Imaging of hepatic hypervascular tumors & clinical implications
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Outcomes of liver resection in hepatocellular adenoma and focal nodular hyperplasia

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OBJECTIVE

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

SUBJECTS AND METHODS

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

RESULTS

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

CONCLUSION

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

INTRODUCTION

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

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

METHODS

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

ASSESSMENT OF SYMPTOMS

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

TREATMENT

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

![Flowchart of the study.](image-url)
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 analyze 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.

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

<table>
<thead>
<tr>
<th>Age, years, median (range)</th>
<th>Diagnosis</th>
<th>Liver function test, n (%)</th>
</tr>
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<tbody>
<tr>
<td>39 (19–72)</td>
<td>HCA</td>
<td>51 (46%)</td>
</tr>
<tr>
<td></td>
<td>FNH</td>
<td>59 (54%)</td>
</tr>
<tr>
<td>Size, cm, median (range)</td>
<td>6.5 (2.2–25.0)</td>
<td>5.5 (0.0–12.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P-value</td>
</tr>
<tr>
<td>Patients, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/10</td>
<td></td>
<td>0.028</td>
</tr>
</tbody>
</table>

RESULTS

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%; angiomylipoma, n = 1, 1%). One patient with HCA (1%) withdrew during the diagnostic workup (Fig. 1). The remaining 110 patients were included in the study (Table 1). Diagnosis was based on histopathological examination in 44 (39%) of the patients with HCA (34/44 resection specimens; 10/44 biopsies) and 39 (66%) of the 59 patients with FNH (16/39 resection specimens; 23/39 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 biopsies and 34 resection specimens. Six samples appeared insufficient for additional immunohistochemical staining. Results in the remaining 38 lesion samples showed inflammatory HCA in 20 lesions, steatotic HCA in eight lesions, and unclassified HCA in 10 lesions. No lesions were identified as being of the β-catenin subtype. In three (6%) patients with HCA and 14 (24%) with FNH, no histopathology was obtained and diagnosis was based on MRI findings alone.

IMAGING CHARACTERISTICS

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

TREATMENT

Results of treatment are summarized in Table 2. Conservative treatment was delivered in 61 (55%) patients, including 18 (35%) patients with HCA and 43 (73%) with FNH (P < 0.001). Eight (16%) patients with HCA presented at the emergency room with acute pain caused by bleeding of the lesion; these eight patients were admitted, stabilized and subjected to selective TAE. One of these eight patients underwent laparotomy within days of TAE because of abdominal compartment syndrome and four underwent elective resection of the lesion(s). Resection was performed in 33 (65%) patients with HCA and in 16 (27%) patients with FNH. Significantly more resections were performed for HCA than for FNH (P < 0.001). Figure 2 shows preoperative MRI, an intraoperative image and postoperative MRI in a patient with HCA. Figure 3 shows preoperative MRI and intraoperative images in a patient with FNH. Minor laparoscopic resection was performed in five (15%) of the 33 HCA patients and in five (31%) of the 16 FNH patients submitted to resection. Minor open resection was performed in 19 (58%) of the 33 HCA patients and in seven (44%) of the 16 FNH patients. Major resection was performed in nine (27%) of the 33 HCA patients and in four (25%) of the 16 FNH patients. Postoperative length of stay (LOS) differed according to the type of procedures.
surgery performed. Significant differences in LoS were found between patients undergoing laparoscopic and open surgery for HCA (P = 0.013), laparoscopic and minor open resection for HCA (P = 0.034), laparoscopic and open resection for FNH (P = 0.005), and laparoscopic and minor open resection for FNH (P = 0.009). 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 = 0.009). In HCA patients, open minor resections took less time than open major resections (P < 0.001). Complications after surgery occurred in both groups and affected 11 of the 33 patients with HCA and seven of the 16 patients with FNH (P = 0.344). Grade I and II complications were most common and were seen in 14 of the 18 patients with complications.

**SYMPTOMS**

In total, 34 of the 49 patients who underwent resection reported abdominal complaints prior to surgery. Symptoms were relieved in 30 of these 34 patients after surgery (Table 3). Symptoms are summarized in Tables 3 and 4. The pain questionnaire was completed by 48 (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 FNH was ‘drilling’ (P = 0.043). Specific pain categories reported by the eight patients who submitted to emergency TAE but not by HCA patients who did not undergo emergency TAE included ‘shooting’ (P = 0.044), ‘lacerating’ (P = 0.032), ‘crushing’ (P = 0.034), ‘splitting’ (P = 0.001) and ‘wrenching’ (P = 0.029) pain. The NWC was higher in the emergency TAE patient group than in the entire HCA patient group (Sensory: P = 0.009; Affective: P = 0.025; Evaluation: P = 0.005; Total: P = 0.011), as was the PRI (Sensory: P = 0.001; Affective: P = 0.006; Evaluation: P = 0.033; Total: P = 0.013). No differences in the NWC and PRI were found between patients with HCA or FNH when corrected for patients who underwent emergency TAE (P = 0.775).
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 parenchymasparing techniques. For example, lesions located in segment I allow the isolated resection of segment I, as was performed in three patients in the present series [19].

