Research article

JHEP|Reports

Long-term outcomes following resection of hepatocellular adenomas with small foci of malignant transformation or malignant adenomas

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JHEP Reports **2021.** https://doi.org/10.1016/j.jhepr.2021.100326

Background & Aims: Malignant transformation of hepatocellular adenoma (MT-HCA) may occur in up to 5% of tumours. However, the prognostic value of this event remains poorly described. In this study, we aimed to analyse the long-term outcomes of patients undergoing liver resection (LR) for MT-HCA compared to those of patients resected for hepatocellular carcinoma (HCC) occurring on normal liver parenchyma (NP-HCC).

Methods: This single-centre retrospective study included all patients who underwent LR for MT-HCA at Beaujon Hospital between 2001 and 2019. MT-HCAs were classified as small foci of malignant transformation HCA (SF-HCA) and as malignant HCA (M-HCA) in cases of predominant HCC foci. Recurrence-free survival (RFS) of MT-HCA was compared with that of NP-HCC after propensity score matching.

Results: Forty patients (24 men, 16 women) underwent LR for MT-HCA, including 23 with SF-HCA and 17 with M-HCA. Of these cases, 16/40 (40%) had β-catenin mutations, 19/40 (47.5%) were inflammatory, 1 was HNF1α-mutated HCA and 4 (10%) were unclassified HCA. Microvascular invasion (12% *vs.* 0%, $p = 0.091$) and satellite nodules (25% *vs.* 4%, $p = 0.028$) were more frequently observed in M-HCA than in SF-HCA. After a median follow-up of 67 months, 10 (25%) patients with MT-HCA had tumour recurrence, including 9 with M-HCA and 1 with SF-HCA ($p = 0.007$). M-HCA was linked to significantly poorer 1-, 3-, 5- and 10-year RFS rates than SF-HCA (76%, 63%, 39%, 37% *vs.* 100%, 100%, 100%, 91%, $p = 0.003$). Multivariate analysis showed that SF-HCA was independently associated with improved RFS (hazard ratio 0.064; 95% CI 0.008–0.519; $p = 0.01$). After propensity score matching, NP-HCC was associated with significantly poorer 1-, 3-, 5- and 10-year RFS rates than MT-HCA ($p = 0.01$).

Conclusions: HCA with malignant transformation yields a better long-term prognosis than NP-HCC. Among MT-HCA, SF-HCA is associated with a better prognosis than M-HCA.

Lay summary: The prognostic relevance of malignant transformation of hepatocellular adenoma (HCA) remains unknown. Thus, the aim of our study was to compare the outcomes of patients undergoing liver resection for malignant transformation to those of patients undergoing liver resection for hepatocellular carcinoma (HCC). The main long-term risk after resection for carcinoma is recurrence. In this study, 10/40 patients with malignant transformation of HCA relapsed after resection and we identified age >55 years, presence of satellite nodes, and microvascular invasion as risk factors for long-term recurrence. Compared to patients with HCC, patients who underwent liver resection for HCA with malignant transformation had better long-term survival.

Introduction

Hepatocellular adenoma (HCA) is a group of rare benign liver tumours that mainly occur in women using oral contraception.[1] The occurrence of HCA has also been associated with metabolic syndrome, diabetes, and the use of androgens.[2] The main complications of these tumours include malignant transformation, which occurs in 3–5% of cases,[3–6] and haemorrhage in 10–20% of cases.[7] Historically, size (HCA larger than 5 cm) or the presence of β-catenin mutations in women or HCA occurring in men were recognized as the main indications for liver resection to prevent malignant transformation.[8] The recent discovery that specific

Keywords: Hepatocellular adenoma; malignant transformation; liver resection; recurrence.

Received 6 January 2021; received in revised form 12 May 2021; accepted 11 June 2021; available online 29 June 2021

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mutations cause specific phenotypes has led to changes in the management of HCA.[9] The current molecular classification of HCA defines 6 major subgroups: hepatocyte nuclear factor 1 A-mutated hepatocellular adenoma (H-HCA), inflammatory HCA (IHCA), β-catenin-mutated HCA (β-HCA), including exon 3 and exons 7-8 *CTNNB1* mutations, sonic hedgehog HCA (Sh-HCA) and unclassified HCA (U-HCA).[10–13] Of these, exon 3-mutated β-catenin-IHCA is reportedly associated with a higher risk of malignant transformation into hepatocellular carcinoma (HCC).[14]

In the event of malignant transformation, discriminating HCA from very well-differentiated HCC by morphological imaging or histology of tumour biopsy, remains challenging, especially in men, and even for expert pathologists.[15] Hence, the diagnosis of malignant transformation of HCA (MT-HCA) is often secondary to the discovery of pathological features of HCA in patients undergoing liver resection for HCC or to the presence of HCC foci on preoperative biopsies or resected specimens of patients operated on for HCA. Nevertheless, the clinical implications of MT-HCA remain poorly described, and the long-term prognosis of these lesions has never been assessed. In this setting, the aim of the present study was to evaluate the long-term risk of recurrence in patients with MT-HCA following liver resection compared to that in patients with HCC occurring on normal parenchyma (NP-HCC), using propensity score matching.

