

## ORIGINAL ARTICLE

# Early postoperative outcomes following hepatic resection for benign liver disease in 79 consecutive patients

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## Abstract

**Background:** Liver resection is an accepted treatment modality for malignant disease of the liver. However, because of its potential morbidity and mortality, the practice of liver resection in benign disease is more controversial. This study was designed to assess the early outcomes of 79 consecutive liver resections for benign disease over a 12-year period and compare these with early outcomes of 390 consecutive liver resections for metastatic colorectal cancer (MCRC) during the same period.

**Methods:** Consecutive liver resections were carried out in a single hepatopancreatobiliary (HPB) centre between 1996 and 2008. Patient demographics and early outcomes were recorded. Statistical analyses were performed using SPSS (Version 15).  $P < 0.05$  was considered to be significant.

**Results:** There was no difference in median age between the benign group vs. the MCRC group ( $P = 0.181$ ). However, there was a significant trend towards a lower ASA grade in the benign group ( $P < 0.001$ ). There was no difference in median blood loss ( $P = 0.139$ ) or hospital stay ( $P = 0.262$ ). Morbidity rates were 8.9% in the benign group and 20.5% in the MCRC group ( $P = 0.002$ ). The rate of serious complications was 1.3% in the benign group compared with 4.4% in the MCRC group ( $P = 0.041$ ). There were no postoperative deaths in the benign group and eight (2%) in the MCRC group ( $P = 0.004$ ).

**Conclusions:** Liver resection for benign liver tumours can be undertaken with a mortality rate approaching zero and minimal morbidity in specialist HPB units.

## Keywords

liver resection, benign liver disease

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## Introduction

Liver resection is an accepted treatment modality for primary and secondary malignant disease of the liver. The associated reported morbidity of 30% and mortality of 1–2% are acceptable given the nature of the underlying disease.<sup>1–3</sup> However, the practice of liver resection in benign disease is more controversial.<sup>4</sup> The indications for liver resection for benign tumours include severe or progressive symptoms, uncertain diagnosis with a suspicion of malignancy and risk of haemorrhage or rupture.<sup>4</sup> However, arriving at the correct diagnosis and making the decision to undergo formal liver resection can be challenging.

Several small series in the literature have presented local results following liver resection in benign disease, but fewer articles have described longterm effects.<sup>4</sup> We present a series of 79 consecutive

liver resections in benign disease in a single high-volume liver unit over a 12-year period. This article also compares the short-term outcomes of these patients with those of patients undergoing liver resections for colorectal liver metastases (CRLM) in the same liver unit during the same period.

## Materials and methods

Consecutive liver resections for benign disease performed from 1996 to 2008 in a single high-volume liver unit were included. Data were collected prospectively by a full-time data clerk and then analysed retrospectively. Factors recorded included age, American Society of Anesthesiologists (ASA) grade, type of liver resection, underlying disease, intraoperative blood loss, blood transfusion rate, hospital stay, morbidity and mortality.

Postoperative mortality was defined as death within 30 days of surgery or before discharge. Complications were classed according to the classification proposed by Dindo *et al.*,<sup>5</sup> and were considered to be severe if they were grade III or greater.

Preoperative assessment included ultrasound, computerized tomography (CT), magnetic resonance imaging (MRI) and, where appropriate, positron emission tomography (PET). Indications for liver resection included: persistent symptoms of pain despite alternative measures, such as cessation of oral contraceptive steroids in patients with focal nodular hyperplasia (FNH); rapid growth; inability to exclude malignancy; risk of malignant transformation; risk of rupture or haemorrhage, and, in a few instances, presence of rupture or haemorrhage necessitating emergency liver surgery. Only patients who underwent formal liver resection were included in the study.

Early outcomes were then directly compared with those of 390 consecutive liver resections for metastatic colorectal cancer (MCRC) carried out during the same period by the same surgeon in the same institution.

Liver parenchyma transection was achieved using the Cavitron ultrasonic surgical aspirator (CUSA). Haemostasis was achieved by a combination of the argon beam coagulator, sutures, and ligatures and vascular staplers, where appropriate. During the intraoperative period, the patient's central venous pressure (CVP) was reduced using anaesthetic techniques.

