Clinicopathological features and post-resection outcomes of hepatocellular adenoma

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Backgrounds/Aims: Hepatocellular adenomas (HCA) are rare benign liver tumors with the potential of malignant transformation and risk of bleeding. We investigated the clinicopathological features and outcomes of HCA in 19 patients who underwent surgical resection.

Methods: This retrospective observational study included 19 patients who underwent hepatic resection during a 9-year period from 2011 to 2019.

Results: The incidence of HCA was 0.18% of all hepatic resection cases during the study period. The mean age of the patients was 34.3±9.6 years, and 12 patients (63.2%) were female. Abdominal pain was present as initial clinical manifestation in 5 patients and the other 14 patients had no specific symptoms. HCA was diagnosed in 7 out of 8 patients who underwent liver biopsy. R0 resection was performed in 18 patients (94.7%) and laparoscopic liver resection was performed in 11 patients (57.9%). The mean tumor size was 5.6±3.6 cm and 17 patients had a single tumor. Immunohistochemical analysis of the resected tumor specimens revealed hepatocyte-nuclear-factor-1α mutated HCA in 2 (10.5%), β-catenin-mutated HCA in 2 (10.5%), inflammatory HCA in 12 (63.2%) and unclassified HCA in 3 (15.8%). There were no pathognomonic findings in the preoperative liver imaging studies among these four groups. Currently, all patients are alive with a mean follow-up period of 40.1±26.3 months. One patient showed residual tumors after incomplete resection.

Conclusions: Surgical resection may be indicated if imaging studies show diagnostic ambiguity, growing tumor or symptomatic mass. Because of the risk of tumor recurrence and malignant transformation, long-term follow-up is necessary. (Ann Hepatobiliary Pancreat Surg 2021;25:25-33)

Key Words: Malignant potential; Focal nodular hyperplasia; Bleeding; Resection; Abdominal pain

INTRODUCTION

Hepatocellular adenomas (HCA) are rare benign liver tumors with the potential of malignant transformation and risk of bleeding. Epidemiologic studies report the prevalence of HCA as approximately 3-4 cases per 100,000 people in Europe and North America,¹ and lower prevalence in Asian countries.² The highest prevalence has been described in females taking oral contraceptives, but other risk factors, such as anabolic steroid use, obesity and metabolic syndrome have also been defined.²³

In 2006, four subtypes of HCA have been proposed, which were based on genotype-phenotype analyses.⁴ Of them, the β-catenin-mutated subtype is known to be associated with an increased risk of malignant transformation into hepatocellular carcinoma (HCC).⁵⁸ Approximately 9% of HCA may transform into HCC with risk factors including male sex, androgen use, large tumors (> 5 cm) and β-catenin-mutated HCA.⁹

The diagnostic workup of HCA is mainly based on cross-sectional imaging studies, of which magnetic resonance imaging (MRI) and computed tomography (CT) are commonly used to assess this lesion. The most sensitive method to differentiate ICA from other similar intrahepatic mass is MRI with hepatobiliary contrast.¹⁰⁻¹² If the findings of imaging studies are inconclusive, a percutaneous liver biopsy may be necessary for the final diagnosis.¹³
In the present study, the clinicopathological features and outcomes of HCA in 19 patients who underwent surgical resection were investigated.

MATERIALS AND METHODS

Patients

The primary liver cancer database at our institution was extensively searched to identify patients diagnosed with HCA following hepatic resection. We identified 19 patients over a 9-year period from January 2011 to December 2019. During this study period, 10,753 cases of hepatic resection were performed for patients with various diseases in our institution; these 19 cases of HCA comprised approximately 0.18% of all the hepatic resection cases.

The medical records of the patients were retrospectively reviewed following the approval of the Institutional Review Board at our institution (IRB No. 2019-1347), which waived the requirement for informed consent due to the retrospective nature of the study. This study was performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki 2013. The patients were followed up until August 2020 by medical record review and with the assistance of the National Health Insurance Service.

Preoperative evaluation, surgical procedures, and postoperative follow-up

Routine preoperative evaluation for primary liver tumors has been described elsewhere. In general, the hepatic resection patients with borderline malignancy were followed up every 3-4 months during the first year after surgery and every 3-6 months thereafter. The general principles for the treatment of recurrent liver tumors were applied to our patients.

