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A nationwide assessment of hepatocellular adenoma resection: Indications and pathological discordance

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Abstract

Hepatocellular adenomas (HCAs) 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 HCAs < 50 mm compared to HCAs ≥ 50 mm. Changes in final postoperative diagnosis were assessed. We performed a retrospective study that included patients who underwent resection for (suspected) HCAs in the Netherlands from 2014 to 2019. Indication for resection was analyzed and stratified for small (<50 mm) and large (≥50 mm) tumors. Logistic regression analysis was performed on factors influencing change in tumor diagnosis. Out of 222 patients who underwent surgery, 44 (20%) patients had a tumor <50 mm. Median age was 46 (interquartile range [IQR], 33–56) years in patients with small tumors and 37 (IQR, 31–46) years in patients with large tumors ($p = 0.016$). Patients with small tumors were more frequently men (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 received operations because of tumor size >50 mm (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 <50 mm (adjusted odds ratio [aOR], 3.4; $p < 0.01$), male sex (aOR, 3.7; $p = 0.03$), and lack of hepatobiliary contrast-enhanced magnetic resonance imaging (CE-MRI) (aOR, 1.8; $p = 0.04$). Resection for small (suspected) HCAs was mainly indicated by suspicion of (pre)malignancy, whereas for large (suspected) HCAs, tumor size was the most prevalent indication. Male sex, tumor size < 50 mm, and lack of hepatobiliary CE-MRI were independent risk factors for post-operative change in tumor diagnosis.

INTRODUCTION

Hepatocellular adenomas (HCAs) are benign liver tumors that are frequently associated with chronic oral contraceptive pill use and obesity.[1,2] Complications are associated with tumor size ≥50 mm. Large HCAs (≥50 mm) 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 rare in HCAs < 50 mm.[3–6] According to current international guidelines, size >50 mm is an indication for resection.[7,8] The role of liver resection for the treatment of smaller HCAs, however, remains unclear.[7]

The key to noninvasive 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 6 months

before surgery in HCAs ≥ 50 mm in women, after which HCA response is evaluated.[7] Invasive treatment is recommended if HCA size remains ≥ 50 mm, whereas a noninvasive approach is advocated in HCAs < 50 mm.[7] The 50-mm diameter cutoff for invasive treatment is regardless of any significant response in terms of regression in size. International guidelines unequivocally recommend intervention for HCAs in all male patients because of the 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 HCAs are clear and concise in current European guidelines, which discourage resection of HCAs < 50 mm in women. However, up to one third of all resected benign liver tumors, including HCAs, are <50 mm. Data on indications for resection in this specific group remain scarce.[13–15] Evaluation of indications for resection of HCAs, and especially HCAs < 50 mm, 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) HCAs < 50 mm in comparison to larger HCAs (≥ 50 mm) in a nationwide cohort. We also analyzed changes in final postoperative diagnosis.

MATERIALS AND METHODS

A nationwide observational cohort study was performed in the Netherlands. Data were retrieved from the Dutch Hepato Biliary Audit, which is 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. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were adhered to in study design and manuscript preparation.[17] The Medical Ethical Committee of the University Medical Center Groningen (UMCG) 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 before 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) HCAs (i.e., patients with suspected HCA but later with a proven alternate diagnosis, for example, focal nodular hyperplasia [FNH] or malignancy, were also included). Inclusion period was defined as patients having an operation between January 1, 2014, and December 31, 2019, and registered in the mandatory audit before April 1, 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 HCAs as determined by the local (multidisciplinary tumor board) practitioner(s), stratified for small HCAs (largest tumor diameter < 50 mm) and large HCAs (largest tumor diameter ≥ 50 mm). Indications were compared between regional hospital versus tertiary referral hospitals. When multiple HCAs 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 for 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 HCAs and diameter of largest HCA before treatment as well as subtype of HCA. Treatment characteristics included surgical approach (i.e., open or minimally invasive approach), major (three or more 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 was 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 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 were 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 UMCG.[19,20]

RESULTS

Baseline characteristics

A total of 222 patients who underwent surgery for (suspected) HCAs were included, of whom 44 (20%) patients had small tumors (<50 mm) and 178 (80%) patients had large tumors (≥50 mm) (Figure S1). Patients with small tumors were older (46 years vs. 38 years, $p = 0.016$) and more frequently men (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 one tumor and 20% with two 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 five (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%; $p < 0.001$) before surgery.

