) HCA tussen 2014 en 2019 werden geanalyseerd, wat resulteerde in inclusie en analyse van 222 patiënten. Vierenveertig (20%) patiënten onderging chirurgie vanwege een kleine tumor (<5 cm). De patiëntgroep met een kleine tumor bevatte 21% mannen, in vergelijking met 5% mannen in de groep geopereerd vanwege een grote tumor. Indicaties voor chirurgie verschilden tussen patiënten met een kleine en grote tumor. Patiënten met een grote tumor werden geopereerd vanwege tumorgrootte (52%), verdenking op (een voorstadium van) kanker (28%), en (eerdere) tumorbloeding (5,1%). De preoperatieve verdenking op HCA werd vaker gewijzigd naar FNH na het definitieve tumorweefselonderzoek bij de patiënten met een kleine tumor. Dit kan een aanwijzing zijn dat patiënten met kleine tumoren niet altijd optimale preoperatieve diagnostiek hebben gekregen, waardoor misdiagnoses zijn ontstaan.

Naast de ontwikkeling van HCA ten gevolge van verhoogde hormoonspiegels, kunnen HCA ook ontstaan bij patiënten met een stofwisselingsziekte. In totale zin vormt deze subgroep van HCA vormen slechts een klein deel van alle HCA. Toch zijn de stofwisselings-HCA klinisch relevant, omdat ze zeer vaak voorkomen bij de patiënten die door deze stofwisselingsziekte getroffen zijn. Een van deze ziekten is glycogeenstapelingsziekte (GSD). GSD kan gezien worden als een soort omgekeerde suikerziekte (diabetes mellitus). Bij diabetes mellitus is de insulineproductie of

-gevoeligheid verstoord, waardoor, als er geen kunstmatige insuline wordt toegediend, de bloedsuiker te hoog kan worden na een maaltijd. Opgenomen glucose (suiker) wordt normaliter compact opgeslagen als glycogeen in de lever of de skeletspieren. Indien de suikerspiegel te laag is, wordt het glycogeen weer afgebroken tot glucose, zodat het beschikbaar is voor de stofwisseling. Dit laatste proces is verstoord bij GSD-patiënten door dysfunctie van het glucose-6-fosfatase (G6P) enzym waardoor éénrichtingsverkeer plaatsvindt en de het glycogeen zich stapelt in de lever en spieren. Als een GSD-patiënt stopt met het eten van suikers (of koolhydraten) dan gaat hij dood ten gevolge van afwezigheid van suiker. GSD-patiënten drinken overdag "complexe" koolhydraten, vaak gekookt maïszetmeel (Maizena). 's Nachts druppelt een katheter in de neus de Maizena in de slokdarm. Bij een te lage bloedglucosespiegel probeert het lichaam energie uit een alternatieve bron te halen, namelijk vetzuren. Hierdoor is de vetzuurspiegel (triglyceride; TG) in het bloed een omgekeerde afspiegeling van de bloedglucosespiegel. De snelheid waarmee TG schommelt in het bloed is lager dan glucose; bloedglucose is hoog na het eten van een broodje en laag na vasten. TG kan hierdoor klinisch goed gebruikt worden om de effectiviteit en therapietrouw aan de gekozen dieetbehandeling over een langere periode te meten. Er zijn verschillende subtypes GSD, en binnen één GSD-subtype ook een verscheidenheid aan mate waarmee de G6P-enzymfunctie (en daarmee glycogeenafbraak) verstoord is. Het GSD subtype Ia (ziekte van Von Gierke) is het meest geassocieerd met HCA-vorming.

Ondanks dat er verschillende studies zijn verschenen over HCA bij GSDIa patiënten, was er zeer beperkte data beschikbaar over de risicofactoren voor de HCA-vorming. **Hoofdstuk 7** onderzoekt de invloed van het type mutatie van de glucose-6-fosfatase katalytische subunit (*G6PC1*), geslacht en de waarde van de TG-concentratie in het bloed tijdens de jeugd voor het ontwikkelen van HCA. *G6PC1* mutaties werden gecategoriseerd als ernstig/niet-ernstig aan de hand van hun invloed op de G6P-functie. Jeugd-TG werd gedefinieerd als de mediane TG <12 jaar oud en patiënten werden gecategoriseerd als boven of onder 5,65 mmol/L (500 mg/dL). Er werden 53 patiënten geanalyseerd, waarvan 23 vrouwen. Zesentwintig (49%) patiënten ontwikkelde een HCA tijdens een mediane follow-up van 32 jaar. De vrouwelijke GSDIa-patiënten

ontwikkelden vaker HCA, en ontwikkelden HCA op jongere leeftijd dan mannelijke GSDIa-patiënten. Er werd echter geen relatie gezien tussen ernstige en niet ernstige dan wel specifieke *G6PC1*-mutaties. Mediane jeugd-TG was 4,6 mmol/L. Patiënten met jeugd-TG >5,65 mmol/L ontwikkelden 15 jaar eerder HCA, ten opzichte van patiënten met TG <5,65 mmol/L (18 jaar vs. 33 jaar). Vrouwelijke patiënten hadden hogere jeugd TG dan mannelijke patiënten. Multivariate analyse middels Cox-regressie met in het model geslacht, jeugd-TG en een interactievariabel geslacht-jeugd TG. Dit model jeugd-TG >5,65 als onafhankelijke risicofactor voor HCA-ontwikkeling (HR 6,0). **Hoofdstuk 7** toont dat latere HCA-ontwikkeling voorspeld kan worden middels TG-concentraties tijdens de jeugd. Deze studie zal bijdragen aan verdere individualisering van de GSD-behandeling.