Patients and methods

Study population

All consecutive patients who underwent hepatectomy for MT-HCA at Beaujon Hospital between 2001 and 2019 were included in this study and retrospectively analysed. Recorded data included clinical, radiological, perioperative and pathological characteristics along with long-term follow-up. The long-term outcomes of MT-HCA patients were compared to those of patients undergoing liver resection for NP-HCC between 2012 and 2017 (Fig. 1).

This study complied with the ethical guidelines of the 1975 Declaration of Helsinki. Given the purely observational nature of the study and because no patient was contacted for the purpose of this study, informed written consent was waived according to French legislation.

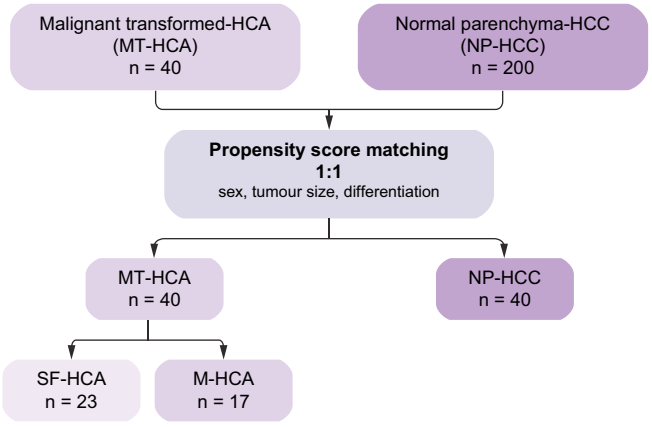

Fig. 1. Study flowchart. HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; SF-HCA, small foci of malignant transformation HCA.

Radiological assessment

Radiological assessment was performed on preoperative MRI and included the largest diameter of the tumour and its location. Whenever possible, HCA subtypes were classified on MRI. H-HCA was characterized by the presence of diffuse and homogeneous signal dropout on chemical shift T1-weighted sequences; IHCA was defined by the presence of a marked hyperintense signal on T2-weighted sequences; β-HCA, β-IHCA and U-HCA were non-specific on MRI and showed various degrees of arterial phase hyperenhancement and washout.[16] Features suggestive of malignant transformation were the presence of nodules-in-nodules on T2W and arterial phase and/or washout on delayed phase. Preoperative HCA diagnosis was established by either contrast-enhanced MRI, histological examination on biopsy or both.

Surgical procedure

HCA other than H-HCA and larger than 5 cm in women or HCA regardless of the size in men were always considered for LR. In HCA <5 cm where the liver biopsy showed the presence of β-catenin mutation, liver resection was considered on a case-by-case basis.

All resections were performed with curative intent. Whenever possible, the laparoscopic approach was attempted. Liver transection was performed with the crush-clamp technique or an ultrasonic dissector under low central venous pressure (less than 5 mmHg). Intermittent pedicle clamping was performed in cases of bleeding or routinely in some patients to obtain a bloodless operative field. Major liver resection was defined as the resection of at least 3 segments. Limited liver resection was preferentially used when no MT-HCA was suspected, and anatomical resection was preferred in suspected MT-HCA or in HCC cases.

Pathological findings and HCA subtypes

All 40 resected specimens were analysed to characterize the HCA subtype, map the site of malignant transformation and analyse the adjacent liver parenchyma. For the purpose of this study, MT-HCAs were classified into 2 distinct groups based on histological findings: (i) small foci of malignant transformation HCA (SF-HCA), defined by the presence of small foci of malignancy <1 cm within an HCA, and malignant HCA (M-HCA), defined by the presence of macroscopic malignant HCC nodules larger than 1 cm. HCAs were subtyped according to their pathomolecular classification into telangiectatic/inflammatory, liver fatty acid binding protein (LFABP)-negative steatotic, β-catenin-activated (with or without cell atypia) and unclassified types based on both morphological and immunophenotypical features. Immunohistochemical analysis was performed as previously described[5]: Glutamine synthetase staining was performed routinely to improve the diagnostic accuracy of β-catenin inactivation. For LFABP, staining was considered positive (+) when the protein was expressed in most tumourous hepatocytes, as well as in non-tumorous hepatocytes. SAA was considered positive when at least 10% of tumourous hepatocytes displayed cytoplasmic staining. β-catenin positive staining corresponded to nuclear and cytoplasmic expression independent of the number of tumour-stained hepatocytes. Staining for glutamine synthetase suggestive of β-catenin mutations was considered positive when strong and diffuse expression was observed in the tumour. Glypican-3 staining was positive when tumour hepatocytes displayed membranous and/or cytoplasmic positivity, regardless of the number of stained tumour cells. Non-tumorous liver fibrosis was staged according to Kleiner *et al.*[21]: no fibrosis (stage

0), zone 3 perisinusoidal or portal fibrosis (stage 1), and perisinusoidal and portal fibrosis without bridging (stage 2). No patients had a fibrosis score >2 in this study. Macro- and microvacuolar steatosis in the adjacent liver parenchyma was identified and quantified.

Long-term follow-up

Patients with MT-HCA or HCC were followed-up every 3 months for the first 2 years, then every 6 months for 3 years, and every year thereafter. Clinical examinations and CT or MRI were performed at each visit to detect signs of tumour recurrence.

