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Outcomes of liver resection in hepatocellular adenoma and focal nodular hyperplasia

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Abstract

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

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

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

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

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Introduction

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

The diagnostic workup of HCA and FNH is based mainly on cross-sectional imaging studies, of which magnetic resonance imaging (MRI) and computed tomography (CT) are commonly used to characterize lesions. The most sensitive method of

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differentiating HCA and FNH is MRI with hepatobiliary contrast (Primovist® or MultiHance®).[9–11] If imaging modalities are inconclusive, a liver biopsy may be necessary to achieve a final diagnosis.[12]

When a patient is considered for surgery, he or she should be well informed and should ideally be included in a shared decision-making process. Subjective symptoms and impact on daily life are just as important as the statistics of surgical risks. Given these dilemmas in clinical decision making, the present study was conducted to assess the outcomes of surgical intervention in terms of complications and the relief of symptoms in patients presenting with lesions compatible with HCA or FNH.

Materials and methods

Patient population and diagnostic workup

Between January 2008 and September 2011, all consecutive patients with suspected FNH or HCA of >2 cm based on imaging studies were enrolled in this prospective study (follow-up ended in September 2012). The local medical ethics committee approved the study protocol and written informed consent was obtained from all included patients.

Exclusion criteria were suspected (metastatic) malignant disease and the presence of risk factors for malignant liver lesions, including chronic hepatitis, cirrhosis, elevated α-fetoprotein (α-FP) or carcinoembryonic antigen (CEA) in blood serum, and pregnancy.

Standard of reference

Patients underwent MRI of the liver with Gd-EOB-DTPA (gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid; Primovist®) using a 1.5-T MRI scanner (Avanto; Siemens Healthcare AG, Munich, Germany). The dynamic contrast-enhanced T1-weighted volumetric interpolated breath-hold examination (VIBE) sequences were made at 30 s (arterial), 60 s (venous), 90 s and 180 s (late) after i.v. bolus injection of 0.025 mmol/kg gadoxetate disodium. Axial and coronal hepatobiliary phase images were made at 20 min after injection using single breath-hold sequences. The diagnosis of HCA was based on arterial enhancement, with possible washout during the portal phase, the presence of bleeding, fat or glycogen, and the absence of a central scar. The diagnosis of FNH was based on the presence of a central scar, arterial enhancement and the absence of signs of washout during the portal phase of imaging. Finally, the lesions were evaluated for signal intensity compared with surrounding liver tissue on the T1-weighted hepatobiliary series at 20 min after injection. An isointense or hyperintense signal status of the lesion was regarded as diagnostic for FNH, and hypointensity was considered diagnostic for HCA. Any MRI scans of lesions without these characteristics were regarded as inconclusive. The largest lesion in each patient was evaluated.

Until the MRI with Primovist® was proven sensitive for differentiating HCA from FNH,[11] a core biopsy of the lesion and normal surrounding liver parenchyma was standard in this study (using a 16-gauge needle, two lesional biopsies and one or two normal liver tissue samples). The morphological characteristics of HCA include hepatocellular proliferation without cytonuclear atypia, with solitary arteries and the absence of portal tracts. A well-developed reticulin framework is seen, without pseudoglandular growth patterns. In addition to standard liver stainings, including haematoxylin and eosin, collagen and CK7, additional immunohistochemical staining was performed to classify molecular subtypes of HCA.[13] Morphological characteristics of FNH include fibrotic strands, no nuclear atypia, and typical map-like glutamine synthetase (GS) expression on immunohistochemical staining. Halfway through 2011, the policy of standard biopsy was changed to one of biopsy only in the event of inconclusive MRI findings in lesions of >5 cm with or without symptoms.

Assessment of symptoms

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

Treatment

Selective transarterial embolization (TAE) represented the treatment of choice in patients presenting with haemodynamic instability caused by tumoral bleeding. Surgical treatment of HCA was undertaken if the lesion was >5 cm. Smaller lesions were only resected if the patient presented with persisting complaints which could not be explained by other underlying causes including gallbladder, gastric, bowel, kidney or gynaecological conditions. Depending on the patient's history and the physical examination and imaging findings already available, patients underwent additional endoscopy and/or colonoscopy, and abdominal imaging if the standard workup for the liver did not cover other plausible causes of discomfort. Focal nodular hyperplasia was only resected if symptoms were severe (VAS scores of ≥ 7 for >6 months, with the patient describing the complaint as 'unbearable' and 'restrictive' in daily life) and other possible causes of discomfort had been investigated and excluded.

Liver resections were classified as major, defined as the resection of three or more Couinaud's segments, or minor; defined as the resection of fewer than three liver segments, including enucleation and (sub)segmental resections. Surgery was performed using standard techniques. All major resections were performed in an open procedure, whereas minor resections were performed in open surgery or laparoscopically depending on the tumour's location.