Er zijn verschillende grote studies verricht naar de uitkomsten na leverchirurgie. Deze onderzoeken zijn voornamelijk gedaan naar patiënten met leverkanker; een patiëntengroep die sterk verschilt van de veelal gezondere en jongere patiënten met goedaardige levertumoren. **Hoofdstuk 8** onderzoekt de uitkomsten van alle Nederlandse patiënten die geopereerd werden vanwege FNH, HCA of leverhemangioom tussen 2014 en 2019. Resultaten werden vergeleken tussen patiënten geopereerd via een kijkoperatie (laparoscopische lever resectie; LLR) of open leverresectie (OLR). Om de analyse zuiverder te maken werden vergelijkbare patiëntkoppels gemaakt qua onder andere leeftijd, geslacht en bijkomende ziekten (comorbiditeiten) via propensity score matching. In totaal werden 415 patiënten geanalyseerd, waarvan 230 (55%) LLR ondergingen. PSM resulteerde in 250 gekoppelde patiënten. Opnameduur was significant korter voor LLR dan OLR (4 dagen vs. 6 dagen). LLR resulteerde ook in minder complicaties binnen 30 dagen dan OLR (12% vs. 22%). Univariate (enkelvoudige) analyse toonde LLR (aangepaste odds ratio [aOR] 0,55, leeftijd >65 jaar (aOR 2,65), voorgeschiedenis van leverziekte (aOR 4,20) en uitgebreide leverresectie (>3 leversegmenten; aOR 1,94) geassocieerd met toegenomen complicaties na 30 dagen. Multivariate analyse toonde LLR geassocieerd met minder complicaties binnen 30 dagen. Sterfte en ernstige complicaties binnen 30 dagen waren vergelijkbaar tussen LLR en OLR. Deze studie beschrijft voor de eerste maal uitkomsten na chirurgie voor goedaardige levertumoren

in een grootschalig nationaal cohort. Wij concludeerden dat LLR is aanbevolen boven OLR op moment van chirurgische behandeling van goedaardige levertumoren, mits technisch (anatomisch) haalbaar. De resultaten kunnen arts en patiënten helpen om een afgewogen behandelbesluit te maken.

In de appendix, **Hoofdstuk 9**, wordt het studieprotocol beschreven van de BELIVER-studie. Dit is een landelijke studie waartoe alle volwassen patiënten met een klinisch relevante goedaardige levertumor zich kwalificeren. De BELIVER-studie onderzoekt de kwaliteit van leven via een visueel-analoge pijnschaal met daarnaast een nieuw ontwikkeld instrument voor patiëntgerapporteerde uitkomsten (PROMs). De PROMs zijn opgesteld middels groepsgesprekken met HCA- en FNH-patiënten. De vragenlijst wordt tweemaal per jaar verstuurd. Indien een operatie wordt gepland, volgt een vragenlijst 3, 6 en 12 maanden na de operatie. Inclusie van patiënten is open tot 2024, en de studie wordt beëindigd in 2025, zodat elke patiënt minimaal 12 maanden wordt gevolgd.

Discussie

De in dit proefschrift beschreven resultaten kunnen helpen bij het ontwikkelen van toekomstige richtlijnen voor de behandeling van goedaardige levertumoren.

De analyse van de internationale richtlijnen in **Hoofdstuk 2** legt meerdere belangrijke verschillen tussen aanbevelingen aangaande de 3 typen goedaardige levertumoren bloot. Ook werden er meerdere verschillen in de dagelijkse Europese praktijk die geobserveerd in het vragenlijstonderzoek in **Hoofdstuk 3**. Er blijkt een grotere onzekerheid ten aanzien van FNH te bestaan, ondanks wetenschappelijke consensus omtrent adviezen voor de veiligheid van het gebruik van OAC en de follow-up van (mannelijke) FNH-patiënten. Daarnaast leiden de beschreven gevallen met HCA tijdens de zwangerschap ook tot discussie. De data uit **Hoofdstuk 2** en **Hoofdstuk 3** kan in de toekomst gericht (in Delphi-vergaderingen) bediscussieerd en/of wetenschappelijk onderzocht worden om zo hiaten in de huidige kennis te dichten, en de aanbevelingen uit de richtlijnen gelijk te trekken.