Statistical analysis

All statistical tests were 2-tailed, and a p value <0.05 was considered statistically significant in all analyses. Continuous variables are presented as median (IQR) and were analysed using the Kruskal–Wallis or Mann-Whitney U test, as appropriate. Categorical variables are shown as numbers with percentages and were compared using $\chi 2$ or Fisher's exact test. For survival estimation, Kaplan-Meier analysis and log-rank tests were performed.

Factors associated with recurrence were identified using conditional backward logistic regression including non-collinear clinically relevant factors. To assess the risk of recurrence independently of preoperative characteristics, a propensity score matching analysis was performed. The propensity score was estimated using a multivariable logistic regression model, with recurrence as the dependent variable and matching variables as covariables: sex, tumour size, and differentiation grade. Matching was performed using 1:1 matching without replacement (greedy matching algorithm), with a calliper width equal to 0.2 of the propensity score. Statistical analyses were performed with SPSS® software version 24.0 (SPSS Inc., an IBM Company, Chicago, Il, USA) and GraphPad Prism 8 Software (GraphPad, La Jolla, CA).

Results

Characteristics of the patients with MT-HCA

The characteristics of the 40 patients with MT-HCA are summarised in Table S1. These included 24 (60%) men and 16 (40%) women. Median age was 54 years (range 40–65). Nine women had a history of oral contraceptive use, and 1 man had a history of steroid use. Median BMI was 25 kg/m^2 (range 22–30). Metabolic syndrome was present in 10 (25%) patients. Five (12.5%) patients had chronic hepatitis B infection, and 1 patient had MODY-3 diabetes.

The median tumour diameter was 8 cm (range 6–11), and 36 (90%) patients had a tumour larger than 5 cm. In 4 patients, 2 women and 2 men, the maximal diameter of the HCA was less than 5 cm. Metabolic syndrome was more frequent in men than in women. The characteristics of MT-HCA according to sex are summarised in Table S3. MT-HCA was solitary in the majority (90%) of patients, and only 4 (10%) patients had multiple HCAs. Preoperative MRI was performed in 33/40 (83%) patients. Features suggestive of malignant transformation, such as nodule-in-nodule appearance on T2W and arterial phase and/or washout on delayed phase, were present in 16 (48%) patients. High preoperative levels of serum alpha fetoprotein were present in 5 (12.5%) patients in the MT-HCA group (80 ng/ml, range 7–2,000). Preoperative biopsy was performed in 22 (55%) patients, and malignant transformation was preoperatively diagnosed on tumour biopsy in 8 (36%) patients. Twenty-two (55%) patients underwent major liver resection.

The malignant component was well differentiated in 25 (62.5%) cases and moderately differentiated in 15 (37.5%) cases. Microvascular invasion was present in 2 (5%) patients, and satellite nodes were present in 6 (15%) patients. Underlying parenchyma showed steatosis in 13 (32.5%) patients, including steatosis >30% in 10 (25%) cases. F2 underlying fibrosis was present in 9 (22.5%) patients. MT-HCA was IHCA, β-catenin-mutated HCA, unclassified HCA and H-HCA in 19 (47.5%), 16 (30%), 4 (10%) and 1 (2.5%) cases, respectively. The type of β-catenin mutation was available for 7 cases: 6 had *CTNNB1* exon 3 mutations, while 1 had *CTNNB1* exon 7 mutations.

Comparison of SF-HCA and M-HCA

On pathological examination, 23/40 (57.5%) and 17/40 (42.5%) patients had SF-HCA and M-HCA (Fig. 2 and 3), respectively. The comparison of their characteristics is summarised in Table 1. SF-

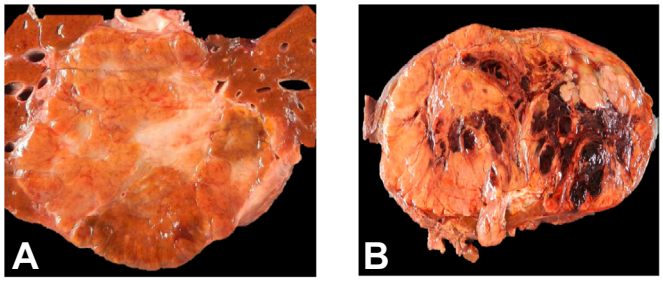

Fig. 2. Macroscopic view of operative specimen. (A) Hepatocellular adenoma with foci malignant area, and (B) well-differentiated hepatocellular carcinoma.

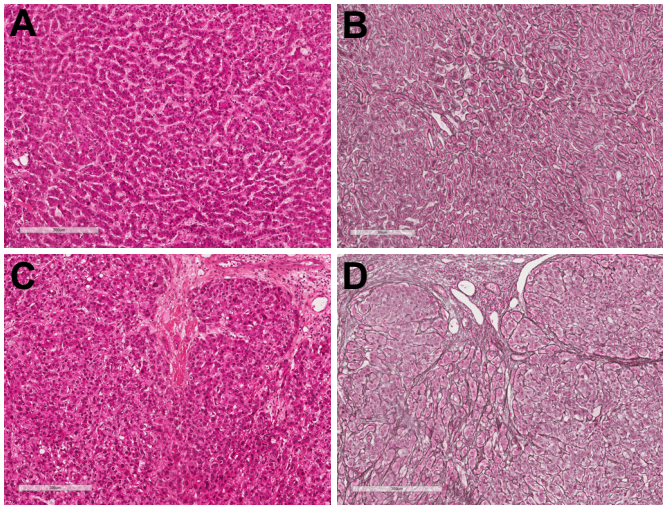

Fig. 3. Pathological features of hepatocellular adenoma with malignant transformation. (A) HES staining: area of hepatocellular adenoma with tumour cells without cytological atypia arranged in thin plates. (B) Reticulin staining: intact reticulin framework with plates of 1 or 2 cells thick. (C) HES staining: area of well-differentiated hepatocellular carcinoma with tumour cells with mild to moderate atypia arranged in thick plates. (D) Reticulin staining: reticulin framework is present but surrounds thick plates of tumour cells (>3 cells thick).