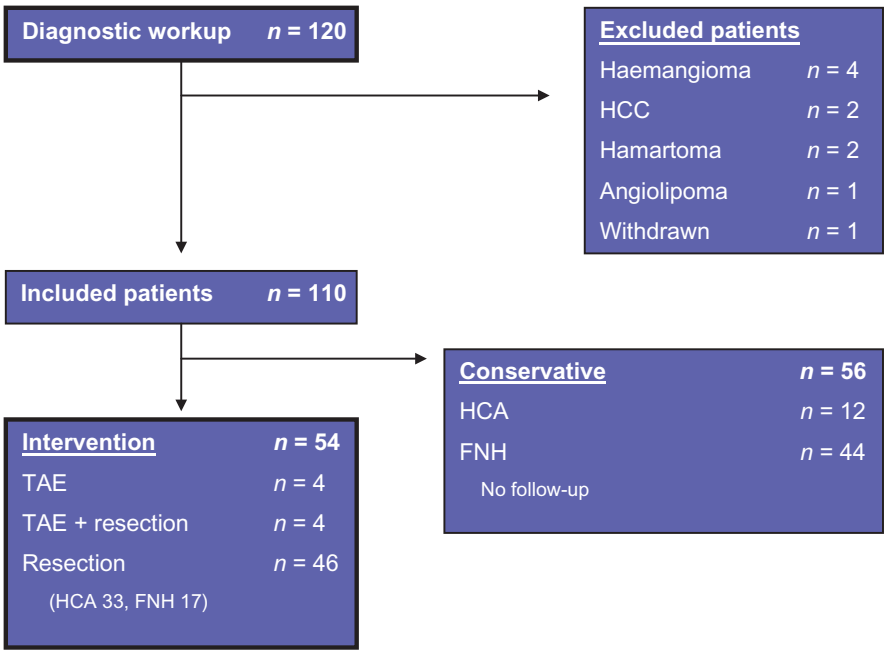

Figure 1 Flowchart of the study. HCC, hepatocellular carcinoma; TAE, transarterial embolization; HCA, hepatocellular adenoma; FNH, focal nodular hyperplasia

Tumour characteristics, type of liver resection, postoperative morbidity (Dindo–Clavien class[16]) and mortality were recorded.

Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics for Windows Version 20 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for the study population. The Mann–Whitney *U*-test for medians was used to analyse continuous data. Pearson's chi-squared, Fisher's exact and Spearman correlation tests were used for categorical data analyses, including gamma and Somers' D measures for ordinal by ordinal analyses.[17] Statistical tests were evaluated at the 5% level of significance.

Results

Patient population and standard of reference

A total of 120 patients with suspected HCA or FNH were initially enrolled. Nine patients (8%) were given other diagnoses after an initial diagnostic workup with MRI (haemangioma, $n = 4$, 3%; hepatocellular carcinoma, $n = 2$, 2%; hamartoma, $n = 2$, 2%; angiomyolipoma, $n = 1$, <1%). One patient with HCA (<1%) withdrew during the diagnostic workup (Fig. 1). The remaining 110 patients were included in the study (Table 1).

Diagnosis was based on histopathological examination in 44 (86%) of the 51 patients with HCA (34/44 resection specimens; 10/44 biopsies) and 39 (66%) of the 59 patients with FNH (16/39 resection specimens; 24/39 biopsies). Because of sampling errors, biopsy materials of four (8%) HCA and four (7%) FNH lesions were not sufficient for diagnosis and diagnosis was therefore based on MRI findings. The subclassification of HCA was undertaken in 10 biopsy and 34 resection specimens. Six samples appeared insufficient for additional immunohistochemical staining. Results in the remaining 38 lesion samples showed inflammatory HCA in 20 lesions, steatotic HCA in eight lesions, and unclassified HCA in 10 lesions. No lesions were identified as being of the β-catenin subtype. In three (6%) patients with HCA and 14 (24%) with FNH, no histopathology was obtained and diagnosis was based on MRI findings alone.

Imaging characteristics

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

Treatment

Results of treatment are summarized in Table 2. Conservative treatment was delivered in 61 (55%) patients, including 18 (35%)

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

Sex, male/female, *n*	4/106		
Age, years, median (range)	39 (19–72)		
Diagnosis	HCA	FNH	*P*-value
Patients, *n* (%)	51 (46%)	59 (54%)	
Size, cm, median (range)	6.5 (2.2–25.0)	5.5 (2.0–12.6)	0.828
Liver function test, *n* (%)			
Unknown	0	4	
Normal	14 (27%)	30 (51%)	
Abnormal	36 (72%)	26 (46%)	0.019
AST, U/l (normal < 40 U/l), median (range)	*n* = 4, 55 (50–110)	*n* = 1, 41 (NA)	0.400
ALT, U/l (normal < 45 U/l), median (range)	*n* = 7, 82 (50–128)	*n* = 3, 59 (48–85)	0.517
α-FP, U/l (normal < 120 U/l), median (range)	*n* = 11, 226 (129–466)	*n* = 5, 141 (122–258)	0.180
γ-GT, U/l (normal < 60 U/l), median (range)	*n* = 15, 101 (62–369)	*n* = 10, 148 (70–774)	0.015
Lesions, *n* (%)			
Solitary	14 (27%)	31 (53%)	0.011
2–5	21 (41%)	28 (47%)	0.507
6–9	3 (6%)	0	0.074
≥ 10	12 (24%)	0	<0.001
Undetected post-bleeding	1 (2%)	0	
Location, *n* (%)			
Left liver	22 (43%)	27 (46%)	0.782
Right liver	29 (57%)	32 (54%)	

HCA, hepatocellular adenoma; FNH, focal nodular hyperplasia; NA, not applicable; AST, aspartate aminotransferase; ALT, alanine transaminase; α-FP, α-fetoprotein; γ-GT, γ-glutamyl transferase.
Overall, liver function tests were more often abnormal in HCA in comparison with FNH; median γ-GT was significantly higher in patients with HCA than in patients with FNH. Lesions were often solitary in FNH, whereas HCA more often showed multiple lesions. Locations of the lesions throughout the liver were similar across both patient groups.

patients with HCA and 43 (73%) with FNH ($P < 0.001$). Eight (16%) patients with HCA presented at the emergency room with acute pain caused by bleeding of the lesion; these eight patients were admitted, stabilized and subjected to selective TAE. One of these eight patients underwent laparotomy within days of TAE because of abdominal compartment syndrome and four underwent elective resection of the lesion(s).