Hoofdstuk 4 vat de beschikbare literatuur over HCA tijdens zwangerschap samen en brengt het kraambed als mogelijk gevaarlijke periode aan het licht. Mogelijkerwijs is het aanleiding tot een grotere Europese dossierstudie om meer data te verschaffen over HCA >5 en >10 cm tijdens en na de zwangerschap.

Hoofdstuk 5 geeft sterke ondersteuning voor de effectiviteit en veiligheid van de in de richtlijn aanbevolen leefstijladviezen. De enige beïnvloedende factor op significante HCA-regressie was HCA-diameter. Deze data bevestigt bevindingen uit andere studies om langer dan de aanbevolen 6 maanden af te wachten bij grote HCA alvorens te besluiten tot invasieve behandeling en zo onnodige ingrepen te voorkomen.

Het onderzoek naar de indicaties voor leverresectie in **Hoofdstuk 6** toont significant verschillende chirurgische indicaties tussen HCA >5 cm en <5 cm. Er zijn aanwijzingen dat in sommige gevallen te defensief is gehandeld, met suboptimale beeldvorming (geen MRI of MRI zonder leverspecifiek contrast). Nadere studies naar het diagnostisch proces moeten dit bevestigen. Daarnaast worden er meerdere patiënten geopereerd vanwege onzekerheid. Dit is een indicatie om toekomstig onderzoek te richten op de psychische gevolgen van de HCA-diagnose.

De analyse van HCA-ontwikkeling bij GSDIa-patiënten in **Hoofdstuk 7** bevat 3 belangrijke conclusies: 1) HCA-ontwikkeling is onafhankelijk van niet-ernstig/ernstige dan wel specifieke *G6PC1*-mutaties, 2) vrouwelijke patiënten tonen hogere jeugd-TG en ontwikkelen vaker en vroeger HCA en 3) een hoog jeugd-TG (>5,65 mmol/L) is een onafhankelijke voorspeller voor latere HCA-ontwikkeling. Deze bevindingen stellen artsen beter in staat om een patiënt-specifieke behandeling en follow-up af te stemmen.

De chirurgische uitkomsten na leverresectie voor goedaardige levertumoren in **Hoofdstuk 8** zijn goed. De resultaten uit de studie benadrukken de superioriteit van laparoscopie boven open buik chirurgie indien (anatomisch) haalbaar.

De BELIVER-studie, waarvan het studieprotocol in **Hoofdstuk 9** wordt beschreven, zal meer gegevens verstrekken over de psychische last van goedaardige levertumoren. Mocht er een significante psychische invloed blijken te bestaan, dan kan deze worden meegenomen in de overwegingen tot invasieve behandeling en follow-up.

Concluderend, het huidige proefschrift heeft de behandeling van goedaardige levertumoren voorbij de huidige richtlijn verkend en is relevant voor patiënten, medici en onderzoekers. De beschreven resultaten en interpretaties bevatten de informatie die kunnen helpen bij de verbetering van zorg voor deze patiëntengroep. Daarnaast zal de data aanleiding geven tot vervolgstudies om de huidige trend van individualisering in de behandeling van goedaardige levertumoren voort te zetten.

APPENDICES

Publications included in this thesis

Scoping review of clinical practice guidelines on the management of benign liver tumors. **M.P.D. Haring**, F.J.C. Cuperus, E.W. Duiker, R.J. de Haas, V.E. de Meijer. BMJ Open Gastroenterology. 2021;8(1):e000592.

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Curriculum Vitae

Martijn Haring (1992) completed pre-university education parallel to the Oxford International Baccalaureate English A2 at the Rijnlands Lyceum Oegstgeest. Thereafter, he commenced medicine in Groningen. During the bachelor's degree he was active in with various extracurricular activities: instructing at sailing school 't Stekelbaarsje (Elahuizen), chairman of the Groninger Studentenwaterskiclub 'The Bares', and chairman of the founding committee for the Vereniging Chirurgie voor Medisch Studenten Master Academy. After his bachelor's degree, he lived in Berlin attending the Goethe Institut (Zertifikat B2). He started research on benign liver tumors (BLT) with prof. dr. V.E. de Meijer during his first junior rotation in the University Medical Center Groningen (UMCG) in 2016, Together with prof. dr. V.E. de Meijer, dr. B.V. van Rosmalen, Martijn founded the Dutch Benign Liver Tumor Group (DBLTG). The DBLTG facilitates and coordinates nationwide BLT research. After endorsement of various medical specialty societies it was officially merged in the Dutch Society of Hepatology (NVH) as working group in 2022.

After obtaining his medical degree in 2019, Martijn started in the UMCG as a PhD candidate (promotores dr. K.P. de Jong & prof. dr. V.E. de Meijer, and copromotor dr. R.J. de Haas) on BLT. To fund his research, he was employed as a UMCG donor organ perfusionist.

After finishing his PhD thesis in 2022 he started working at the surgical department in the Isala Klinieken, Zwolle. In his spare time he enjoys photography, race cycling, sailing, various mountain sports, and reading.