Indications for surgery

Indications for resection differed between patients with small and large tumors ($p < 0.001$). In patients with small tumors <50 mm, 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%) (Table S1). The main indication for resection of large tumors ≥50 mm was tumor size (52%), followed by suspicion of (pre)malignancy (27%), histopathological features of beta-catenin-mutated HCAs (b-HCAs; 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 HCAs 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 receiving an operation due to male sex received an MRI, and no difference in MR contrast was observed ($p = 0.11$).

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 (Table S1). At final pathology, 10 of those were diagnosed as HCAs and one as FNH. Sixty-one out of 175 (35%) patients without preoperative biopsy were operated on because of suspected (pre)malignancy on MRI. Of those, 34 patients (56%) had undergone a preoperative CE-MRI with liver-specific contrast agent (7/20 [44%] patients with tumors <50 mm and 27/41 [66%] patients with tumors ≥50 mm [$p = 0.22$]).

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, comprising 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 workup, and in 14 patients (64%), a liver-specific contrast agent was administered. In the total cohort, use of hepatobiliary CE-MRI was similar for male and female patients ($p = 0.10$). In patients with tumors <50 mm,

TABLE 1 Baseline characteristics of patients with (suspected) HCA, stratified by tumor diameter

Characteristic	Tumor < 50 mm (n = 44)		Tumor ≥ 50 mm (n = 178)		p value[a]
Female sex	35	(80)	169	(95)	0.002
Age at surgery (years)	46	(33–56)	38	(31–46)	0.016
Body mass index (kg/m2)	27	(22–32)	28	(24–32)	0.68
Charlson Comorbidity Index					0.70
CCI 0/1	43	(98)	169	(95)	
CCI ≥ 2	1	(2)	9	(5)	
American Society of Anesthesiology					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	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					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	15	(34)	74	(42)	0.43

Note: Data show number (%). Continuous values are provided as median and interquartile range.
Abbreviations: ASA, American Society of Anesthesiology; CCI, Charlson Comorbidity Index; FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.
[a]$p < 0.05$ is significant.

hepatobiliary CE-MRI was used in the diagnostic workup of three men (33%) and in 19 women (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 < 50 mm, 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 HCCs, all in female patients with tumors ≥ 50 mm (Figure 1B). Indication for resection of two HCCs was because of tumor size ≥ 50 mm (with co-occurring tumor growth), and one HCC was resected because of suspicion of (pre)malignancy.

Analysis of significant changes in preoperative 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%) 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 CE-MRI compared to patients with hepatobiliary CE-MRI available ($p < 0.05$). No differences were seen between patients with or without 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 <50 mm (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, and use of hepatobiliary CE-MRI (Figure 3). All included variables proved independent risk factors for change in diagnosis: tumors <50 mm (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; $p = 0.48$).