Resection was performed in 33 (65%) patients with HCA and in 16 (27%) patients with FNH. Significantly more resections were performed for HCA than for FNH ($P < 0.001$).

Figure 2 shows preoperative MRI, an intraoperative image and postoperative MRI in a patient with HCA. Figure 3 shows preoperative MRI and intraoperative images in a patient with FNH.

Minor laparoscopic resection was performed in five (15%) of the 33 HCA patients and in five (31%) of the 16 FNH patients submitted to resection. Minor open resection was performed in 19 (58%) of the 33 HCA patients and in seven (44%) of the 16 FNH patients. Major resection was performed in nine (27%) of the 33 HCA patients and in four (25%) of the 16 FNH patients. Postoperative length of stay (LoS) differed according to the type of surgery performed. Significant differences in LoS were found between patients undergoing laparoscopic and open surgery for HCA ($P = 0.013$), laparoscopic and minor open resection for HCA ($P = 0.034$), laparoscopic and open resection for FNH ($P = 0.05$), and laparoscopic and minor open resection for FNH ($P = 0.003$). However, no differences in postoperative LoS were seen between patients undergoing minor open and major open resection for either HCA or FNH ($P = 0.740$ and $P = 0.263$, respectively) (Table 2).

Laparoscopic procedures took less time than open surgeries (HCA: $P = 0.005$; FNH: $P = 0.005$). In HCA patients, open minor resections took less time than open major resections ($P < 0.001$).

Complications after surgery occurred in both groups and affected 11 of the 33 patients with HCA and seven of the 16 patients with FNH ($P = 0.344$). Grade I and II complications were most common and were seen in 14 of the 18 patients with complications.

Symptoms

In total, 34 of the 49 patients who underwent resection reported abdominal complaints prior to surgery. Symptoms were relieved in 30 of these 34 patients after surgery (Table 3). Symptoms are summarized in Tables 3 and 4.

Table 2 Treatment of hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH). Overall, 65% of patients with HCA and 27% of patients with FNH underwent resection, with surgical time[a] and postoperative length of stay[b] in the laparoscopic patient group significantly lower than in the open procedures group

Hepatocellular adenoma (*n* = 51)					
Conservative treatment, *n* (%)	18 (35%)				
Size, cm, median (range)	5.4 (2–10)				
Transarterial embolization, *n*	9				
Emergency care (bleeding), *n* (%)	6 (12%)				
Preventive care, *n* (%)	3 (6%)				
	Overall	**Laparoscopic**	**Open minor**	**Open major**	***P*-value**
Resection					
Patients, *n* (%)	33 (65%)	5	19	9	
Size, cm, median (range)	7 (3–25)	8.4 (6–11)	7.4 (3–13)	7 (6–25)	
ASA classification, *n*					
ASA 1	17	3	9	5	
ASA 2	15	2	9	4	
ASA 3	1	0	1	0	
Surgical time, min, median (range)	175 (58–406)	100[a] (69–144)	170 (58–231)	226 (200–406)	0.005[a]
Postoperative LoS, days, median (range)	7 (2–13)	5[b] (2–7)	7 (3–13)	7 (5–11)	0.013[b]
Complications, *n*					
None	22	2	14	6	
Grade I or II	10	3	5	2	
Grade III	1	0	0	1	
Focal nodular hyperplasia (*n* = 59)					
Conservative treatment, *n* (%)	43 (73%)				
Size, cm, median (range)	6 (2–11)				
	Overall	**Laparoscopic**	**Open minor**	**Open major**	***P*-value**
Resection					
Patients, *n* (%)	16 (27%)	5	7	4	
Size, cm, median (range)	6.2 (3–126)	4 (3–7)	5.8 (4–12)	8.6 (7–13)	
ASA classification, *n*					
ASA 1	9	3	3	3	
ASA 2	7	2	4	1	
ASA 3	0	0	0	0	
Surgical time, min, median (range)	144 (62–267)	94[a] (62–107)	161 (58–231)	202 (100–267)	0.005[a]
Postoperative LoS, days, median (range)	6 (2–22)	4[b] (2–5)	7 (5–9)	7 (6–22)	0.05[b]
Complications, *n*					
None	9	5	2	2	
Grade I or II	4	0	3	1	
Grade III or IV	3	0	2	1	

ASA, American Society of Anesthesiologists physical status classification system; LoS, length of stay.