Pathological diagnosis

Four subtypes of HCAs are recognized based on genotype-phenotype analyses: hepatocyte-nuclear-factor-1α mutated (H-HCA), β-catenin-mutated type with upregulation of glutamine synthetase (b-HCA), inflammatory type with serum-amyloid-A overexpression (I-HCA), and unclassified type (u-HCA). Inactivating mutations in the HNF1A (TCF1) gene lead to loss of hepatocyte nuclear factor 1α (HNF-1α) expression define H-HCA, which are characterized histologically by marked steatosis and bland hepatocyte cytology. Activating mutations of β-catenin (b-HCA) are associated with an increased risk of malignant transformation into HCC. Histologically, I-HCA is marked by inflammatory infiltrates or telangiectatic features with increased expression of serum amyloid A and C-reactive protein (CRP). A small proportion of HCA does not appear to fall into any of the above categories and was considered unclassifiable by current testing approaches (u-HCA).

The immunohistochemical analysis includes staining with serum amyloid A, liver fatty acid-binding protein, glutamine synthetase, β-catenin, Ki-67, cytokeratin 19, CD34, CRP and reticulin. Liver fatty acid-binding protein-negative cases were classified as H-HCA. HCA with strong and diffuse glutamine synthetase staining and/or β-catenin nuclear staining, regardless of the serum amyloid A staining status, was categorized as b-HCA. The remaining HCA with serum amyloid A positivity was classified as I-HCA.

Statistical analysis

Numeric data are presented as means and standard deviation or as median and range. As there were no cases of tumor recurrence, survival analysis was not performed. Statistical analyses were performed using SPSS version 22 (IBM, New York, NY).

RESULTS

Patient demographics and preoperative diagnosis

The clinicopathological features of the 19 patients with HCA are presented in Table 1. The mean age of the patients was 34.3±9.6 years (range: 17-56 years), and 12 patients (63.2%) were female. Hepatitis B virus (HBV) infection was present in one patient, and none of the patients had hepatitis C virus infection or non-viral liver cirrhosis. Abdominal pain was present as an initial clinical manifestation in 5 patients. The other 14 patients had no specific symptoms and the liver mass was detected incidentally on routine health screening or surveillance for other diseases.

In 8 patients who were suspected with HCA, percutaneous liver biopsy showed HCA-compatible pathological findings in 7 patients and no mass was identified in 1
Table 1. The clinicopathological features of the 19 patients with hepatocellular adenoma

| Case No. | Sex | Age (yrs) | Initial findings | Clinical diagnosis | Liver biopsy | AFP (ng/ml) | PIVKA-II (mAu/ml) | Extent of resection | Type of operation | Tumor size (cm) | Tu- mor duration (mos) | Follow-up | Survival status | Tumor recurrence |
|----------|-----|-----------|------------------|-------------------|-------------|------------|-----------------|-------------------|------------------|----------------|---------------------|----------|----------------|---------------|
| H-HCA_1  | F   | 43        | Abdominal pain, SPK | HCC, HCA | No mass | 1.7        | 42              | 25.4             | LMS              | Open            | 3                   | 1       | 13             | Alive        | No             |
| H-HCA_2  | F   | 40        | Health screening   | HCC, HCA | HCA | 2.7        | 27              | 14               | LH               | Laparoscopy      | 2.9                   | 1      | 14             | Alive        | No             |
| B-HCA_1  | F   | 25        | Abdominal pain     | FNH, HCA | HCA | 3.5        | 155             | 7.6              | RH               | Laparoscopy      | 7.6                   | 1      | 42             | Alive        | No             |
| B-HCA_2  | F   | 36        | Health screening   | FNH, HCA | HCA | 3.5        | 207             | 26.9             | LMS              | Laparoscopy      | 6.9                   | 1      | 55             | Alive        | No             |
| I-HCA_1  | M   | 34        | FNH growth for 4 years | FNH   | HCA | 4.1        | 37              | 8.5              | LLS              | Open            | 14.5                  | 1     | 38             | Alive        | No             |
| I-HCA_2  | M   | 24        | Health screening   | HCC, HCA | HCA | 2.6        | 32              | 15.2             | S56              | Open            | 9.7                   | 1      | 50             | Alive        | No             |
| I-HCA_3  | F   | 34        | Fatigue            | HCA | HCA | 4.5        | 25              | 47.2             | LLS              | Open            | 8.5                   | 1      | 15             | Alive        | No             |
| I-HCA_4  | F   | 32        | Follow-up after acute HAV   | FNH | HCC | 3.5        | 32              | 3.5              | LH               | Open            | 6.5                   | 1      | 111            | Alive        | No             |
| I-HCA_5  | M   | 32        | Liver cirrhosis screening | FNH | HCA | 2.5        | LLS             | Open            | 6.1              | 1               | 51             | Alive        | No             |
| I-HCA_6  | F   | 30        | Health screening   | HCA | HCA | 4.6        | 29              | 13               | RH               | Laparoscopy      | 4                   | 1      | 12             | Alive        | No             |
| I-HCA_7  | F   | 47        | Health screening   | HCC | HCA | 2.7        | 28              | 24.1             | LH               | Laparoscopy      | 2.8                  | 1     | 25             | Alive        | No             |
| I-HCA_8  | F   | 32        | Liver cirrhosis screening | HCA | HCA | 1.7        | 27              | 18.8             | LH               | Laparoscopy      | 2.8                  | 6    | 23             | Alive        | No             |
| I-HCA_9  | M   | 42        | Health screening   | HCC | HCA | 1.8        | 22              | 6.5              | RPS              | Laparoscopy      | 2.6                  | 1    | 20             | Alive        | No             |
| I-HCA_10 | F   | 56        | Health screening   | HCA | HCA | 2.4        | 15              | 15               | RAS              | Laparoscopy      | 2.3                  | 1    | 52             | Alive        | No             |
| I-HCA_11 | F   | 27        | Health screening   | HCA | HCA | 2.2        | 18              | LLS              | Laparoscopy      | 2                   | 10   | 87             | Alive        | Yes- > TACE |
| I-HCA_12 | M   | 40        | Gallstone work-up   | HCC | AML | 2.7        | 28              | 2               | S1               | Open            | 11.6                 | 1    | 62             | Alive        | No             |
| u-HCA_1  | F   | 20        | Abdominal pain     | HCA | HCA | 1.1        | 58              | 6.5              | RH               | Open            | 11.6                 | 1    | 62             | Alive        | No             |
| u-HCA_2  | M   | 41        | FNH growth for 2 years | HCA | FNH | 2.4        | 24              | 4.5              | Laparoscopy      | 4.5                 | 1    | 38             | Alive        | No             |
| u-HCA_3  | F   | 17        | Abdominal pain     | HCA | HCA | 1         | 23              | LMS              | Open            | 4.5                 | 1    | 38             | Alive        | No             |