Statistical analyses including *t*-test, chi-squared test, Fisher's exact test and tests of proportionality were carried out using *SPSS* (Statistical Package for Social Sciences, Version 15; SPSS, Inc., Chicago, IL, USA) and the Patient Management & Analysis System 2004 (P.A.M. Ltd, Buckinghamshire, UK).<sup>6,7</sup> Multivariate analyses of predictors of morbidity and mortality were carried out using the Cox regression method. *P*-values < 0.05 were considered significant.

## Results

### Benign liver resections

Between 1996 and 2008, 79 consecutive liver resections for benign disease were undertaken. Table 1 summarizes the diagnoses and the types of liver resection that took place. Table 2 summarizes early outcomes, including patient demographics, morbidity,

mortality, median hospital stay, median tumour size and median blood loss. Table 3 categorizes the indications for liver resection in benign disease.

### Comparison with liver resections for MCRC

Over the same period, 390 liver resections were undertaken for MCRC. Table 2 summarizes patient demographics and early outcomes, and compares these with those of the benign group.

There was no difference in demographics between the MCRC group and the benign group, other than that the benign group showed a significant trend towards a lower ASA grade compared with the MCRC group (Table 2).

### Indications for liver resections in benign disease

The indications for liver resection in benign disease are categorized in Table 3. In total, 45 (57%) patients underwent liver resection for symptomatic disease; 26 (33%) of these patients had symptomatic disease alone and 19 (24%) underwent liver resection for a combination of symptomatic disease and suspicion of malignant disease. Following liver resection for symptomatic benign disease, 37 patients (82%) had complete symptomatic relief, seven (15.5%) had partial symptomatic relief and one (2.2%) had no symptomatic relief.

Of the patients with symptomatic cystic disease with no suspicion of malignancy (*n* = 13), five had previously undergone repeated needle aspiration procedures, followed by liver resection. These patients were treated during the initial 3 years of the series. The remaining eight patients with symptomatic cystic disease had undergone repeated (two or more) de-roofing procedures before proceeding to liver resection for recurrent cyst formation. Of the patients with liver cysts, four had autosomal dominant polycystic disease and two had features suspicious for hydatid disease.

Forty-one (52%) patients underwent liver resection for disease in which malignancy could not be excluded. Fifteen (37%) of these patients had previous malignant disease elsewhere, including colorectal cancer (*n* = 11), pancreatic adenocarcinoma (*n* = 1), malignant melanoma (*n* = 2), and pancreatic insulinoma (*n* = 1). The remaining 26 patients had radiological features which did not satisfactorily exclude malignant disease.

**Table 1** Liver resections in benign disease

	Patients	Seg	R hemi	Ext R hemi	L hemi	Ext L hemi	Wedge
FNH	16	8	7				1
Haemangioma	14	6	3	1	1	1	2
HCA	11	6	3		1	1	
Cyst	34	5	11	5	8	2	3
Scar tissue	4	2	1				1
<b>Total</b>	<b>79</b>	<b>27</b>	<b>25</b>	<b>6</b>	<b>10</b>	<b>4</b>	<b>7</b>

Ext L hemi, extended left hemihepatectomy; Ext R hemi, extended right hemihepatectomy; FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; L hemi, left hemihepatectomy; R hemi, right hemihepatectomy; Seg, segmentectomy; Wedge, wedge excision

**Table 2** Outcomes following liver resection

	Liver resections in benign disease ( <i>n</i> = 79)	Liver resections in MCRC ( <i>n</i> = 390)	<i>P</i> -value
Median age, years	53.6 (20.6–81.5)	65.9 (26.5–85.4)	0.181
Male : female	0.32 : 1	1.47 : 1	N/A
ASA grade, <i>n</i> (%)			
1	36 (45.6%)	72 (18.5%)	<0.0001
2	24 (30.4%)	218 (55.9%)	<0.0001
3	6 (7.6%)	50 (12.8%)	0.132
4	0	5	0.024
Not recorded	13	45	
Type of liver resection			0.587
• Hemi- or extended hemi-hepatectomy	45 (57%)	238 (61%)	
• Parenchyma-sparing resection	34	152	
Median intraoperative blood loss, ml (range)	200 (<20 to 1700)	250 (<20 to 6000)	0.139
Median hospital stay, days (range)	10 (1–48)	9 (2–67)	0.262
Morbidity, <i>n</i> (%)	7 (8.9)	80 (20.5)	0.002
Serious complications ( $\geq$ grade III <sup>9</sup> ), <i>n</i> (%)	1 (1.3)	17 (4.4)	0.041
Mortality, <i>n</i> (%)	0	8 (2)	0.004
Patients requiring blood transfusions, <i>n</i> (%)	4 (5.1)	21 (5.4)	0.912
Use of intraoperative Pringle clamp, <i>n</i> (%)	36 (45.6)	208 (53.3)	0.213
Median tumour size, mm (range)	30 (0–220)	32 (4–160)	0.134

