ORIGINAL ARTICLE

Outcome after a liver resection of benign lesions

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Abstract

Background: Benign liver tumours represent a challenge in clinical management. There is considerable controversy with respect to the indications for surgery as the evidence for surgical treatment is variable. The aim of this retrospective study was to analyse the indication and outcome after resection of benign, solid liver lesions.

Methods: Data of 79 patients, who underwent liver resection between 2001 and 2012, were analysed for demographic and outcome parameters.

Results: Thirty-eight patients with focal nodular hyperplasia (48%), 23 patients with haemangioma (29%) and 18 patients with hepatocellular adenoma (23%) underwent a hepatic resection. A major hepatic resection was performed in 23 patients (29%) and a minor resection in 56 patients (71%). The post-operative mortality rate was zero and the 30-day morbidity rate 13.9%. After a median follow-up of 64 months, 75 patients (95%) were alive, and no patient had developed recurrent disease. Fifty-four patients (68%) were pre-operatively symptomatic, of which, 87% had complete or partial relief of symptoms after a liver resection. The incidence of symptoms increased with the lesions' size.

Discussion: The management of benign liver lesions necessitates an individualized therapy within a multidisciplinary, evidence-based, treatment algorithm. Resection of benign liver lesions can be performed safely in well-selected patients without mortality and low post-operative morbidity.

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Introduction

There is considerable controversy with respect to the indication for a liver resection (LR) in patients with benign liver lesions, and this is as a result of the heterogeneity of the diseases.[1] Benign liver lesions can be classified into (hyper-) regenerative lesions (such as focal nodular hyperplasia and an inflammatory pseudotumour) and neoplastic lesions (including hepatocellular adenoma, haemangioma and angiomyolipoma). The widespread use and availability of cross-sectional imaging has increased the detection of hepatic lesions. The majority of so-called hepatic incidentalomas are benign with a prevalence of up to 15% in the population.[2]

Thus, careful and accurate selection and investigation is required to establish a precise diagnosis with a clear distinction between benign lesions and malignant tumours. In particular, being able to differentiate between hepatocellular adenoma (HCA) (with all of its immunohistochemically defined subtypes), well-differentiated hepatocellular carcinoma (HCC) and focal nodular hyperplasia (FNH) is sometimes difficult.[3] In the majority of patients, modern imaging studies using liver-specific contrast agents have allowed precise diagnosis of the most common benign, solid liver lesions, such as haemangioma and FNH.[4] However, the nature of the lesion remains uncertain 5–10% of patients. When the diagnosis of a benign liver lesion is established, a team of hepato-biliary specialists (with the inclusion of a radiologist, pathologist, hepatologist and a liver surgeon) must decide whether an observational, interventional or a surgical approach is appro-

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priate. The treatment approaches for benign, solid liver lesions are not based on the highest level of evidence. The clinical decision-making process is heavily influenced by the reliability of the diagnostic and the accurate assessment of the symptoms. In the case of a symptomatic patient, whether or not the lesion is causing the symptoms has to be evaluated. Should there be patients with inconclusive imaging results, large lesions with an invasive and dislodging growth pattern, signs of bleeding, or lesions that are highly susceptible to ruptures (e.g. lesions larger 5 cm), the contemporary hepato-biliary advice is resection of the lesion. This is especially true for HCA patients of the ß-catenin-mutated subtype in whom the two major complications (such as bleeding and the risk of malignant transformation) have to be avoided. However, it has to be carefully evaluated whether or not the biological risk posed by the lesion outweighs the risk of LR. Nowadays, a strategy of a shared decision-making process involving the treating physicians together with the patients should be routine prior to surgery.

Here, the single-centre experience with patients undergoing LR for benign, solid lesions is reported.

Patients and methods

Between 2001 and 2012, 2042 LRs were performed in the Department of General, Visceral and Transplant Surgery, University Hospital Heidelberg, Germany. Patients with concomitant resections as a result of other extrahepatic diseases were excluded from the analysis. Informed consent was obtained from all patients prior to surgical treatment. Data collection and analysis were performed according to institutional guidelines that conform to the ethical standards of the Helsinki Declaration and was approved by the local ethics committee (S390/2012).