The pain questionnaire was completed by 48 (94%) of the 51 patients with HCA. Pain categories present in at least one third of the patients with HCA and FNH are shown in Table 4. Specific to HCA rather than to FNH was 'drilling' ($P = 0.045$). Specific pain categories reported by the eight patients who submitted to emergency TAE but not by HCA patients who did not undergo emergency TAE included 'shooting' ($P = 0.044$), 'lacerating' ($P = 0.032$), 'crushing' ($P = 0.034$), 'splitting ($P = 0.001$) and 'wrenching' ($P = 0.023$) pain. The NWC was higher in the emergency TAE patient group than in the entire HCA patient group (Sensory: $P = 0.009$; Affective: $P = 0.026$; Evaluation: $P = 0.005$; Total: $P = 0.011$), as was the PRI (Sensory: $P = 0.001$; Affective: $P = 0.036$; Evaluation: $P = 0.033$; Total: $P = 0.015$). No differences in the NWC and PRI were found between patients with HCA or

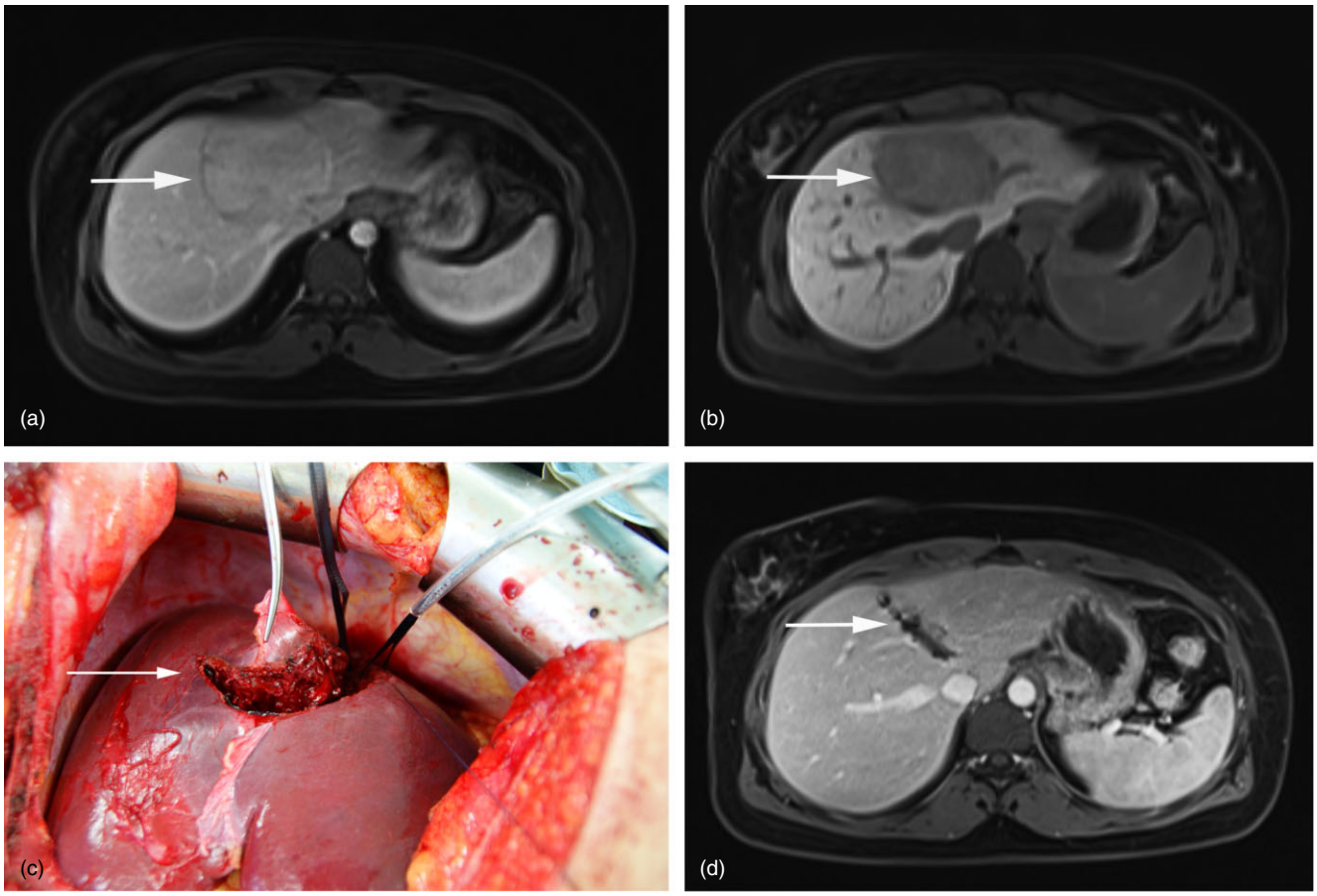

Figure 2 Imaging of hepatocellular adenoma (HCA). (a) Transverse magnetic resonance imaging (MRI) in the arterial phase with Primovist® shows a hyperintense lesion (arrow) in the centre of the liver. (b) In the hepatobiliary phase of scanning no uptake of contrast is seen within the lesion (arrow), which is consistent with HCA. (c) At laparotomy, the lesion is enucleated to minimize the loss of healthy liver parenchyma (arrow). (d) A few months after surgery, MRI shows a hypointense area where the lesion used to be, consistent with postoperative changes

FNH when corrected for patients who underwent emergency TAE ($P = 0.775$).