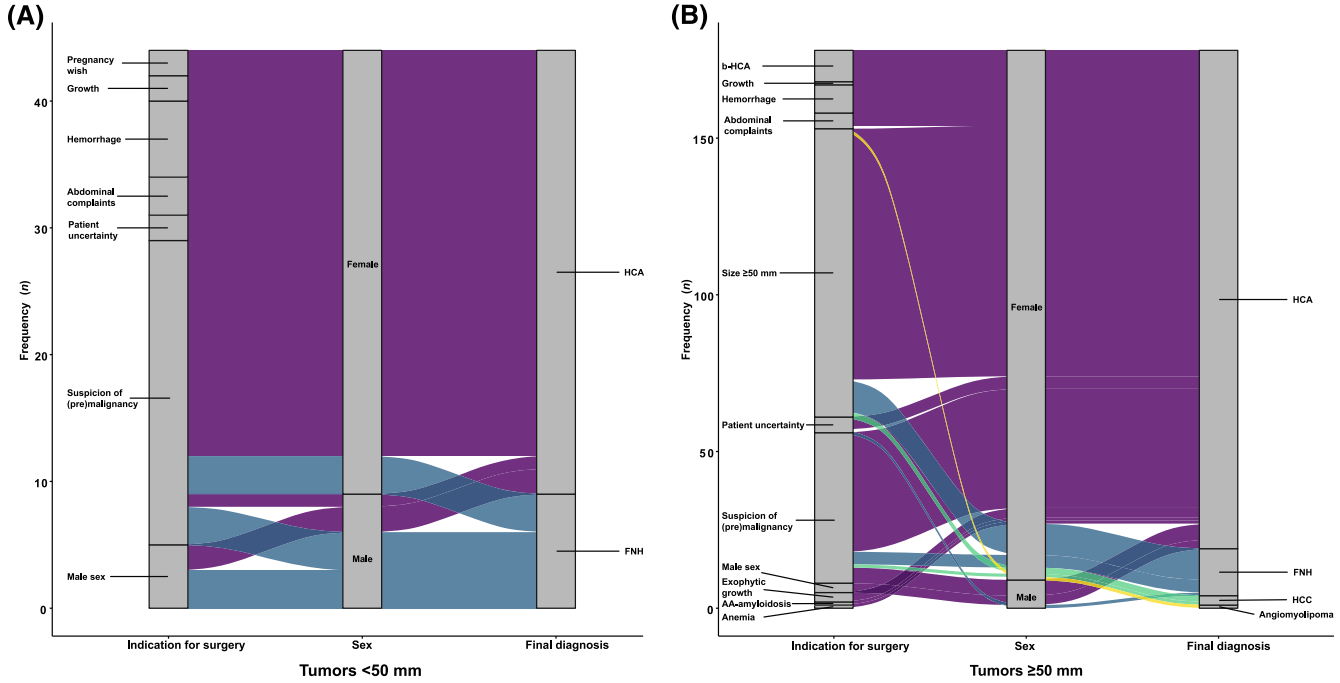

FIGURE 1 Alluvial plots depicting the individual distribution of indication for resection in patients with (A) HCAs < 50 mm or (B) HCAs ≥ 50 mm, grouped by sex and final diagnosis. AA-amyloidosis, amyloid A amyloidosis; b-HCA, beta-catenin mutated hepatocellular adenoma; FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma.

Surgical outcomes

No difference in frequency of surgery was observed throughout the years. During the inclusion period, there was a trend toward 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).

DISCUSSION

In this study, indications for resection of small (suspected) HCAs compared to large HCAs were investigated in a nationwide cohort. The study included 222 patients, of whom 44 patients (20%) underwent surgery for small tumors (< 50 mm). Half of patients with small tumors were operated on because of suspicion of (pre)malignancy, and the remaining patients mainly underwent surgery because of (previous) hemorrhage or male sex; 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 tradeoff 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

TABLE 2 Grouped indications for surgery and postoperative diagnosis of patients with hepatocellular adenoma, 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 ≥ 50 mm	22	(42)	70	(41)	
Atypia tumor	15	(29)	67	(39)	
Male sex	6	(12)	2	(1.2)	
Other	2	(3.8)	15	(8.8)	

**$p < 0.01$.

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

Characteristic	Tumors < 50 mm (n = 44)		Tumors ≥ 50 mm (n = 178)		*p* value[a]
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)	
HCA subtype				0.13	
I-HCA	18	(41)	99	(56)	
H-HCA	5	(11)	14	(7.9)	
b-HCA / b-IHCA	0	(−)	11	(6.2)	
U-HCA	2	(4.5)	8	(4.5)	
No subtype analyses performed	10	(23)	27	(15)	
Alternate tumor than HCA	9	(21)	19	(11)	
Postoperative change in tumor diagnosis	31	(71)	65	(37)	< 0.001
Operative characteristics and outcomes					
Year of surgery				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					< 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)	
30-day major morbidity[b]	1	(2)	3	(1.7)	1.00
30-day mortality	0	(−)	1	(0.6)	1.00

Note: Data show number (%); continuous values are provided as median and interquartile range.
Abbreviations: b-HCA, beta-catenin mutated HCA; b-IHCA, hybrid b-HCA; FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; H-HCA, hepatocyte nuclear factor 1A inactivated HCA; I-HCA, inflammatory HCA; U-HCA, unclassified HCA.
[a]$p < 0.05$ is significant.
bDefined as Clavien-Dindo score ≥ 3a.