The majority of patients were transferred to the centre on the advice of their general practitioners after a period of observation during which, an exacerbation of the symptoms, an increase in the size of the known benign liver lesions or the presence of unclear liver lesions had been detected by routine assessment for unspecified abdominal symptoms via ultrasonography or CT scan. All the patients were seen in an interdisciplinary, hepato-biliary outpatient clinic and the standard assessment, which comprised of a clinical evaluation, liver function tests, tumour markers detection tests and magnetic resonance imaging [using the liver-specific contrast agent Primovist© (from 2006 onwards (Bayer Schering Pharma AG, Berlin, Germany)], had been carried out. An additional endoscopy/colonoscopy was performed in the majority of patients to exclude a potential malignant origin of the liver lesions. The symptoms were assessed before and 12 months after LR. The assessment consisted of a questionnaire that was based on a visual analogue scale to determine pain and discomfort levels.

The indication for LR was given for every entity on the following basis: FNH – all symptomatic patients and patients with risk factors such as growth dislodging other organs, cholestasis, compression of vessels, or a significant increase in tumour size during the observation period; for haemangioma – all symptomatic patients, patients with tumours larger than 5 cm with a significant increase in size during the follow-up and patients with signs of acute bleeding and no possibility of control by interventional radiology; for HCA – symptomatic patients independent from the size, patients with tumours larger than 5 cm, patients with an increase in size after discontinued use of oral contraceptives, patients with suspected malignant features on imaging, patients with histologically proven ß-catenin-mutated adenoma independent from the size owing to the significant risk of malignant transformation and patients with histological atypia.[5] Furthermore, patients with unclear imaging results and no clear histology after biopsy were resected (Table 1).

Transection of the liver parenchyma was performed as recently described by our group.[6–8]

Given that laparoscopic LR was established in the Department of General, Visceral, and Transplant Surgery in 2011, the procedure was performed in patients with small, single and well-accessible tumours. An LR of three or more Couinaud's

Table 1 Treatment of benign liver lesions

HCA: biopsy all
Resection
All symptomatic after exclusion of other reasons for symptoms
All > 5 cm
All male patients – higher risk of transformation
All ß-catenin mutated
<5 cm if evidence of
Pathological atypia
Growth after stopping oral contraceptives
Suspected malignant features on imaging
FNH: biopsy all with atypical imaging features and / or significant growth during observation
Resection
All symptomatic patients
Patients with risk factors such as growth dislodging other organs, cholestasis, compression of vessels or significant increase in size during the observation period
Haemangioma: no biopsy
Resection
All symptomatic patients
Patients with lesions >5 cm
Patients with significantly increasing size during the follow-up
Patients with signs of acute bleeding and no possibility of control by interventional radiology

segments was classified as a major resection. No cell saver was used in the reported patients. According to the institutional multidisciplinary standard operating procedures, in otherwise healthy patients without any cardiovascular disease, a haemoglobin of 5.5 mg/dl is accepted without substitution of blood products as long as they are not symptomatic. Surgical complications were graded according to the Clavien–Dindo classification.[9–12] Patients who did not undergo a resection after initial presentation were seen on a regular basis every 6 to 12 months for follow-up and an indication for LR was given when the lesion's size increased or lesion-related symptoms developed.

Statistical analysis

The SAS software (Release 9.1, SAS Institute, Inc. Cary, NC, USA) was used for statistical analysis. The quantitative variables were expressed as the median with an interquartile range (IQR) or range. The Mann–Whitney *U*-test was used to compare a laparoscopic and an open liver resection. Two-sided *P*-values were always computed, and a difference was considered statistically significant at $P \leq 0.05$.

Results

Patients' characteristics

Seventy-nine consecutive patients who underwent LR for benign, solid liver lesions were identified from the institutional LR database. Of the latter, 71 were female (90%), and the median age of the total cohort was 40.6 years. One patient with haemangioma was resected under emergency conditions for spontaneous rupture of the lesion. The final histopathological evaluation confirmed the diagnosis of FNH in 38 patients (48%), haemangioma in 23 patients (29%) and HCA in 18 patients (23%). There was a significant difference in tumour size at the time of resection among the tumour entities [FNH median maximal tumour size was 6 cm (range 1–13 cm), haemangioma median maximal size was 11 cm (range 1–23 cm) and HCA had a median size of 7 cm (range 5–16 cm); $P = 0.010$]. Single lesions were found in 42 patients (53%), 2–10 lesions in 32 patients (41%) and more than 10 lesions in five patients ($n = 3$ haemangiomatosis, $n = 2$ adenomatosis). Eleven patients (14%) underwent a biopsy of the lesion before resection owing to unclear imaging results. Transarterial embolization was performed in four cases ($n = 1$ ruptured FNH and $n = 3$ haemangioma) for bleeding before LR (Table 2).