Discussion

This prospective study of outcomes of treatment of HCA and FNH shows that resection of the lesion(s) is safe and results in the relief of complaints in the majority of symptomatic patients with HCA or FNH. No mortality occurred and most postoperative complications were minor according to the Clavien–Dindo classification (Grade I or II). These findings are in accordance with a previous publication from the present authors' institution, showing that liver resection for benign hepatobiliary lesions was not associated with mortality and resulted in less morbidity than it did in patients undergoing resection for malignancies.[18]

Because HCA and FNH are benign tumours, limited resections usually suffice to remove all tumour tissue. Most of these tumours are amenable to parenchyma-sparing techniques. For example, lesions located in segment I allow the isolated resection of segment I, as was performed in three patients in the present series.[19] Of note are the blood transfusions required for minor resections in this series (two patients). Both HCA and FNH are hypervascular tumours and thus, in dissection, many blood vessels that traverse the interface between tumour and surrounding liver parenchyma are encountered. Enucleation of the tumour, therefore, may result in considerable blood loss. In the authors' experience, the use of the Cavitron® Ultrasonic Surgical Aspirator (CUSA®), in combination with a Pringle manoeuvre, enables the surgeon to follow the plane between the tumour and adjacent parenchyma and to manage the blood vessels selectively. In addition, non-anatomical resections may result in longer dissection times and larger wound surfaces, both of which contribute to greater blood loss during the procedure.

Although both HCA and FNH are benign hepatic lesions, associated findings are quite different, as this study shows. Patients with HCA more often had elevated serum liver function tests

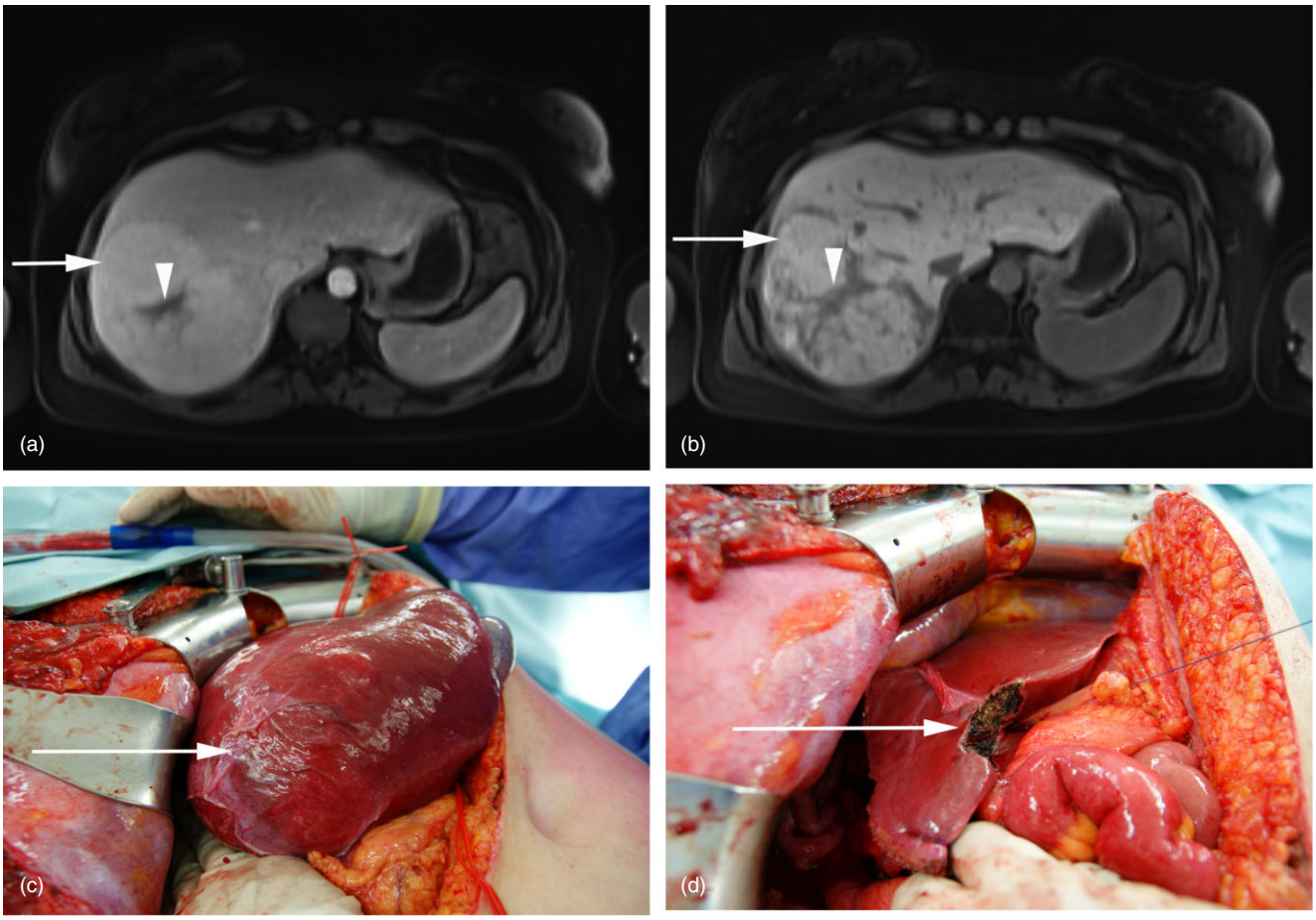

Figure 3 Imaging of focal nodular hyperplasia (FNH). (a) Transverse magnetic resonance imaging (MRI) in the arterial phase with Primovist® shows a large, slightly hyperintense lesion (arrow), with a hypodense centre, in the right liver, consistent with a central scar (arrowhead). (b) The central scar is more prominent in the hepatobiliary phase of scanning and the lesion is isointense in comparison with the surrounding liver parenchyma, which is consistent with FNH. (c) At laparotomy, the lesion protrudes from the liver and (d) can be removed with minimal damage to the liver parenchyma