AFP, alpha-fetoprotein; PIVKA-II, protein induced by Vitamin K absence or antagonist-II; CA19-9, carbohydrate antigen 19-9; M, male; F, female; HCA, hepatocellular adenoma; H-HCA, hepatocyte-nuclear-factor-1α mutated HCA; b-HCA, β-catenin-mutated HCA; I-HCA, inflammatory HCA; u-HCA, unclassified HCA; HCC, hepatocellular carcinoma; FNH, focal nodular hyperplasia; AML, angiomyolipoma; RH, right hepatectomy; LH, left hepatectomy; RAS, right anterior sectionectomy; RPS, right posterior sectionectomy; LMS, left medial sectionectomy; LLS, left lateral sectionectomy; S56, resection of segment V and VI; S1, isolated caudate lobectomy; TACE, transarterial chemoembolization; SPK, simultaneous pancreas-kidney transplantation.

Two patients showed progressive growth of the liver tumor over 2 and 4 years, respectively under the clinical diagnosis of FNH. One patient underwent simultaneous pancreas-kidney transplantation 6 years before and liver mass was detected owing to abdominal pain. One patient...
had a history of oral contraceptive administration for 10 years.

The mean and median levels of alpha-fetoprotein (AFP; reference: 7.5 ng/ml) were 2.6±1.1 ng/ml and 2.6 ng/ml, those of protein induced by Vitamin K absence or antagonist-II (PIVKA-II; reference: 40 mAU/ml) were 46.1±50.8 mAU/ml and 28 mAU/ml, and those of carbohydrate antigen 19-9 (CA19-9; reference: 37 ng/ml) were 16.3±12.4 ng/ml.

![Fig. 1](image1)

**Fig. 1.** Preoperative computed tomography findings and gross photographs of the surgical specimens of two patients with hepatocyte-nuclear-factor-1α mutated hepatocellular adenoma. Numbers denote case numbers. Arrows indicate hepatocellular adenoma.

![Fig. 2](image2)

**Fig. 2.** Preoperative computed tomography findings and gross photographs of the surgical specimens of two patients with β-catenin-mutated hepatocellular adenoma. Numbers denote case numbers.
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Outcomes after hepatic resection

One patient underwent preoperative portal vein embolization for right hepatectomy. The extent of hepatic resection comprised of right hepatectomy (n=4), left hepatectomy (n=4), right anterior sectionectomy (n=2), right posterior sectionectomy (n=1), left medial sectionectomy (n=3), left lateral sectionectomy (n=4), segment V and VI resection (n=1), and isolated caudate lobectomy (n=1). Laparoscopic liver resection was performed in 11 patients (57.9%). All operations except one (I-HCA Case No. 11) were macroscopic curative resection with tumor-negative resection margins. None of the patients experienced surgical complications that required any intervention or surgical treatment.