Liver resection

The median time between diagnosis and resection was 43 months for FNH, 22 months for haemangioma and 3 months for HCA. Thirty-eight patients (48%) were resected within 3 months after a presentation from their GPs as they fulfilled our resection criteria at the time of presentation. The other patients were resected owing to an increasing size of the lesion, when patients became more symptomatic, or when bleeding was evident in imaging studies (Table 3).

Table 2 Characteristics of 79 patients with benign solid liver lesions undergoing a liver resection

	Total cohort $n = 79$	FNH $n = 38$ ($n = 4$ male)	Haemangioma $n = 23$ ($n = 4$ male)	HCA $n = 18$
Gender *n* (%)				
Male	8 (10)	4 (11)	4 (17)	–
Female	71 (90)	34 (89)	19 (83)	18 (100)
Age, years median (IQR)	40.6 (16.0)	42 (17.5)	45 (16.0)	36 (14.5)
Size, cm median (IQR)	7.6 (5.0)	6.5 (4.5)	10.0 (6)	6.5 (5.0)
Oral contraceptives *n* (%)	56 (71)	24 (65)	16 (70)	16 (88)
ASA score *n* (%)				
ASA 1	9 (11)	5 (13)	2 (9)	2 (11)
ASA 2	64 (81)	32 (84)	17 (74)	15 (83)
ASA 3	6 (8)	1 (3)	4 (17)	1 (6)
BMI, kg/m^2 median (IQR)	25.5 (7.5)	24 (7.5)	25 (6.0)	28 (9.5)
Number of lesions *n* (%)				
Singular	42 (54)	24 (63)	9 (39)	9 (50)
2–3	25 (32)	13 (35)	9 (39)	4 (22)
3–9	6 (8)	1 (2)	2 (9)	3 (16)
≥10	5 (6)	–	3 (13)	2 (11)
Location *n* (%)				
Left liver (Seg 2/3 + 4)	26 (33)	11 (29)	7 (30)	8 (44)
Right liver (Seg 5–8)	38 (48)	22 (58)	9 (39)	7 (39)
Both	15 (19)	5 (13)	7 (31)	3 (17)

FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; BMI, body mass index; ASA, American Society of Anesthesiologists; IQR, interquartile range.

A major LR was performed in 23 patients (29% of the entire group) and a minor hepatic resection in 56 patients (71%). A laparoscopic LR was performed in nine patients (11% of the group; all atypical resection). Of those, the median tumour number was one lesion (with a range of 1–3 lesions) and the median tumour size was 8 cm (with a range of 2–10 cm). Both the median blood loss (laparoscopic resection 170 ml versus open resection 660 ml) and the post-operative hospital stay (laparoscopic resection 6 days versus open resection 9 days) were significantly lower compared with an open resection ($P = 0.050$; $P = 0.010$).

While there was no mortality after LR, the post-operative 30-day morbidity rate was 13.9% ($n = 11$). According to the Clavien–Dindo classification, a Grade II complication occurred in six patients, Grade IIIa occurred in four patients in whom drainage of a pleural effusion was necessary and a Grade IIIb

Table 3 Type of resection and outcome in 79 patients with benign solid liver lesions

	Total cohort $n = 79$	FNH $n = 38$ ($n = 4$ male)	Haemangioma $n = 23$ ($n = 4$ male)	HCA $n = 18$
Resection *n* (%)				
Open	70 (88)	31 (81)	22 (95.6)	17 (94)
Laparoscopic	9 (12)	7 (19)	1 (4.4)	1 (5.3)
Hepatectomy right	18 (23)	10 (27)	2 (8.8)	6 (31.6)
Hepatectomy left	5 (6)	3 (8)	–	2 (10.5)
Atypical resection	53 (67)	25 (65)	21 (91.2)	10 (55)
Blood loss; median (range)	325 (20–4000)	670 (20–4000)	600 (10–2000)	370 (200–800)
Intermediate care unit stay; days median (range)	1 (1–9)	2 (2–9)	2 (2–4)	2 (2–4)
Hospital stay days; median (range)	8 (4–32)	8 (4–18)	12 (6–32)	8 (5–10)
Mortality rate	–	–	–	–

FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma.

complication in one patient in whom a surgical revision as a result of acute bleeding was performed. Surgical re-intervention was necessary for five patients owing to an incisional hernia more than 1 year after the resection. Three of those patients had a wound infection with prolonged wound healing after the first operation.