(72%), hepatic steatosis (57%) and multiple lesions. Eight of the patients with HCA presented at the emergency room with acute pain caused by the bleeding of the lesion, whereas none of the patients with FNH needed emergency care. Significantly more resections were performed in HCA than in FNH patients. Without intervention, patients with HCA showed symptom relief over time. The differences between the groups may in part be explained by the occurrence of bleeding in HCA: some bleeding in HCA will need emergency intervention, and part of the discomfort caused by bleeding HCA will subside over time as the haematoma is absorbed.

This study showed not only differences between the types of hepatic lesion, but also similarities. Resection of HCA and FNH resulted in the relief of symptoms in both groups. These results are in line with those reported by Perrakis *et al.*, who noted relief in 95% of symptomatic patients with HCA.[3] Patients with lesions in the left lateral segments that give rise to abdominal complaints and additional gastric complaints benefit particularly from surgery, which can achieve complete symptom relief. Gastric complaints could not be explained by any causes other than the lesion in the left liver. However, in the present study, size was not correlated with symptoms. This probably reflects some degree of selection bias as patients with abdominal complaints will seek medical attention and those without will present only if the lesion is found incidentally. The high rate of resections for FNH is also explained by this selection bias as patients with severe complaints will seek medical assistance and will be more persistent in their wish for (even invasive) treatment. Complications in FNH are rare and are cited only in case reports.[20] Assessing the severity of symptoms and whether these originate from the detected liver lesion remains difficult. Abdominal pain or discomfort can have a number of other causes, which should be ruled out before surgery is planned.

When feasible, a laparoscopic resection is preferred over an open procedure, especially for lesions in the left or anterior liver

Table 3 Visual analogue scale (VAS), symptoms and presentation

Presentation	Hepatocellular adenoma (*n* = 51)			Focal nodular hyperplasia (*n* = 59)			
	Patients, *n* (%)	VAS score, median (range)	*P*-value	Patients, *n* (%)		VAS score, median (range)	*P*-value
Incidental finding	20 (39%)			27 (46%)			
Symptomatic	31 (61%)	7 (2–10)		32 (54%)		6 (1–10)	
Gastric complaints	6 (12%)			11 (19%)			
Left liver	5/22		0.044	10/28	0.004	6 (0–9)	0.008
Right liver	1/29			2/31		0 (0–9)	
Treatment							
TAE emergency care	8	8 (5–10)	0.005	NA			
TAE preventive care	2						
No TAE	41	1 (0–10)		NA			
No resection	18 (35%)			43 (73%)			
Baseline		0 (0–10)	0.013			0 (0–8)	<0.001
Follow-up		0 (0–7)				0 (0–8)	
Resection	33 (65%)			16 (27%)			
Baseline		7 (0–10)	0.008			6 (0–10)	0.008
Follow-up		0 (0–8)				0 (0–7)	

TAE, transarterial embolization; NA, not applicable.

segments. It is well documented that the postoperative LoS is shorter after laparoscopic surgery and, particularly in this young and mainly female group of patients, the cosmetic result plays an important role.[21] However, the feasibility of a laparoscopic approach should not influence perceptions of indications for resection.

Few treatment options other than surgical intervention have been proposed. Percutaneous radiofrequency ablation (RFA) has been performed for HCA and FNH with good results and cost-efficiency ratios.[22,23] However, the procedure is limited by the location and size of the tumour. It is possible that residual tumour tissue is less problematic in a benign tumour. In the treatment of lesions of < 3 cm, RFA is a good treatment option and, depending on the location of the lesion, may even be selected as the treatment of choice. Further research should determine the longterm outcomes and limitations of RFA in the ablation of HCA and FNH.

At the present authors' institution, TAE is considered the first-line treatment modality when a patient presents with massive bleeding and rupture of a hepatic tumour, including HCA.[24,25] Through the close collaboration of a skilled interventional radiologist and surgeon, laparotomy can be avoided in these emergencies. The technique can also be used as a minimally invasive, preventive intervention that hypothetically decreases the risk for future bleeding; it was applied in this study in an HCA patient who was a Jehovah's Witness. As yet, no data are available on tumour behaviour after TAE, including the risk for malignant transformation of the remaining adenomatous tissue.

Based on the findings of the present study and the available literature, the present authors propose the following approach should be taken in patients with HCA and FNH. Diagnostic workup should include hepatobiliary contrast MRI.[11] In patients diagnosed with FNH, resection is advised only if abdominal complaints are severe and other causes of symptoms have been excluded. All patients with HCA should discontinue oral contraceptives. Until risk analyses during pregnancy have been properly studied, all patients should undergo close follow-up during pregnancy.[26] Hepatocellular adenoma in male patients and of >5 cm in female patients should be resected.[5] Liver adenomatosis is an arbitrary diagnosis when more than nine HCA lesions (whatever their size) are found, but in the present authors' practice, it is not an indication for liver transplantation. Patients are treated according to the sizes of lesions and the presence of bleeding and symptoms, like any other patient with HCA. In addition, HCA lesions of < 5 cm in size, and FNH lesions, if severely symptomatic, can be considered for resection after other possible causes of abdominal complaints have been evaluated.