Table 1. Comparison of the characteristics between M-HCA and SF-HCA.

	SF-HCA (n = 23)	M-HCA (n = 17)	*p* value[†]
Age (years)[‡]	51 (36–62)	62 (43–68)	0.095[*]
Sex ratio (M:F)	15 : 8	9 : 8	0.433
BMI (kg/m^2)[‡]	25 (22–30)	27 (23–31)	0.511[*]
>25 kg/m^2	10 (43)	8 (47)	0.822
Comorbidities			
Cardiovascular disease	8 (36)	9 (56)	0.224
Diabetes	7 (31)	1 (6)	0.107
Metabolic syndrome	8 (36)	2 (12)	0.145
Hepatitis B infection	4 (20)	1 (6)	0.355
Alcohol	1 (4)	3 (18)	0.294
Symptoms			
None	16 (70)	13 (76)	0.729
Abdominal pain	4 (17)	3 (17)	0.988
Haemorrhage	3 (14)	1 (6)	0.373
Oral contraception or steroid use	4 (18)	6 (35)	0.274
Adenomatosis	4 (18)	0 (0)	0.134
Maximal diameter of HCA (cm)[‡]	80 (60–100)	100 (55–125)	0.510[*]
≥5 cm	22 (96)	14 (82)	0.294
Tumour location			
Right liver	14 (61)	15 (88)	0.073
Left liver	9 (39)	2 (12)	
HCA subtype			
H-HCA	1 (4)	0 (0)	0.468
IHCA	9 (39)	10 (59)	
β-HCA	7 (30)	5 (29)	
β-IHCA	4 (17)	0 (0)	
U-HCA	2 (9)	2 (12)	
CTNNB1 10/40			
ex 3	2 (9)	6 (35)	0.834
ex 7	0 (0)	1 (10)	
Liver resection			
Laparoscopic	8 (35)	6 (35)	0.973
Conversion	0	1 (6)	0.425
Major resection[#]	11 (48)	11 (65)	0.289
Pringle manoeuvre	16 (70)	13 (76)	0.968
Duration (min)[‡]	32 (5–60)	23 (5–45)	0.459[*]
Blood loss (ml)[‡]	300 (100–1200)	500 (240–975)	0.212[*]
Transfusion[‡]	3 (14)	3 (18)	0.134
Margin (mm)[‡]	10 (3–12)	3 (2–25)	0.728[*]
Operative duration[‡]	225 (170–340)	270 (120–300)	0.245[*]
Postoperative complications			
Dindo-Clavien ≥3	4 (17)	1 (5.9)	0.372
CCI[*]	18.5 ±5.6	8.3 ±3.2	0.265
CV	2 (9)	2 (12)	0.785
Pulmonary	6 (27)	5 (29)	0.790
Sepsis	7 (32)	3 (18)	0.469
Biliary fistula	2 (9)	1 (6)	0.999
PHLF	1 (4)	0 (0)	0.999
Reoperation	3 (13)	1 (6)	0.624
Underlying parenchyma			
Steatosis	11 (47)	10 (59)	0.537
Macrovacuolar steatosis (%)	14 (5–20)	10 (5–30)	0.396[*]
Fibrosis			
F0	15 (65)	7 (41)	0.163
F1-F2	8 (25)	10 (60)	
HCC differentiation[**]			
Grade 1	16 (70)	9 (53)	0.335
Grade 2	7 (30)	8 (47)	
Microvascular involvement	0 (0)	2 (12)	0.184
Satellite nodules	1 (4)	6 (35)	**0.029**
Recurrence	1 (2)	9 (53)	**0.002**
Liver	1 (2)	8 (47)	**0.001**
Other site	0 (0)	1 (6)	0.425
Early recurrence ≤1 year	0 (0)	4 (15)	0.026

Bold *p* values are significant.
β-HCA, β-catenin-mutated HCA; β-IHCA, β-catenin-mutated inflammatory HCA; CCI, comprehensive complication index; CV, cardiovascular; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; H-HCA, HNF1α-mutated HCA; IHCA, inflammatory HCA; LR, liver resection; M-HCA, malignant HCA; PHLF, post-hepatectomy liver failure; SF-HCA, small foci of malignant transformation HCA; U-HCA, unclassified HCA.
[#] Major resection: ≥3 segments.
[**] Edmondson and Steiner grade.
[†] Chi-square test or Fisher exact test.
[*] Mann-Whitney *U* test.
[‡] Values are median (IQR).

Table 2. Pathological features, immunohistochemical markers, molecular classification of patients with MT-HCA, with or without recurrence.