The suspected histology was confirmed in 66 patients (84%). In three patients with suspected HCA, final histo-pathological evaluation showed FNH in two and haemangioma in the other patient. In patients with unclear imaging results and pre-operative biopsy, the final histo-pathological evaluation revealed FNH in six and HCA in three patients. In total, HCA was classified after histo-pathological evaluation as HNF1A-inactivated subtype in two patients and an inflammatory subtype in 16 patients. There was no malignant transformation detectable in any patient.

Outcome

After a median follow-up of 64 months, 75 patients were alive; three patients died as a result of a malignant disease that was not related to the liver lesion, and one patient committed suicide. No patient developed recurrent disease. No further surgical intervention was needed during the follow-up period for the patients with ≥ 10 haemangioma and the patients with adenomatosis.

Pre-operative symptoms were found in 54 patients. Overall, the symptoms were heterogenous with abdominal pain, a feeling of unspecific abdominal pressure, nausea and fatigue as mentioned by the majority of patients. Forty patients reported a worsening of the symptoms within 1 year prior to the LR. The incidence of symptoms increased with the size of the lesion; 38% of patients with tumours larger than 5 cm and 67% of patients with tumours larger than 10 cm complained about abdominal pain and a feeling of unspecific pressure ($P = 0.075$). Twenty-five patients (32%) were asymptomatic at the time of the LR. Complete or partial relief of symptoms was reported by 47 patients (87%) after LR; however, 10 patients (19%) reported persistent impairment of their daily activities after surgery. The majority of them had abdominal pain, followed by digestive symptoms, and paraesthesia of the abdominal scar. Patients with post-operative complications after the LR had more post-operative symptoms [medium visual analogue scale (VAS) score 6] compared with those without complications (medium VAS score 4) ($P = 0.002$; Table 4).

Discussion

The presented data clearly shows that resection of benign lesions can be performed safely in well-selected patients without mortality and with low post-operative morbidity. Furthermore, a total or partial relief of the symptoms can be achieved in the majority of the patients.

This has clear implications for the management of patients with benign liver tumours. In general, LR is commonly discussed in one of the two following scenarios: first, as an already known and observed benign liver lesion with an increase in size with or without clinical symptoms and second, as a new, incidentally detected liver lesion with diagnostic uncertainty.

The evidence for LR or interventional treatment of benign, solid liver lesions is variable as randomized, controlled clinical trials are pending. Apart from HCA, clear guidelines for the clinical management have not been established, thus the treatment of these patients is based on the clinical experience of the responsible centre and the indication for LR is often an individualized decision.[13–16]

Herein, we have proposed a treatment algorithm for patients with benign, solid liver lesions based on the experience gained treating the reported patients and retrospective studies as well

Table 4 Effect on symptoms, based on complete questionnaires from 54 patients

Total *n* = 54	Symptoms		
	Complete release *n* = 9 (17%)	Partial release *n* = 35 (65%)	Persistent *n* = 10 (18%)
Tumour entity *n* (%)			
FNH (*n* = 28)	6 (21)	17 (61)	5 (18)
Haemangioma (*n* = 19)	3 (16)	13 (69)	3 (16)
HCA (*n* = 7)	–	5 (72)	2 (29)
Tumour size *n* (%)			
−5 cm (*n* = 15)	2 (13)	10 (67)	3 (20)
5–10 cm (*n* = 23)	5 (22)	14 (61)	4 (17)
>10 cm (*n* = 16)	2 (13)	11 (69)	3 (19)
Type of resection *n* (%)			
Open (*n* = 46)	6 (13)	32 (70)	8 (18)
Laparoscopic (*n* = 8)	3 (38)	3 (38)	2 (25)
Major (*n* = 17)	2 (12)	7 (41)	8 (47)
Minor (*n* = 37)	7 (19)	28 (76)	2 (5)
Complication *n* (%)			
Yes (*n* = 11)	–	4 (36)	7 (64)
No (*n* = 43)	9 (21)	31 (72)	3 (7)

FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma.

as case reports.[4,5,17] Before a resection, the different treatment options, including repetitive imaging to observe for a lesional change, biopsy, conservative management and LR techniques, are discussed with the patient to follow the principles of informed consent. Nevertheless, the optimal time to perform a resection is under debate.