MCRC, metastatic colorectal cancer; N/A, not applicable; ASA, American Society of Anesthesiologists

**Table 3** Indications for liver resection in benign disease

	Patients, <i>n</i> (%)	Symptomatic despite conservative measures	Inability to exclude malignancy radiologically	Symptomatic and inability to exclude malignancy radiologically	Risk of malignant transformation	Rupture or haemorrhage
FNH	16 (20.3)	4	10	2		
Haemangioma	14 (17.7)	6	4	4		
HCA	11 (13.9)	2	1	3	4	1
Cyst	34 (43)	13	5	10		6
Scar tissue	4 (5.1)	1	2			1
<b>Total (%)</b>	<b>79 (100)</b>	<b>26 (32.9)</b>	<b>22 (27.8)</b>	<b>19 (24)</b>	<b>4 (5.1)</b>	<b>8 (10.1)</b>

FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma

## Morbidity and mortality

There were no deaths in the perioperative period in the benign group, compared with eight (2.0%) in the MCRC group ( $P=0.004$ ; Table 2). Multivariate analysis demonstrated that benign disease was an independent factor for reduced mortality ( $P=0.022$ ). Other factors placed in the multivariate analysis model included ASA grade ( $P=0.062$ ) and >10 days in hospital ( $P=0.182$ ).

There were seven (8.9%) complications in the benign group, compared with 80 (20.5%) in the MCRC group ( $P=0.002$ ; Table 4). One (1.3%) of the complications in the benign group was considered to be severe according to the classification published by Dindo *et al.*<sup>5</sup> This consisted of a bile leak which required

percutaneous drainage. By contrast, there were 17 (4.4%) complications classified as grade III or above in the MCRC group ( $P=0.041$ ; Table 2). Multivariate analysis demonstrated that benign disease was an independent factor for reduced morbidity ( $P=0.048$ ). Other factors placed in the multivariate analysis model included ASA grade ( $P=0.087$ ) and >10 days in hospital ( $P=0.274$ ).

## Discussion

Morbidity and mortality rates of major liver resection in malignant disease have steadily decreased over recent years as a result of improved patient assessment and selection, enhanced surgical techniques and better perioperative care.<sup>8</sup> As a result, specialist

**Table 4** Morbidity following liver resection

Complication	Liver resections in benign disease (n = 79), n (%)	Liver resections for MCRC (n = 390), n (%)
Bile leak	5 (6.3)	15 (3.8)
Wound infection	1 (1.3)	8 (2.1)
Respiratory failure		7 (1.8)
Aspiration pneumonia		1 (0.3)
Upper gastrointestinal bleed		2 (0.5)
Pneumothorax		3 (0.8)
Hepatic insufficiency		6 (1.5)
Sub-phrenic collection		4 (1)
Thromboembolism	1 (1.3)	1 (0.3)
Acute renal failure		2 (0.5)
Cardiac complications		
Atrial fibrillation		10 (2.6)
Myocardial infarction		3 (0.8)
Pulmonary oedema		1 (0.3)
Heart block		1 (0.3)
Bradycardia requiring pacing		1 (0.3)
Pleural effusion		1 (0.3)
Acute confusion		2 (0.5)
Prolonged ileus requiring TPN		2 (0.5)
Pneumonia		9 (2.3)
Superficial wound dehiscence		1 (0.3)
<b>Total (%)</b>	<b>7 (8.9)</b>	<b>80 (20.5)</b>

$P = 0.002$ , comparison of total morbidity between the two groups. MCRC, metastatic colorectal cancer; TPN, total parenteral nutrition

hepatopancreatobiliary (HPB) units have slowly increased the number of liver resections carried out in benign disease.<sup>4,9,10</sup> However, this surgery still carries a potential risk of morbidity and mortality; therefore, strict indications for liver resection in benign disease are vital.