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 on because of their sex in combination with (suspicion of) HCA diagnosis. Male sex is an independent risk factor for malignant transformation, and the premalignant b-HCAs occur more often in men, which may justify the indication for resection.[3,4,6] Male

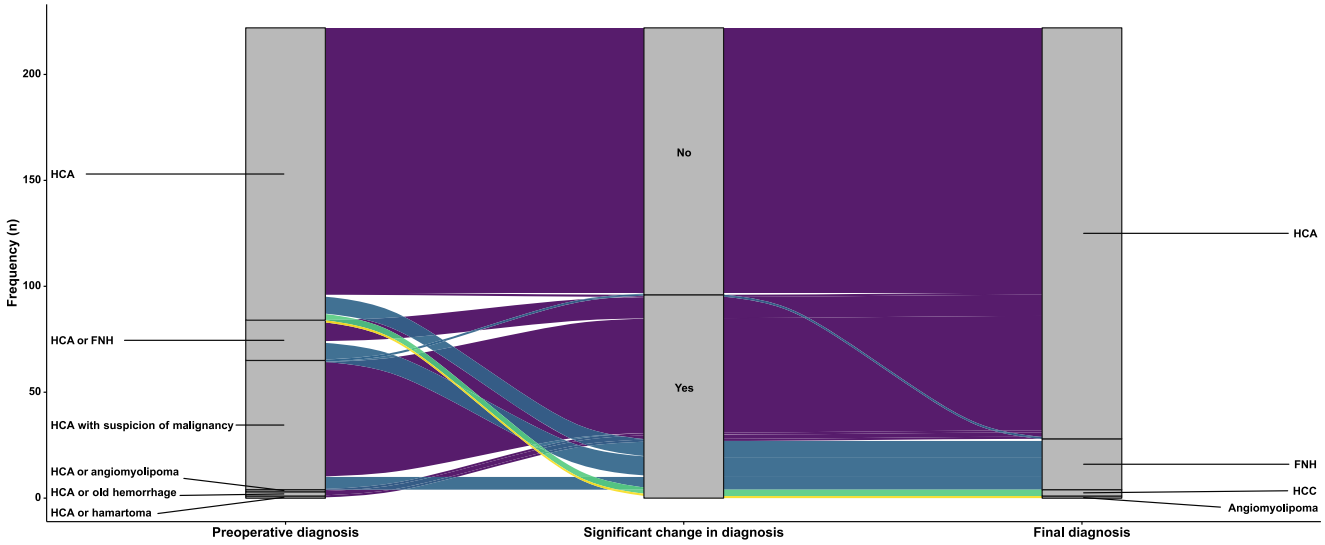

FIGURE 2 Alluvial plot depicting the change in tumor diagnosis before and after resection in the total cohort. FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma.

patients with HCAs due to metabolic disease, like hepatocyte nuclear factor 1A (*HNF1A*) 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 HCAs (H-HCAs), which can be preceded by diabetic symptoms, are observed in a (male) patient.[21] Because H-HCAs 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 but have been observed in 1.5% of resected HCCs, 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 five (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 <50 mm, is another important indication for invasive tumor treatment.[5,6] Tumor size was the deciding factor in half of patients with large tumors ≥50 mm. Risk of HCA bleeding is especially increased in exophytic HCAs.[5,25] In our series, exophytic growth was an indication for only three 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 HCAs, previous hemorrhage can be a relative indication for intervention. Before deciding on HCA treatment after bleeding, HCAs should first be observed for posthemorrhagic necrosis-induced regression, which might remove the need for tumor resection.[25] Finally, current European guidelines recommend HCA resection if size remains >50 mm 6 months after lifestyle alterations (i.e., ceasing oral contraceptive pill use and weight loss). However, 6 months might be a too short interval for large HCAs

