

ORIGINAL ARTICLE

# European experience of 573 liver resections for hepatocellular adenoma: a cross-sectional study by the AFC-HCA-2013 study group

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## Abstract

**Background:** Hepatocellular adenoma (HCA) is a benign hepatic lesion that may be complicated by bleeding and malignant transformation. The aim of the present study is to report on large series of liver resections for HCA and assess the incidence of hemorrhage and malignant transformation.

**Methods:** A retrospective cross-sectional study, from 27 European high-volume HPB units.

**Results:** 573 patients were analyzed. The female: male gender ratio was 8:2, mean age: 37 ± 10 years. Of the 84 (14%) patients whose initial presentation was hemorrhagic shock (Hemorrhagic HCAs), hemostatic intervention was urgently required in 25 (30%) patients. No patients died after intervention. Tumor size was >5 cm in 74% in hemorrhagic HCAs and 64% in non-hemorrhagic HCAs ( $p < 0.001$ ). In non-hemorrhagic HCAs ( $n = 489$ ), 5% presented with malignant transformation. Male status and tumor size >10 cm were the two predictive factors. Liver resections included major hepatectomy in 25% and a laparoscopic approach in 37% of the patients. In non-hemorrhagic HCAs, there was no mortality and major complications occurred in 9% of patients.

**Discussion:** Liver resection for HCA is safe. Presentation with hemorrhage was associated with larger tumor size. In males with a HCA >10 cm, a HCC should be suspected. In such situation, a preoperative biopsy is preferable and an oncological liver resection should be considered.

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Hepatocellular adenoma (HCA) is a rare liver tumor with malignant potential. The annual incidence is estimated to be 1/10<sup>6</sup> in historical epidemiological studies.<sup>1,2</sup> Histologically, HCA is a benign tumor composed of hepatocytes growing in a normal or near normal liver.<sup>3,4</sup> Although the exact pathophysiological mechanisms remain unknown, the use of oral contraceptives (OCs)<sup>1</sup> has been recognized as the main factor associated with the occurrence of HCAs. Other factors include anabolic steroids exposure and rare pathological conditions including in Fanconi Anemia,<sup>5</sup> glycogen storage disease types I, III and IV<sup>6</sup> and familial adenomatous polyposis.<sup>7</sup>

Recently, a French group described a genotype/phenotype classification of HCA into four subgroups closely related to clinical, pathological and radiological features: HCA mutated for HNF1A, HCA with activating mutations of  $\beta$ -catenin, inflammatory HCA and unclassified HCA.<sup>7</sup> HNF1A mutated HCAs are characterized by the presence of steatosis and HNF1A germline mutations pre-dispose patients to MODY 3 diabetes and familial adenomatosis. Inflammatory infiltrate, sinusoidal dilatation and dystrophic arteries all characterize inflammatory HCA. As reported recently, an association between obesity and inflammatory HCA has been identified.<sup>7,8</sup> Finally, HCA with activating mutations of  $\beta$ -catenin have a higher risk of malignant transformation.

HCAs are usually discovered either incidentally on abdominal imaging performed for unrelated reasons or for liver function test abnormalities. Alternatively, symptoms including right upper quadrant pain or discomfort or palpation of an abdominal mass may precipitate investigation. Rarely patients can present acutely with symptoms and signs of tumor hemorrhage. In contrast to focal nodular hyperplasia it can be difficult to definitively diagnose HCA on imaging alone. In the presence of a solid liver mass other diagnoses need to be considered. In males, this includes well differentiated hepatocellular carcinoma (HCC). For these reasons, pathological examination remains the gold standard and therefore is recommended to confirm an accurate diagnosis.<sup>9</sup>

Most studies report single-center experiences in the clinical management of HCA, and therefore include only a limited number of patients.<sup>10–15</sup> Therefore the AFC-HCA-2013 study group was created in 2010, under the hospitals of the French Association of Surgery (AFC), to produce a retrospective registry of HCA patients who had undergone surgery. The aim of the present study is to describe presentation, surgical outcomes and incidence of malignant transformation in patients undergoing hepatic resection for HCA.

## Patients and methods

### Population study

The target population included all patients who had undergone a liver resection between 1986 and 2013, in a HPB surgical center identified by an individual member of the Association Française de Chirurgie (AFC), for a proven or suspected HCA.

Hemorrhagic HCA is a potentially life-threatening situation with a unique presentation therefore patients were divided into two groups: hemorrhagic HCAs and non-hemorrhagic HCAs. The Amsterdam bleeding classification was used to describe hemorrhagic HCAs: grade I (intratumoral bleeding), grade II (intrahepatic bleeding) or grade III (extrahepatic i.e. bleeding into the peritoneal cavity).<sup>16</sup>

Liver resection was classified according to Brisbane's classification.<sup>17</sup> Perioperative mortality was defined as mortality that occurs during the same hospitalization or within 90 days. Perioperative morbidity was defined according to Clavien<sup>18</sup> and classified as follow: minor morbidity as grade I or II and major morbidity as grade III or IV.

### Data collection

A retrospective cross-sectional study, was initiated in January 2010 when a questionnaire was sent to 117 HPB European surgical centers. This questionnaire included items concerning medical history, biology, radiology, pathology and surgery.

All statistical analyses were performed using R (version 3.1.1 – R Foundation for Statistical Computing). The Chi-square test was used to compare the categorical data whereas the Mann-Whitney U-test was used to compare contiguous variables. Multivariate analyses were performed using a logistic regression to identify predictive factors of HCC. A p value of <0.05 was considered as statistically significant.

## Results

Twenty seven (23%) of 117 HPB European surgical centers responded. Six hundred and twenty-two patients dataset were returned (Fig. 1), with a median of 8 patients (IQR: 4–33) per centers.

### Hemorrhagic HCAs

For 84 (15%) patients the first symptom was hemorrhagic shock. Patients and tumor factors features are reported in Table 1.

Twenty seven (32%) patients received a transfusion of packed red blood cells (median 1, range: 1–3). All patients underwent contrast enhanced CT scan. Based on this CT scan, the hemorrhagic HCAs were grade II or grade III in 51 (61%) and 33 (39%) patients, respectively.

After initial management, 44 patients (52%) had no further treatment. Fifteen (18%) patients, required additional arterial embolization was performed.

A hemostatic intervention was urgently required in the 25 (30%) patients including upfront laparotomy in 11 (13%) patients, and arterial embolization in 14 (17%) patients. All were grade III and required transfused. In two (14%) patients, arterial embolization was ineffective and an urgent hepatectomy was performed.

All 13 patients that required emergency surgical hemostasis were performed after the year 2000. In these thirteen patients, the median size of the largest HCA was 9.0 cm (: 4–15). Eight (51%)

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