Future studies should determine whether different subtypes of HCA carry different profiles of risk for bleeding, recurrence (however small the risk) and malignant transformation. Subtype classification, however, requires the obtaining of biopsy material of the lesion, which is subject to sampling errors. Improvements in MRI techniques may play a role in the non-invasive assessment of these subtypes and facilitate the more accurate selection of patients who will benefit from surgery.

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

Table 4 Pain categories and index[a14,15,27]

Common categories (≥ 33% of patients)		Hepatocellular adenoma (*n* = 48)		Focal nodular hyperplasia (*n* = 57)		
		NWC	PRI	NWC	PRI	*P*-value
1	*Flickering, flashing, shooting*	12	25	10	21	0.754
	TAE (*n* = 8): ***shooting***	**4**	**9**			**0.044**
3	*Pricking, boring,* ***drilling***	**23**	**51**	22	42	**0.045**
4	*Sharp, cutting, lacerating*	20	34	20	36	0.886
	TAE (*n* = 8): ***lacerating***	**6**	**10**			**0.032**
5	*Pinching, pressing, crushing*	24	38	26	39	0.650
	TAE (*n* = 8): ***crushing***	**5**	**9**			**0.034**
6	*Tugging, pulling, splitting*	13	20	12	20	0.086
	TAE (*n* = 8): ***splitting***	**5**	**8**			**0.001**
10	*Tight, squeezing, wrenching*	19	48	19	51	0.791
	TAE (*n* = 8): ***wrenching***	**5**	**11**			**0.023**
12	*Dull, gnawing, persisting*	22	39	28	46	0.746
	Total sensory 1–7, median (range)	3 (0–12)	5 (0–33)	2 (0–12)	2 (0–30)	**NWC,** 0.781 **PRI,** 0.821
	TAE (*n* = 8) total sensory, median (range)	**7** (6–10)	**15** (8–22)			**NWC, 0.009 PRI, 0.001**
13	*Tiring, arduous, exhausting*	26	48	29	47	0.897
14	*Cranky, disconsolating, depressing*	13	28	14	27	0.668
15	*Tense, suffocating, sickening*	19	32	21	36	0.370
16	*Fearful, frightful, terrifying*	19	34	20	36	0.066
	Total affective 13–16, median (range)	1 (0–5)	2 (0–15)	1 (0–5)	1 (0–15)	**NWC,** 0.486 **PRI,** 0.113
	TAE (*n* = 8) total affective, median (range)	**4** (1–5)	**5** (1–12)			**NWC, 0.026 PRI, 0.036**
18	*Light, moderate, bad, severe*	21	58	27	68	0.675
19	*Bearable, troublesome,* ***intense, unbearable***	**23**	**59**	**28**	**57**	**0.012**
20	*Bothersome, gruelling, vicious, killing*	22	44	27	46	0.796
	Total evaluation 18–20, median (range)	1 (0–3)	1 (0–12)	0 (0–3)	0 (0–12)	**NWC,** 0.237 **PRI,** 0.260
	TAE (*n* = 8) total evaluation, median (range)	**3** (2–3)	**6** (3–10)			**NWC,** 0.005 **PRI,** 0.021
	Overall, median (range)	6 (0–20)	10 (0–59)	4 (0–20)	6 (0–56)	**NWC,** 0.851 **PRI,** 0.545
	TAE overall, median (range)	**13** (10–18)	**22** (16–44)			**NWC,** 0.011 **PRI,** 0.015

NWC, number of words count; PRI, pain rating index; TAE, transarterial embolization.
The first 12 categories are 'sensory' categories. 12 categories means a maximum score of 12 NWC per patient and every count has three severity gradations: mild, intermediate and severe. The maximum PRI is therefore $3 \times 12 = 36$ per patient. Categories 13–16 are 'affective' categories, with a maximum NWC of 4 per patient and maximum PRI of $4 \times 3 = 12$ per patient. The final categories 17–20 are 'evaluation' categories, with a maximum NWC of 4 and maximum PRI of $4 \times 4 = 16$ per patient. Total NWC and PRI are given for each group of categories, and for all categories combined (sensory, affective and evaluation; median and range per patient).
Patients in need of emergency TAE have a different pain pattern compared with HCA patients who are not in need of emergency care, with a higher NWC and PRI in all categories.

Conflicts of interest

None declared.

References

1. Colli A, Fraquelli M, Massironi S, Colucci A, Paggi S, Conte D. (2007) Elective surgery for benign liver tumours. *Cochrane Database Syst Rev* (1)CD005164.
2. Cherqui D. (2001) Benign liver tumours. *J Chir* 138:19–26.
3. Perrakis A, Muller V, Oeckl K, Adamietz B, Demir R, Hohenberger W *et al*. (2012) Indications and longterm outcome after elective surgery for hepatocellular adenoma. *Am Surg* 78:80–85.
4. Dokmak S, Paradis V, Vilgrain V, Sauvanet A, Farges O, Valla D *et al*. (2009) A single-centre surgical experience of 122 patients with single and multiple hepatocellular adenomas. *Gastroenterology* 137:1698–1705.