	Recurrence n = 10	No recurrence n = 30	*p* value[†]
HCA subtypes			0.143
H-HCA	0	1	0.727
IHCA	4 (40)	15 (52)	0.727
β-HCA	2 (20)	9 (31)	0.263
β-IHCA	0	2 (5)	0.548
U-HCA	4 (40)	2 (7)	**0.048**
SF-HCA	1	29 (96)	**0.001**
M-HCA	9 (90)	1	
Maximal tumour diameter (cm)[‡]	87 (50–150)	80 (70–110)	0.540[*]
>5 cm	9 (90)	26 (89)	0.975
Microvascular involvement	2 (20)	0	**0.015**
Satellite nodules	4 (40)	2 (8)	**0.039**
Differentiation grade[**]			0.709
1	7 (70)	18 (60)	
2	3 (30)	12 (40)	
Margins (mm)[‡]	6 (2–15)	4.5 (1–13)	0.753[*]
Underlying parenchyma			
Fibrosis F1-F2	6 (60)	12 (40)	0.351
Steatosis	6 (60)	14 (48)	0.716
Inflammatory infiltration	6 (60)	13 (48)	0.451
Hepatocyte Ballooning	1	3 (11)	0.745
Immunohistochemical markers			
FABP1 decrease	2 (20)	3 (10)	0.252
SAA/CRP overexpression	4 (40)	8 (27)	0.819
Nuclear β-cat GS expression increase	4 (40)	10 (34)	0.520
CTNNB1 (n = 10)			
ex 3	2 (20)	6 (20)	0.834
ex 7	0	1	

β-HCA, β-catenin-mutated HCA; β-IHCA, β-catenin-mutated inflammatory HCA; HCA, hepatocellular adenoma; H-HCA, HNF1α-mutated HCA; IHCA, inflammatory HCA; M-HCA, malignant HCA; MT-HCA, malignant transformation of HCA; SF-HCA, small foci of malignant transformation HCA; U-HCA, unclassified HCA.
** Edmondson and Steiner grade.
‡ Values are median (IQR).
† Chi-square test or Fisher exact test.
* Mann-Whitney *U* test.

HCA tended to occur more frequently in the context of metabolic syndrome than M-HCA (34.8% *vs.* 11.8%, $p = 0.097$), while M-HCA was associated with increased rates of pejorative pathologic characteristics, including microvascular invasion (12% *vs.* 0%, $p = 0.091$) and satellite nodules (25% *vs.* 4%, $p = 0.028$).

Recurrence following liver resection for MT-HCA

The median follow-up after liver resection for MT-HCA was 67 (31–115) months. Following liver resection for MT-HCA, 10 (25%) patients experienced tumour recurrence, including 9 in the M-HCA group and 1 in the SF-HCA group ($p = 0.007$). This latter patient had chronic HBV infection and experienced intrahepatic recurrence 7 years after liver resection for a 9 cm SF-HCA. Overall, recurrences were intrahepatic in 8 cases and pulmonary in 2 cases. The comparison of MT-HCA patients experiencing recurrence with those who did not experience recurrence is provided in Table 2. The characteristics of the patients with recurrence are summarised in Table S4.

After liver resection for MT-HCA, the 1-, 3-, 5- and 10-year recurrence-free survival (RFS) rates were 89%, 83%, 72% and 67%, respectively. The comparison of RFS between M-HCA and SF-HCA is provided in Fig. 4A. M-HCA was associated with significantly poorer 1-, 3-, 5- and 10-year RFS rates than SF-HCA