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

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

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

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Hepatocellular adenoma (n = 51)</th>
<th>Focal nodular hyperplasia (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidental finding</td>
<td>20 (39%)</td>
<td>27 (46%)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>31 (61%)</td>
<td>32 (54%)</td>
</tr>
<tr>
<td>Gastric complaints</td>
<td>6 (12%)</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>Left liver</td>
<td>5/22</td>
<td>19/28</td>
</tr>
<tr>
<td>Right liver</td>
<td>1/29</td>
<td>2/31</td>
</tr>
<tr>
<td></td>
<td><strong>VAS score, median (range)</strong></td>
<td><strong>VAS score, median (range)</strong></td>
</tr>
<tr>
<td></td>
<td>0.044</td>
<td>0.004</td>
</tr>
<tr>
<td>Surgery</td>
<td>0.008</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**Treatment**

- **TAE emergency care** 8 (8–10)
- **TAE preventive care** 2
- **No TAIE** 41 (1–10)
- **No resection** 18 (35–65)
- **Baseline** 0 (0–10)
- **Follow-up** 0 (0–7)
- **Resection** 33 (65–95)

**Visual analogue scale (VAS), symptoms and presentation**

- **Incidental finding**
- **Symptomatic**
- **Gastric complaints**
- **Left liver**
- **Right liver**

**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.
Common categories (n = 28% of patients) | Hepatocellular adenoma (n = 48) | Focal nodular hyperplasia (n = 57)
--- | --- | ---
1 Flickering, flashing, shooting | NWC 12, PRI 25 | NWC 10, PRI 21 | 0.754
2 TAE (n = 8): shooting | 4 | 9
3 Pinching, boring, drilling | 23 | 51 | 42 | 0.045
4 Sharp, cutting, larerating | 20 | 34 | 20 | 36 | 0.886
5 Pinching, pressing, crushing | 24 | 38 | 26 | 39 | 0.650
6 TAE (n = 8): crushing | 5 | 9
7 Tearing, pulling, spitting | 10 | 20 | 12 | 20 | 0.006
8 TAE (n = 8): splitting | 5 | 8
9 Tight, squeezing, wrenching | 19 | 48 | 19 | 51 | 0.791
10 TAE (n = 8): wrenching | 5 | 11
11 Dull, gnawing, persisting | 22 | 39 | 28 | 46 | 0.746

Total sensory 1-7, median (range) | 5 (0-12) | 5 (0-33) | 5 (0-30) | 0.781 | PRL 0.001

TAE (n = 8) total sensory, median (range) | 7 (10-15) | 8 (22-28) | NWC 0.009 | PRL 0.001

13 Ting, aridious, exhausting | 26 | 48 | 29 | 47 | 0.897
14 Cranky, disconsolating, depressing | 13 | 29 | 14 | 27 | 0.668
15 Tense, suffocating, sickening | 15 | 32 | 21 | 36 | 0.370
16 Fearful, frightful, terrifying | 19 | 34 | 20 | 36 | 0.066

Total affective 13-15, median (range) | 5 (0-5) | 1 (0-5) | 1 (0-5) | 0.486 | PRL 0.113

TAE (n = 8) total affective, median (range) | 4 (1-5) | 5 (1-10) | NWC 0.005 | PRL 0.006

18 Light, moderate, bad, severe | 21 | 58 | 27 | 68 | 0.675
19 Bearable, troublesome, intense, unbearable | 23 | 59 | 26 | 57 | 0.012

20 Bothering, gruelish, vicious, killing | 22 | 44 | 27 | 46 | 0.796

Total evaluation 18-20, median (range) | 2 (0-3) | 1 (0-12) | 0 (0-3) | 0 (0-12) | NWC 0.237 | PRL 0.290

TAE (n = 8) total evaluation, median (range) | 3 (2-3) | 3 (3-10) | NWC 0.005 | PRL 0.021

Overall, median (range) | 10 (0-20) | 10 (0-58) | 6 (0-20) | 6 (0-56) | NWC 0.851 | PRL 0.545

TAE overall, median (range) | 12 (10-18) | 22 (16-44) | NWC 0.011 | PRL 0.015

TABLE 4

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 common category has three severity gradations: mild, intermediate, and severe. The maximum PRI is therefore 3 x 12 = 36 per patient. Categories 13-16 are "affective" categories, with a maximum NWC of 3 for patient and maximum PRI of 4 x 3 = 12 per patient. The final categories 17-20 are "evaluation" categories, with a maximum NWC of 4 and maximum PRI of 4 x 4 = 16 per patient. Total NWC and PRI are given for each group of categories, and for all categories combined (sensory, affective and evaluation; median and range per patient). Patients in need of emergency TAE have a different pain pattern compared with HCA patients who are not in need of emergency care, with a higher NWC and PRI in all categories.

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

Few treatment options other than surgical intervention have been proposed. Percutaneous radiofrequency ablation (RFA) has been performed for HCA and FHN with good results and cost efficiency ratios [22, 23]. However, the procedure is limited by the location and size of the tumour. It is possible that residual tumour tissue is less problematic in a benign tumour. In the treatment of lesions of < 3 cm, RFA is a good treatment option and, depending on the location of the lesion, may even be selected as the treatment of choice. Further research should determine the long-term outcomes and limitations of RFA in the ablation of HCA and FHN. 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 FHN. Diagnosic workup should include hepatobiliary contrast MRI [11]. In patients diagnosed with FHN, 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-
Conclusions

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

References