5. Stoot JH, Coelen RJ, De Jong MC, Dejong CH. (2010) Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas: a systematic review including more than 1600 adenoma cases. *HPB* 12:509–522.
6. Terkivatan T, de Wilt JH, de Man RA, van Rijn RR, Zondervan PE, Tilanus HW *et al*. (2001) Indications and longterm outcome of treatment for benign hepatic tumours: a critical appraisal. *Arch Surg* 136:1033–1038.
7. Cherqui D, Rahmouni A, Charlotte F, Boulahdour H, Metreau JM, Meignan M *et al*. (1995) Management of focal nodular hyperplasia and hepatocellular adenoma in young women: a series of 41 patients with clinical, radiological, and pathological correlations. *Hepatology* 22:1674–1681.
8. Reddy KR, Kligerman S, Levi J, Livingstone A, Molina E, Franceschi D *et al*. (2001) Benign and solid tumours of the liver: relationship to sex, age, size of tumours, and outcome. *Am Surg* 67:173–178.
9. Zech CJ, Grazioli L, Breuer J, Reiser MF, Schoenberg SO. (2008) Diagnostic performance and description of morphological features of focal nodular hyperplasia in Gd-EOB-DTPA-enhanced liver magnetic resonance imaging: results of a multicentre trial. *Invest Radiol* 43:504–511.
10. van den Esschert JW, van Gulik TM, Phoa SS. (2010) Imaging modalities for focal nodular hyperplasia and hepatocellular adenoma. *Dig Surg* 27:46–55.
11. Bieze M, van den Esschert JW, Nio CY, Verheij J, Reitsma JB, Terpstra V *et al*. (2012) Diagnostic accuracy of MRI in differentiating hepatocellular adenoma from focal nodular hyperplasia: prospective study of the additional value of gadoxetate disodium. *AJR Am J Roentgenol* 199:26–34.
12. Bioulac-Sage P, Balabaud C, Bedossa P, Scoazec JY, Chiche L, Dhillon AP *et al*. (2007) Pathological diagnosis of liver cell adenoma and focal nodular hyperplasia: Bordeaux update. *J Hepatol* 46:521–527.
13. Bioulac-Sage P, Laumonier H, Couchy G, Le BB, Sa CA, Rullier A *et al*. (2009) Hepatocellular adenoma management and phenotypic classification: the Bordeaux experience. *Hepatology* 50:481–489.
14. Melzack R. (1975) The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1:277–299.
15. Vanderiet K, Adriaensen H, Carton H, Vertommen H. (1987) The McGill Pain Questionnaire constructed for the Dutch language (MPQ-DV). Preliminary data concerning reliability and validity. *Pain* 30:395–408.
16. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD *et al*. (2009) The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg* 250:187–196.
17. Goodman LA, Kruskal WH. (1954) Measures of association for cross classifications. *J Am Stat Assoc* 49:732–764.
18. Erdogan D, Busch OR, Gouma DJ, van Gulik TM. (2009) Morbidity and mortality after liver resection for benign and malignant hepatobiliary lesions. *Liver Int* 29:175–180.
19. van Gulik T, Lang H. (2005) Isolated resection of segment I of the liver. *Dig Surg* 22:143–146.
20. Bathe OF, Mies C, Franceschi D, Casillas J, Livingstone AS. (2003) Massive haemorrhage and infarction complicating focal nodular hyperplasia of the liver. *HPB* 5:123–126.
21. Herman P, Coelho FF, Perini MV, Lupinacci RM, D'Albuquerque LA, Cecconello I. (2012) Hepatocellular adenoma: an excellent indication for laparoscopic liver resection. *HPB* 14:390–395.
22. van Vledder MG, van Aalten SM, Terkivatan T, de Man RA, Leertouwer T, Ijzermans JN. (2011) Safety and efficacy of radiofrequency ablation for hepatocellular adenoma. *J Vasc Interv Radiol* 22:787–793.
23. van der Sluis FJ, Bosch JL, Terkivatan T, de Man RA, Ijzermans JN, Hunink MG. (2009) Hepatocellular adenoma: cost-effectiveness of different treatment strategies. *Radiology* 252:737–746.
24. Stoot JH, van der Linden E, Terpstra OT, Schaapherder AF. (2007) Life-saving therapy for haemorrhaging liver adenomas using selective arterial embolization. *Br J Surg* 94:1249–1253.
25. Erdogan D, Busch OR, van Delden OM, Ten Kate FJ, Gouma DJ, van Gulik TM. (2006) Management of spontaneous haemorrhage and rupture of hepatocellular adenomas. A single-centre experience. *Liver Int* 26:433–438.
26. van Aalten SM, Broker ME, van Busschbach JJ, de Koning HJ, de Man RA, Steegers EA *et al*. (2012) Pregnancy and liver adenoma management: PALM study. *Gastroenterology* 12:82.
27. van der Kloot WA, Oostendorp RA, van der Meij J, van den Heuvel J. (1995) The Dutch version of the McGill Pain Questionnaire: a reliable pain questionnaire. *Ned Tijdschr Geneeskd* 139:669–673.