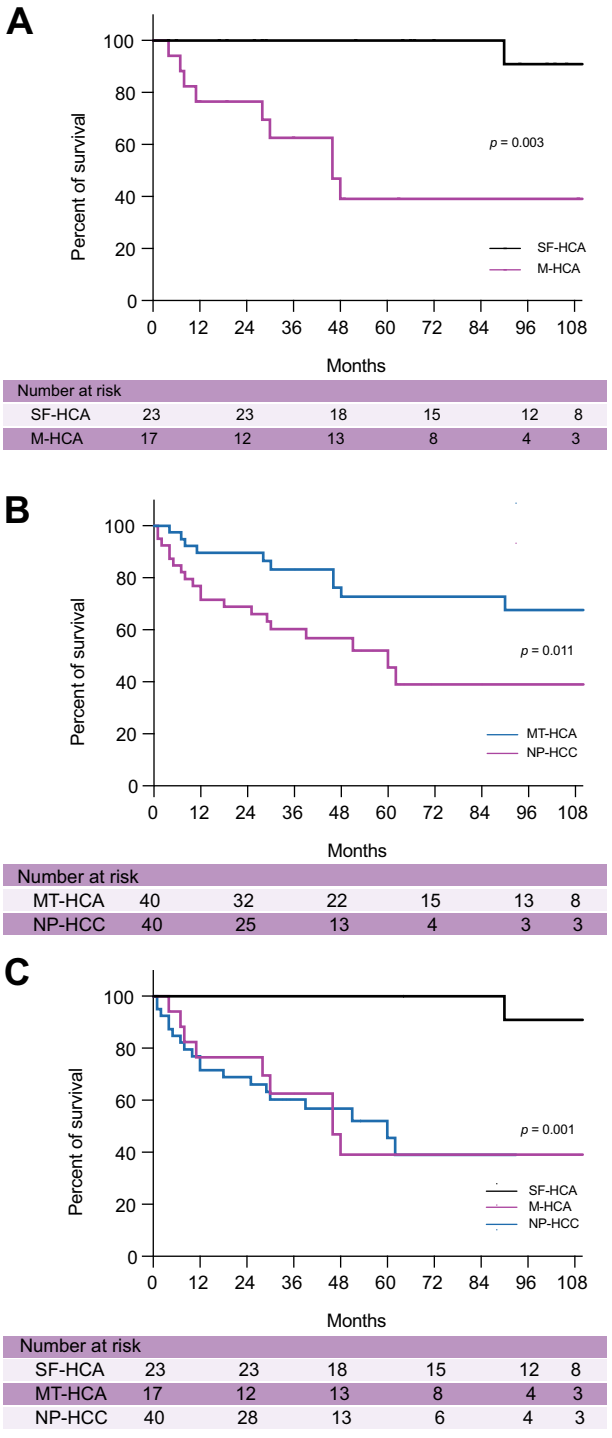

Fig. 4. Kaplan-Meier plots of recurrence-free survival after liver resection. (A) Comparison of SF-HCA to M-HCA. Level of significance: $p = 0.003$ (log-rank test). (B) Comparison of MT-HCA to NP-HCC after matching. Level of significance: $p = 0.011$ (log-rank test). (C): Comparison of SF-HCA, M-HCA and NP-HCC. Level of significance: $p = 0.001$ (log-rank test). HCA, hepatocellular adenoma; M-HCA, malignant HCA; MT-HCA, malignant transformation of HCA; NP-HCC, HCC occurring on normal liver parenchyma; SF-HCA, small foci of malignant transformation HCA.

Table 3. Univariate and multivariate analysis to identify factors associated with recurrence in patients undergoing resection for MT-HCA.

	Univariate analysis		Multivariate analysis	
	OR 95% CI	*p* value	OR 95% CI	*p* value
Age >55 years	8 (1.4–44)	**0.025**	7.5 (1.1–55)	**0.047**
Male sex	0.6 (0.1–3.45)	0.456		
BMI >25 kg/m^2	2.2 (0.5–9.7))	0.300		
Metabolic syndrome	0.6 (0.1–3.9)	0.673		
Hepatitis	2.2 (0.3–16)	0.404		
Hormonotherapy	2.6 (0.6–12.5)	0.206		
Underlying parenchyma				
Steatosis	1.5 (0.3–6.4)	0.721		
Fibrosis	2.1 (0.5–9)	0.465		
M-HCA	24 (2.7–45)	**0.001**	15 (1.7–135)	**0.020**
U-HCA	12 (1.1–26)	**0.017**		
Satellite node	8.3 (1.2–45)	**0.035**	6 (0.6–26)	0.095
Microvascular involvement	4.5 (0.4–21)	0.061	1.4 (0.2–226)	0.458
Differentiation grade	0.5 (0.1–2.4)	0.411		

Multivariate analysis: actors associated with recurrence were identified using conditional backward logistic regression including non-collinear clinically relevant factors. HCA, hepatocellular adenoma; M-HCA, malignant HCA; MT-HCA, malignant transformation of HCA; OR, odds ratio; U-HCA, unclassified HCA.

(76%, 63%, 39%, 37% *vs.* 100%, 100%, 100% 97%, $p = 0.003$). RFS was similar between men and women, and the comparison of RFS according to sex is provided in Fig. S1. Similarly, the comparison of RFS according to the subtype of MT-HCA is provided in Fig. S2.

Univariate and multivariate analyses of the factors associated with recurrence following liver resection for MT-HCA are provided in Table 3. In multivariate analysis, M-HCA (odds ratio 15; 95% CI 1.7–135) and age >55 (OR 7.5; 95% CI 1.1–55) were the only independent risk factors for recurrence.

Comparison with HCC occurring on normal liver parenchyma

Among 200 patients who received NP-HCC resection, 40 could be compared to the 40 patients operated on for MT-HCA after propensity score matching. The comparison of the characteristics of M-HCA and NP-HCC is provided in Table 4 and Table S2. Their characteristics were similar, except for the age of patients (66 *vs.* 53 years, $p = 0.006$), rates of underlying chronic HBV infection (42% *vs.* 14%, $p = 0.006$), rates of underlying F1-F2 fibrosis (67% *vs.* 46%, $p = 0.043$) and rates of microvascular invasion (45% *vs.* 5%, $p < 0.001$), which were higher in M-HCA than in SF-HCA.

The median follow-up after liver resection for NP-HCC was 41 (21–60) months. Overall, NP-HCC patients experienced significantly higher recurrence rates than MT-HCA patients (50% *vs.* 25%, $p = 0.021$). The comparison of 1-, 3-, 5- and 10-year RFS between MT-HCA and NP-HCC is provided in Fig. 4B. MT-HCA had significantly longer 1-, 3-, 5- and 10-year RFS than NP-HCC (89%, 83%, 72%, 67% *vs.* 70%, 60%, 58% 49%, $p = 0.0219$). In more detail, while SF-HCA had significantly better 1-, 3-, 5- and 10-year RFS than NP-HCC (100%, 100%, 100%, 91% *vs.* 70%, 60%, 58% 39%, $p = 0.001$), M-HCA did not have better 1-, 3-, 5- and 10-year RFS than NP-HCC (76%, 63%, 39%, 37% *vs.* 70%, 60%, 58% 39%, $p = 0.988$) (Fig. 4C).