In the present study, the time from diagnosis to resection was significantly longer in patients with FNH compared with patients with haemangioma and HCA, especially in the latter the risk of potential malignant transformation might lead to a more aggressive indication for LR than in the other entities.[18] In the authors' institution, the indication for resection of HCA has been frequently made in recent years because the knowledge about this entity has increased dramatically.[15,16] There is considerable controversy with respect to the absolute indication for LR in male patients with HCA, independent of the size. Based on studies that reported an increased risk of early HCC mimicking HCA in male patients, all male patients presenting with suspected HCA were resected.[19]

Patients with large heamangiomas have been included in this series because they represent a small proportion of individuals who have been encouraged by their referring GP to seek the medical council of a hepato-biliary specialist. Many patients with haemangioma that was incidentally detected were diagnosed and treated without specialist consultation. The recommendations for the treatment of haemangioma are similarly heterogeneous as for FNH.[20] The vast majority of patients with hepatic haemangiomas do not require an LR; however, patients with big lesions and a sub-capsular location have to be informed about the risk of bleeding complications. Trans-arterial embolization (TAE) was usually applied in patients with signs of bleeding as part of the multidisciplinary treatment approach to allow elective surgery. With this strategy, only one patient needed to be resected as an emergency case owing to a fulminant rupture. However in some centres, TAE is used pre-emptively as a pre-operative intervention to reduce the risk of bleeding or for downsizing lesions with borderline resectability.[21]

Indeed, most of benign liver lesions are amenable to parenchyma-sparing resection techniques. LR in well-selected patients can be performed without mortality, as shown in the present series; however, deaths after the resection of benign lesions have been reported.[22] Previously, Erdogan *et al.* showed that LR for benign liver lesions is also associated with a lower morbidity compared with resections for malignancies owing to a smaller resection volume and very meticulous patient selection.[23] This is in line with the findings of the present study. The morbidity rates of the present analysis are significantly lower compared with resections for primary liver tumours or liver metastases in the present centre.[5,24–26] However, the groups cannot be compared directly as the reported patient cohort is much younger, without the background of chronic liver disease in most cases and no history of pre-operative chemotherapy. About one-third of the patients underwent a major LR. This was necessary owing to the big tumour size and might reflect the impact of the late presentation at our centre and the conservative observational approach in asymptomatic lesions by many GPs. Nevertheless, the 30-day morbidity rate was comparable between patients with minor and major resections. As both HCA and FNH are hypervascular tumours, considerable blood loss can happen during the resection. The need for a blood transfusion is one of the major concerns of many patients before the operation. However, in the present series, no blood transfusions were needed. This is a result of meticulous operation planning with 3-D simulation of the resection plane and an operation technique using vascular staplers for a parenchymal transection.[27] With this approach, a Pringle manoeuvre was not necessary for the reported patients.

Laparoscopic LR gains more and more influence in the surgical management of benign liver lesions.[28] The advantages of an laparoscopic resection, such as the excellent post-operative recovery and the cosmetic results, predestines this technique for the treatment of benign lesions.[29] In the present study, patients undergoing laparoscopic LR had less blood loss and a shorter time of stay compared with patients with an open resection. This might be the result of selection bias, as patients resected laparoscopically had fewer lesions and underwent only minor resections. However, the indication for a resection should be independent of the possibility for a laparoscopic approach and major laparoscopic LR should only be performed by experienced specialists.[30]

Clinical symptoms, which impair the daily life of the patients, are one of the main reasons for a liver resection of benign, solid tumours; to what extent these are the result of the diagnosed lesions is difficult to verify. All other potential reasons for the complaints have to be excluded before surgical treatment. The high rates of resections in patients with FNH and haemangioma are partially based on the symptomatic complaints of the patients and their subjective fear of complications in big lesions. In the present study, there was a correlation between lesion size and symptom intensity. The resection of benign lesions resulted in the total or partial relief of symptoms in the majority of the patients in this trial. There was an overall improvement of the general health status after a resection and a significant amelioration of the symptoms, which is in line with other published reports.[31] Patients with complications after the operation had more persistent post-operative symptoms. The same was reported by Miller *et al.*, who showed that patients with complications have a deterioration of their quality of life at the onset.[32] However, one has to note that some patients have persistent complaints over a long time. Those patients were referred to the chronic pain specialist team after exclusion of visceral reasons to get the best support for their malady.

Conclusion

LR for benign, solid lesions can be performed safely in well-selected patients without mortality and with a low post-operative morbidity. The significant reduction of symptoms is an important part of the success of surgical treatment in these patients. However, the management of benign, solid liver lesions necessitates an individualized therapy within a multidisciplinary, evidence-based, treatment algorithm.

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Conflict of interest

None declared.

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