### Indications for liver resection

The indications for liver resection in benign liver disease include symptomatic tumours, suspicion of malignancy, and risk of malignant transformation, rupture or bleeding.<sup>4,10</sup>

Symptomatic relief has been described in 80–90% of patients following liver resection for severe or worsening symptomatic benign lesions.<sup>4,11,12</sup> Furthermore, Charny *et al.* reported an 86% resolution or regression of symptoms in patients with benign liver lesions with symptoms that were clinically thought to be unrelated to the liver tumour, who were treated conservatively.<sup>12</sup> The challenge lies in determining whether a patient's symptoms are related to his or her benign liver tumour.

Our series supports these findings: 82.0% of patients with symptomatic disease had complete symptom resolution and a further 15.5% experienced partial relief of symptoms.

It is also challenging to determine which tumours carry a risk of potential rupture or bleeding. For example, very few haemangiomas require surgical resection. Their main potential risk is one of rupture, which is infrequent.<sup>4</sup> However, haemangiomas that grow rapidly, develop complications or have persistent symptoms represent indications to resect, as does a need to determine diagnosis.<sup>4</sup> However, this need should be balanced against the potential risk for massive intraoperative haemorrhage.<sup>4</sup>

Hepatocellular adenoma (HCA) and FNH are often found in females and are usually associated with longterm contraceptive steroid use.<sup>4,13</sup> Cases of HCA which are >5 cm, grow rapidly or present with diagnostic uncertainty should be considered for resection as they are often symptomatic and can be associated with spontaneous rupture or malignant transformation.<sup>4</sup> However, for smaller HCAs and FNH it is reasonable to stop contraceptive steroids and observe.<sup>14</sup>

### Morbidity and mortality

There were no postoperative deaths following liver resection for benign disease in the current series. Several large studies have reported zero deaths or a mortality of <5% for benign liver resections.<sup>4,9,10,15</sup> An experienced HPB unit should aim to achieve a postoperative mortality of zero, or approaching zero.

However, morbidity rates of 25–30% have been described for liver resections in benign disease,<sup>4,9</sup> which are similar to those following liver resections for MCRC.<sup>1,3,8,16</sup> Ibrahim *et al.* reported a complication rate of 8.3% for liver resections in benign disease, a rate comparable with our data.<sup>10</sup> However, their population contained a high proportion of patients with hepatitis B and subsequently the majority of their patients underwent liver resection to rule out malignancy.<sup>10</sup> In our series, there was no difference in age between the two groups. However, there was a significant trend towards a lower ASA grade in the benign group, which may have contributed to the reduced morbidity in this group.

It is unusual for articles to categorize complications into mild or severe. In the current series, the rate of severe (grade III or above<sup>5</sup>) complications was 1.3% in the benign group, compared with 4.4% in the MCRC group. It is likely that severe morbidity has a much greater impact on patient outcomes. Of the five patients in the benign group who had bile leaks, four had undergone liver resection for cystic disease and one had benign scar tissue.

Morbidity rates of 25–30% in benign liver resections should not be considered acceptable. Postoperative morbidity and mortality following liver resections for malignant conditions should be compared with the risk of not treating a patient with fatal disease.<sup>9</sup> They also reflect the efforts made by the surgeon to achieve improved longterm survival in high-risk patients.<sup>9</sup> These considerations do not apply in benign disease. Consequently, more patients with benign disease may be offered parenchyma-sparing liver resection, which reduces the surgical impact on the patient.

In addition, there is increased use of neo-adjuvant chemotherapy for MCRC, which may increase the incidence of

non-alcoholic steatohepatitis (NASH), potentially raising the postoperative mortality rate.<sup>3,17</sup> In our series, overall postoperative morbidity and the rate of severe complications were significantly lower in the benign group compared with the MCRC group. This may reflect the standard use of neo-adjuvant chemotherapy in the MCRC group, a higher proportion of parenchyma-sparing liver resections in the benign group, a lower threshold for liver resection in patients with MCRC despite co-morbidity, or a combination of these factors.