Discussion

The current study, which is the largest monocentric series focusing on MT-HCA and the first to assess long-term recurrence and prognosis after liver resection, showed that MT-HCA yields an overall better prognosis than NP-HCC. Specifically, the results of this study demonstrate that classifying MT-HCA into SF-HCA and M-HCA has a prognostic impact and reaffirms the need for early management of HCA at risk of malignant transformation.

Hepatocellular adenoma mainly develops in young patients, and MT-HCA is a rare complication occurring in 3 to 5% of cases.[4,10] The exact mechanism of malignant transformation of HCC is still unknown, and the preoperative diagnosis of malignant transformation of HCA remains challenging. Estimating the risk of recurrence of these patients, who are mostly young, after hepatectomy is critical for follow-up management. The risk of malignant transformation in the literature is associated with male sex, tumour size, metabolic syndrome, and β-catenin subtype of HCA.[5] In this study, patients with MT-HCA were mostly men (60%), with a mean age of 54 years, which is higher than in patients with non-MT-HCA in a large series.[17] In this population of 40 MT-HCA patients, the main subtypes were IHCA (50%) and β-catenin subtype (30%), including 8 patients with a *CTNNB1* exon 3 and 1 patient with a *CTNNB1* exon 7 mutation, which is consistent with previous findings.[5] Only 1 patient had the H-HCA subtype, which confirms the extremely low risk of malignant transformation in this subtype despite their higher incidence.[18]

Determining whether the HCA subtype may influence long-term prognosis could be of clinical interest. In the present study, there was a tendency towards a higher risk of recurrence for U-HCA and poorer survival for U-HCA and β-HCA. In contrast, the results of the multivariate analysis highlighted that the risk of recurrence was significantly higher for M-HCA than for SF-HCA. Interestingly, only 1 patient experienced recurrence in the SF-HCA group, and both context (chronic HBV infection) and timing of recurrence suggest that this recurrence could in fact be considered *de novo* HCC occurring from chronic liver disease. Analogous to the various classifications for other types of cancers, SF-HCA, which did not show any microvascular invasion, could thus account for the "*in situ*" subset of MT-HCA, while M-HCA could represent overt carcinomas. In fact, when compared with matched NP-HCC, M-HCA did not show a better prognosis than NP-HCC, while SF-HCA did. These results may allow a less stringent follow-up in cases of SF-HCA, while M-HCA would require similar follow-up as classical HCCs. In the same manner, liver transplantation could be considered in young M-HCA patients showing features of poor prognosis, such as large size or microvascular invasion.

Recently, a new subtype of HCC defined as "atypical large well-differentiated HCC" beyond 3 cm was reported.[19] In typical HCC, tumour evolution follows an increase in size and a dedifferentiation stage.[20] One of the hypotheses is that atypical large

Table 4. Comparison of patients with MT-HCA and NP-HCC after propensity score matching.

	MT-HCA (n = 40)	NP-HCC (n = 40)	*p* value[†]
Age, year[‡]	53 (40–64)	66 (50–71)	**0.006**[*]
Sex ratio (M:F)	23 : 17	30 : 10	0.155
BMI (kg/m^2)[‡]	25 (21–27)	24 (21–27)	0.137[*]
18-24.9	16 (44)	20 (54)	0.284
25-29.9	11 (30)	13 (35)	
>30	9 (22)	4 (11)	
Comorbidities			
Cardiovascular disease	3 (7)	5 (12)	0.286
Diabetes	8 (20)	15 (37)	0.137
Metabolic syndrome	10 (25)	16 (40)	0.152
Hepatitis B infection	5 (14)	17 (42)	**0.006**
Alcohol	4 (10)	4 (10)	0.644
Symptoms			
None	36 (90)	34 (85)	0.496
Abdominal pain	3 (7)	5 (12)	0.571
Haemorrhage	1 (2)	1 (2)	0.429
Oral contraception or steroid use	10 (25)	4 (5)	**0.001**
Maximal diameter of HCA (cm)[‡]	80 (60–117)	82 (46–130)	0.368[*]
≥5 cm	36 (90)	32 (80)	0.241
Tumour location			
Right liver	29 (72)	23 (57)	0.241
Left liver	11 (28)	17 (43)	
HCA subtype			
H-HCA	1 (2)	NA	
IHCA	19 (47)		
β-HCA	12 (30)		
β-IHCA	4 (10)		
U-HCA	4 (10)		
Liver resection			
Laparoscopic	14 (35)	10 (25)	0.329
Conversion	1 (2)	4 (10)	0.359
Major resection[#]	22 (55)	23 (57)	0.822
Pringle manoeuvre	29 (72)	27 (68)	0.968
Duration, min[‡]	24 (5–45)	28 (5–45)	0.393[*]
Blood loss (ml)	300 (240–975)	400 (200–500)	0.379[*]
Transfusion, n (%)	6 (15)	6 (15)	0.968
Margin (mm)[‡]	6 (2–14)	7 (2–15)	0.181[*]
Operative duration	247 (165–300)	240 (170–300)	0.852
Postoperative complications			
Dindo-Clavien ≥3	5 (12)	10 (25)	0.168
CCI[*]	14.1 ±3.6	19.9±3.5	0.260
CV	4 (10)	5 (12)	0.500
Pulmonary	11 (28)	11 (28)	0.599
Sepsis	10 (25)	5 (12)	0.152
Biliary fistula	3 (7)	3 (7)	0.652
PHLF	1 (2)	1 (2)	0.753
Reoperation	4 (10)	4 (10)	0.644
Underlying parenchyma			
Steatosis	21 (52)	13 (32)	0.113
Macrovacuolar steatosis (%)	14 (5–30)	8 (5–10)	0.396
Fibrosis			
F0	24 (54)	13 (33)	
F1	9 (23)	16 (40)	
F2	9 (23)	11 (27)	0.067
HCC differentiation[**]			
Grade 1	25 (62)	22 (55)	0.264
Grade 2	15 (38)	18 (45)	
Microvascular involvement	2 (5)	18 (45)	**0.001**
Satellite nodules	6 (16)	8 (20)	0.667
Recurrence	10 (25)	20 (50)	**0.021**
Liver	8 (20)	10 (25)	**0.001**
Other site	2 (6)	10 (25)	

