



## Original research

## Outcomes of liver resection for haemorrhagic hepatocellular adenoma



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## HIGHLIGHTS

- The role of liver resection for hemorrhagic liver hepatocellular adenoma remains controversial.
- The present study shows that resection of hemorrhagic adenoma can be performed safely in the era of modern liver surgery.
- Young age and lesions located in the anterolateral liver segments seem to be associated with an increases incidence of haemorrhagic complication of hepatocellular adenoma.

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## ABSTRACT

**Background:** Intratumoral bleeding and/or intraperitoneal rupture occurs in up to 20% of patients with hepatocellular adenoma (HCA). Hepatectomy in the presence of haemorrhagic HCA has been associated with increased morbidity and mortality rates. This study evaluates the outcomes of hepatectomy for haemorrhagic HCA at a single institution.

**Methods:** Between January 1997 and December 2012, 52 consecutive patients underwent liver resection for HCA. Among them, 14 patients were resected for haemorrhagic (H)–HCAs (including 9 cases of intratumoural bleeding and 5 cases of intraperitoneal bleeding) and 38 for non-haemorrhagic (NH)–HCAs.

**Results:** The preoperative characteristics were similar between the two groups except for younger age ( $p = .001$ ) and shorter duration of hormonal use ( $p = .001$ ) in (H)–HCAs. There were no mortalities. Intraoperative blood loss, transfusion rate, and postoperative morbidity were comparable between the two groups of patients ( $p = ns$ ). The length of hospital stay was significantly longer in (H)–HCAs ( $p = .03$ ). In all the resected H–HCAs, pathology showed central haemorrhagic changes with tumoral cells at the periphery of the lesions.

**Conclusions:** Liver resection for H- and NH–HCAs can be achieved with no mortality and comparable short-term outcomes.

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## 1. Introduction

Hepatocellular adenoma (HCA) is one of the most common benign liver tumours. It is most prevalent among young women who use oral contraception. Malignant transformation and tumour

rupture represent the two known life-threatening complications of HCAs. While malignant transformation has recently been associated with the presence of metabolic syndrome in men and mutation in gene coding for  $\beta$ -catenin [1], bleeding complications of HCAs are thought to be related to tumour size and recent hormonal use [2].

A recent systematic review reported a 27.2% rupture rate for HCA [3]. The exact mechanics by which intratumoural haemorrhage and consequent rupture remain not fully explained. Current guidelines call for prophylactic resection of HCAs larger than 5 cm, since they are considered as a risk factor for rupture and malignant

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degeneration [2]. Haemorrhage and consequent rupture have been attributed to specific histological characteristics of HCAs, such as high vascularity, paucity of connective tissue, and lack of a true fibrous capsule [4].

The optimal treatment for ruptured (H) HCAs is not clearly defined. Liver resection, especially in an emergency setting, has historically been associated with increased mortality and morbidity rates [5–7]. Therefore, some recommend delayed hepatectomy after tumour embolization for stabilizing the patient [2,8–10]. Recently, some groups have reported successful non-surgical treatment for patients with ruptured HCAs after embolization alone, with which stable haemostasis was obtained. Some therefore recommend resection only in patients with failed embolization, recurrent bleeding, or tumours larger than 5 cm in diameter because of the risk of malignant degeneration [11–15]. However, defining the exact size of haemorrhagic lesions remains difficult, because tumour burdens are often hidden by parenchymal haemorrhagic changes. The aim of the present study is to update clinical outcome data on a series of hepatectomies for haemorrhagic HCAs.

## 2. Patients and methods

The prospective Hepato-Pancreato-Biliary (HPB) database maintained at the Department of HPB Surgery and Liver Transplantation of the University of Strasbourg was searched to identify patients who underwent surgical resection for hepatocellular adenomas between January 1997 and December 2012. The following variables were retrospectively collected and analysed: age, sex, symptoms, body mass index, use and duration of oral contraceptives, gestational status, number and size of HCAs, presence of malignancy, presence and type of haemorrhagic complication (intratumoural or intraperitoneal), use of interventional procedures or red blood cell transfusion, type of resection, and surgical approach (laparoscopy versus laparotomy).