### Patient selection and assessment

The data in this article show that an overall morbidity rate of 8.9% with a rate of severe complications of 1.3% can be achieved following liver resection in benign disease in a specialist HPB unit. Risk factors for postoperative morbidity include emergency liver resection (e.g. following rupture or bleed of a tumour), and the presence of underlying liver disease, such as cirrhosis or chronic cholestasis.<sup>9</sup> Inappropriate use of intraoperative Pringle manoeuvres,<sup>18</sup> ASA grade and the extent of liver resection are also associated with postoperative mortality.<sup>9</sup> In the current study, patients who underwent liver resection for benign disease had a significantly lower ASA grade than those with MCRC.

Therefore, patient selection and assessment are vital. For malignant conditions in the liver, it is commonplace for patients to be discussed and managed in an HPB multidisciplinary team setting.<sup>8</sup> We believe that patients with benign liver tumours should be assessed by the same process.

### Conclusions

Liver resection for benign liver tumours can be undertaken with a mortality rate approaching zero and minimal morbidity in specialist HPB units in order to achieve improvement in symptoms and exclude malignancy.

### Conflicts of interest

None declared.

### References

- McKay A, Dixon E, Taylor M. (2006) Current role of radiofrequency ablation for the treatment of colorectal liver metastases. *Br J Surg* 93:1192–1201.
- Yasui K, Shimizu Y. (2005) Surgical treatment for metastatic malignancies. Anatomical resection of liver metastases: indications and outcome. *Int J Clin Oncol* 10:86–96.
- Karanjia ND, Lordan JT, Fawcett WJ, Quiney N, Worthington TR. (2008) Survival and recurrence after neo-adjuvant chemotherapy and liver resection for colorectal metastases – a 10-year study. *Eur J Surg Oncol*; doi: 10.1016/j.ejso.2008.09.017.
- Fioole B, Kokke M, van Hillegersberg R, Rinkes IH. (2005) Adequate symptom relief justifies hepatic resection for benign disease. *BMC Surgery* 5:5–7.
- Dindo A, Demartines N, Clavien P-A. (2004) Classification of surgical complications. *Ann Surg* 240:205–213.
- Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV *et al.* (1976) Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 34:585–612.
- Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV *et al.* (1977) Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 35:1–39.
- Lordan JT, Karanjia ND, Quiney N, Fawcett WJ, Worthington TR. (2009) A 10-year study of outcome following hepatic resection for colorectal liver metastases – the effect of evaluation in a multidisciplinary team setting. *Eur J Surg Oncol* 35:302–306.
- Belghiti J, Hiramatsu K, Benoist S, Massault PP, Sauvanet A, Farges O. (2000) Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg* 191:38–46.
- Ibrahim S, Chen C-L, Wang S-H, Lin C-C, Yang C-H, Yong C-C *et al.* (2007) Liver resection for benign liver tumours: indications and outcome. *Am J Surg* 193:5–9.
- Terkivatan T, de Wilt JH, de Man RA, van Rijn RR, Zondervan PE, Tilanus HW *et al.* (2001) Indications and longterm outcome of treatment of benign hepatic tumours. A critical appraisal. *Arch Surg* 136:1033–1038.
- Charny CK, Jarnagin WR, Schwartz LH, Frommeyer HS, DeMatteo RP, Fong Y *et al.* (2001) Management of 155 patients with benign liver tumours. *Br J Surg* 88:808–813.
- Marks WH, Thompson N, Appleman H. (1988) Failure of hepatic adenomas (HCA) to regress after discontinuance of oral contraceptives. An association with focal nodular hyperplasia (FNH) and uterine leiomyoma. *Ann Surg* 208:190–195.
- Nagorney DM. (1995) Benign hepatic tumours: focal nodular hyperplasia and hepatocellular adenoma. *World J Surg* 19:13–18.
- Jarnagin WR, Gohen M, Fong Y. (2002) Improvement in perioperative outcome after hepatic resection: analysis of 1803 consecutive cases over the past decade. *Ann Surg* 236:397–407.
- Lordan JT, Karanjia ND, Quiney N, Fawcett WJ, Worthington TR. (2008) Survival after systemic chemotherapy and liver resection for colorectal metastases: a 10-year audit. *HPB* 10 (Suppl 1):65.
- Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P *et al.* (2008) Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup Trial 40983): a randomized controlled trial. *Lancet* 371:1007–1016.
- Lordan JT, Karanjia ND, Quiney N, Fawcett WJ, Worthington TR. (2008) A 10-year study of early outcomes following hepatic resection in a high-volume tertiary referral unit. *HPB* 10 (Suppl 1):203.