Bold *p* values are significant.
β-HCA, β-catenin-mutated HCA; β-IHCA, β-catenin-mutated inflammatory HCA; CCI, comprehensive complication index; CV, cardiovascular; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; H-HCA, HNF1α-mutated HCA; IHCA, inflammatory HCA; MT-HCA, malignant transformation of HCA; NP-HCC, HCC occurring on normal liver parenchyma; PHLF, post-hepatectomy liver failure; U-HCA, unclassified HCA.
[#] Major resection: ≥3 segments.
[**] Edmondson and Steiner grade.
[‡] Values are median (IQR).
[†] Chi-square test or Fisher exact test.
[*] Mann-Whitney *U* test.

well-differentiated HCC develops on HCA with β-catenin mutations and that *TERT* promoter mutations predispose patients to malignant transformation.[21] Atypical HCC developed on normal liver parenchyma could represent the end of the spectrum.[22] In another study, HCC with *CTNNB1* mutation was reported to be large, well-differentiated HCC and to have better prognostic factors.[23] Although no significant differences were observed regarding subtype between SF-HCA and M-HCA in the present study, further genetic analyses are required to determine the precise mechanisms leading to the progression towards M-HCA.

Naturally, the present study has various limitations. First, the retrospective nature and the long study period, during which imaging modalities and perioperative management dramatically changed, may have led to substantial biases in the interpretation of the results.[24,25] MRI with hepato-specific contrast agent was not available for all patients. In addition, despite significant progress related to advances in radiological diagnostics, MRI hepato-specific contrast agents are not always able to confirm the presence of malignant transformation.[26] MR imaging is accurate for HCA subtyping and is associated with the 2 most common subtypes, H-HCA and IHCA. The sensitivity and specificity of MRI have been reported to reach 90% but not for the other HCA subtypes.[27,28]

Second, the definitions of SF-HCA and MT-HCA were retrospectively determined on operative specimens and defined by the extent of the malignancy foci area. Because not all of the specimens analysed had a molecular analysis and given the length of the study period, this fact should be considered a potential bias, despite immunohistochemistry being available for all of the specimens analysed.

In conclusion, patients with MT-HCA had different clinical, epidemiologic and tumour characteristics compared to patients with HCC that developed on preserved liver parenchyma. Recurrence occurred after liver resection for MT-HCA in 10 patients. Patients with MT-HCA had favourable prognostic factors and had longer RFS after liver resection than patients with NP-HCC. However, the low number of patients included prevents any solid conclusion regarding this finding. Risk factors for recurrence after liver resection were tumour size, presence of satellite nodes and presence of microvascular invasion and were similar between MT-HCA and NP-HCC. A less stringent follow-up may be acceptable in cases of SF-HCA, while M-HCA should require similar follow-up as classical HCCs based on these results.

Abbreviations

β-HCA, β-catenin-mutated HCA; β-IHCA, β-catenin-mutated inflammatory HCA; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; H-HCA, HNF1α-mutated HCAs; IHCA, inflammatory HCA; LFABP, liver fatty acid binding protein; LR, liver resection; MT-HCA, malignant transformation HCA; NP-HCC, HCC occurring on normal parenchyma; RFS, recurrence-free survival; SF-HCA, small foci of malignant transformation HCA; U-HCA, unclassified HCA.

Financial support

There was no funding associated with the completion of the work.

Conflicts of interest

The authors declare no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Participated in research design: SC, FC, OS, NP, MR. Participated in writing of the paper: SC, FC, CH, MR, SD, OF. Participated in performing the research: MB, VV, VP, MR. Contributed new reagents or analytic tools: SC, FC, CH, NP, OF, SD

Participated in data analysis: SC, CH, FC, OS. All authors revised the manuscript critically. All authors read and approved the final manuscript.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Disclaimer

This work was presented as an oral communication at the National Congress of the French Association of Hepatobiliary, Pancreatic Surgery and Transplantation (ACHBT), Paris, November 2019.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2021.100326.

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