Briefly, the indications for elective resection were established during a weekly multidisciplinary meeting among surgeons, a gastroenterologist, and a radiologist. Because of the potential risk of degeneration and bleeding, surgery was indicated for all patients with solitary lesions larger than 5 cm and in patients with multiple lesions for all tumours larger than 5 cm [9]. In the case of haemorrhagic lesions, surgical treatment was tailored according to the lesion characteristics and patient conditions. All haemodynamically stable patients with signs of previous intratumoural haemorrhage (haematoma without active bleeding) were considered for elective resection. Resection was considered only upon obtaining haemodynamic stability in patients with ruptured HCAs and/or intraperitoneal bleeding, and/or intralesional active extravasation showing contrast at preoperative imaging.

The postoperative morbidity and 90-day mortality were recorded according to the Dindo-Clavien classification [16] with major morbidity defined as grade III or higher. Liver failure was defined as serum bilirubin  $>50 \mu\text{mol/L}$  and prothrombin time  $<50\%$  on postoperative day 5 [17]. Bile leaks were defined as bilious discharge from operatively or radiologically placed drains [18]. The technique and details of liver resection were described previously. The extent of liver resection was defined according to the Brisbane classification [19].

The laparoscopic approach to liver resection was introduced in the last ten years of the study period and was used for lesions located in segments 2, 3, 4b, 5, and 6 and according to the surgeon's experience.

## 3. Statistical analysis

In order to assess differences in postoperative outcomes, the

patient population was divided into two groups: patients operated on for H-HCAs and for NH-HCAs. Normal distributed data were expressed as mean values  $\pm$  SD, and non-normally distributed data were expressed as median (range). Categorical variables were analysed using the chi-squared test or Fisher exact test. Continuous variables were analysed using the student's *t* test or the Mann-Whitney *U* test. A *P* value less than 0.05 was considered significant. Statistical analyses were performed with Statview (Abacus Concepts Inc., Berkeley, CA, USA).

## 4. Results

### 4.1. Preoperative characteristics

In the study period, 52 consecutive patients (5 male) with a median age of 38 years (range: 15–57) underwent liver resection for HCAs. Twenty-nine (55.7%) were overweight or obese. Forty-four women (84.6%) were of reproductive age, one (2.1%) was in the last trimester of her pregnancy, thirty-three (70.2%) had a previous history of contraceptive use, and seventeen (36.1%) were on hormonal contraceptives at the time of diagnosis. Lesions were asymptomatic and incidentally discovered in 17 patients, while the remaining lesions were symptomatic.

Right upper quadrant pain was the most commonly reported symptom (89.1%). The majority of patients (83%) had liver lesions discovered at an initial abdominal ultrasound examination (84.6%) or in abdominal computed tomography (CT) (15.4%). The majority of patients (88.6%) underwent preoperative hepatic magnetic resonance imaging (MRI). Solitary lesions were present in 24 patients, 19 patients had between 2 and 10 lesions and 9 had more than 10 lesions. The mean ( $\pm$ SD) size of the largest lesion was  $8 \pm 4$  (range: 3–30 cm). Preoperative workup revealed a mild increase of serum gamma glutamine transferase and alkaline phosphatase in 25% of patients and normal serum levels of alpha fetoprotein in all patients. Nine patients had a preoperative tissue biopsy showing the diagnosis of HCA. All of these patients were referred to our department from other institutions, and none who were first referred to our centre had a preoperative biopsy.

Among the 52 patients, 14 (26.9%) presented with H-HCA, five patients had frank rupture with extratumoural haemorrhage, and nine patients presented with signs of previous intratumoural bleeding (intraparenchymal haematoma). Among the patients with H-HCAs, eleven (78.5%) had a previous history of sudden abdominal pain, while five had a history of haemodynamic instability, requiring fluids or blood resuscitation. Nine of these patients had solitary lesions. All of these patients had preoperative CT-scan examinations, and only nine had preoperative hepatic MRIs.

### 4.2. Intraoperative and postoperative outcomes

Among the 52 resected patients, 13.4% (7) had a major hepatectomy, and 13.4% (7) had liver resection performed laparoscopically (one major liver resection). Intermittent pedicle clamping was used in 36 patients, and 16 patients (30.7%) received intraoperative transfusions (9 heterologous, 7 homologous). The overall mean operative time was  $270 \pm 87$  min, and there was no postoperative mortality. The overall rate of morbidity was 13.4% (7 patients), with major morbidity in one patient. The morbidities included recurrent bleeding requiring reoperation (1), pleural effusion (4), urinary tract infection (1), and central line sepsis (1). Histopathologic analysis of the non-tumoural parenchyma demonstrated liver steatosis in 15 patients (28.8%). Malignant degeneration was identified in one male patient (1.9%).

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