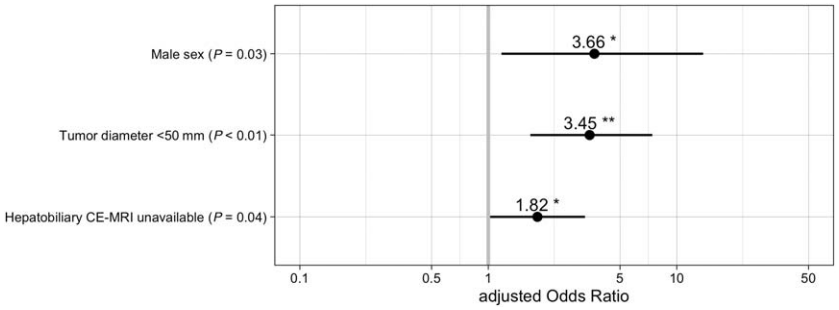

FIGURE 3 Forest plot of logistic regression analysis on risk factors for change in tumor diagnosis. CE-MRI, contrast enhanced magnetic resonance imaging. *$p < 0.05$, **$p < 0.01$.

to regress sufficiently, and data suggest 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 frequently (43%). Although amounting for only a small number of total cases, preoperative diagnosis was altered from HCA or (pre)malignancy to FNH in six out of the nine male patients with tumors <50 mm. A therapeutically defensive approach by resecting tumors not distinguishable between HCAs or FNH in male patients is conceivable; however, preoperative diagnostic workup should be adequate. Our findings that especially male sex, small tumors, and lack of hepatobiliary CE-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 CE-MRI in all patients with (suspected) HCAs, and to perform a percutaneous biopsy whenever there is doubt on tumor diagnosis after this imaging. Furthermore, all (suspected) HCAs in male patients should be confirmed through percutaneous liver biopsy, preferably through histopathological molecular analysis due to higher diagnostic sensitivity.[27] A suspicion of malignant transformation after hepatobiliary CE-MRI needs to be confirmed by liver biopsy, especially in tumors <50 mm and in male patients. In our opinion, potential complications and morbidity following unnecessary surgery outweigh the limited risk of biopsy-induced bleeding. Molecular analysis is more able to diagnose b-HCA (catenin beta 1 gene *CTNNB1*) 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 HCAs transforming into HCCs have been observed.[6,28]

Of note, percutaneous tumor ablation is minimally invasive, effective, and safe in treating hepatic malignancies and HCAs and could be performed in the same session directly after the histologic biopsy in tumors <50 mm.[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 do 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 to 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 HCAs (sh-HCAs) have been discovered in recent years, which represent 4% of HCAs.[6,31] Sh-HCAs 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 GLI family zinc finger 1 (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) HCAs, 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 HCAs was mainly indicated by suspicion of (pre)malignancy, whereas for large (suspected) HCAs, tumor size was the most prevalent indication. Male sex, tumor size <50 mm, 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.

AUTHOR CONTRIBUTIONS

Martijn P. D. Haring: manuscript and figure drafting, data collection, data analysis, study design. Arthur K. E. Elfrink: study design, data analysis, review of manuscript. Christiaan A. J. Oudmaijer, Paul C. M. Andel, Alicia Furumaya, Nenke de Jong, Colin J. J. M. Willems, Thijs Huits, Julie M. L. Sijmons, Joris I. Erdmann, Paul Gobardhan, Robbert J. de Haas, Tjarda van Heek, Hwai-Ding Lam, Wouter K. G. Leclercq, Mike S. L. Liem, Hendrik A. Marsman, Gijs A. Patijn, Türkan Terkivatan, Babs M. Zonderhuis, Izaak Quintus Molenaar, Wouter W. te Riele, Jeroen Hagendoorn, Alexander F. M. Schaapherder, Jan N. M. IJzermans, Carlijn I. Buis, Joost M. Klaase, Koert P. de Jong: study design, data collection, review of manuscript; Vincent E. de Meijer: study design, figure drafting, data analysis supervision, review of manuscript.

CONFLICT OF INTEREST

Nothing to report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

ETHICAL APPROVAL

Ethical approval was obtained from the Medical Ethical Committee in the UMCG (MEC 2020-004 & UMCG Research Registry 201900849), and confimed all other partipating centers. All data was collected and processed according to relevant privacy laws.

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