The mean and median tumor sizes were 5.6±3.6 cm and 4.5 cm, respectively. Each one patient had 6 and 10 tumors, and the other 17 patients had a single tumor. The location of the tumor was the right liver in 8 patients, the left liver in 10 patients, and the caudate lobe in 1 patient.

Immunohistochemical analysis of the resected tumor specimens revealed H-HCA in 2 patients (10.5%, Fig. 1), b-HCA in 2 patients (10.5%, Fig. 2), I-HCA in 12 patients (63.2%, Fig. 3) and u-HCA in 3 patients (15.8%, Fig. 4). There were no pathognomonic findings in the preoperative liver CT scans among these four groups.

Currently, all patients are alive over a mean follow-up period of 40.1±26.3 months (range, 12-111 months). Only one patient (I-HCA Case No. 11) who had undergone incomplete tumor removal showed slow growth of the residual tumors, thus this patient underwent transarterial chemoembolization (TACE) at 7 months after hepatic resection (Fig. 5). The largest 2 cm-sized tumor was regressed after TACE, but other new small masses were re-

Fig. 3. Preoperative computed tomography findings and gross photographs of the surgical specimens of 12 patients with inflammatory hepatocellular adenoma. Numbers denote case numbers. Arrows indicate hepatocellular adenoma.
maining; thus, this patient has been closely observed under imaging study follow-up every 6 months with consideration of liver transplantation. The other 18 patients did not show disease recurrence during follow-up to date.

**DISCUSSION**

Diagnostic workup for HCA should include hepatobiliary contrast MRI because it is helpful for discrimination from FNH. In most of the cases, the diagnoses can be differentiated based on signal intensity and dynamic vascular patterns after intravenous gadolinium injection MRI. Under the condition of uncertainty, a biopsy should be taken, especially for larger lesions, as the clinical management will differ depending on the pathology. Although HCA is a hypervascular tumor with a risk of procedure-associated bleeding, percutaneous needle liver biopsy was performed in 8 of 19 patients in this study, and 7 of 8 patients were pathologically diagnosed with HCA.

Hepatic resection has been considered as the treatment of choice because complete surgical removal of HCA can be achieved. Elective surgical resection is considered for HCA > 5 cm in diameter. Hepatic resection for HCA is a safe procedure with acceptably low morbidity and mortality rates. There was no major surgical complication in our 19 patients.

In this study, 11 of 19 patients underwent laparoscopic resection primarily because of the high proportion of young female patients and the benign nature of HCA. Laparoscopic resection is increasingly popular worldwide. de'Angelis et al. reported about 62 HCA patients who underwent either an open procedure or laparoscopy, in which there was no difference in postoperative morbidity and zero mortality, with no long-term complications or re-

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**Fig. 4.** Preoperative computed tomography findings and gross photographs of the surgical specimens of three patients with unclassified hepatocellular adenoma. Numbers denote case numbers. Arrows indicate hepatocellular adenoma.
Fig. 5. Postoperative sequences of residual tumors in the inflammatory hepatocellular adenoma (Case No. 11). (A) At 5 months after hepatic resection, the slow progression of multiple residual tumors can be seen. (B) Transarterial chemoembolization was performed at 7 months after hepatic resection. (C) Magnetic resonance imaging taken at 7 years after hepatic resection shows no changes in the multiple tumors. Arrows indicate hepatocellular adenomas.

currence of HCA. Patients with smaller lesions were preferentially treated with laparoscopic approach.

In rare circumstances, the treatment of HCA may also involve liver transplantation, a procedure described in a case report by Vennarecci et al.\textsuperscript{21} Our patient with multiple recurrences was diagnosed with hepatic adenomatosis, and is under consideration of liver transplantation.

Few treatment options other than surgical resection have been proposed. Percutaneous radiofrequency ablation has been performed for HCA with good results.\textsuperscript{22} For HCAs <3 cm, radiofrequency ablation can be a good treatment option depending on the location of the lesion.

As HCAs are hypervascular arterial lesions, bleeding may be treated by transarterial embolization (TAE) in cases where patients present with hemodynamic instability. The embolization of HCAs is a safe but relatively challenging procedure due to multiple small feeding vessels.\textsuperscript{23} In cases of spontaneous rupture and bleeding, TAE should be considered as a first-line treatment as it is highly successful and minimally invasive in an acute setting. Although high success rates have been described for TAE, there exists limited data in the literature.\textsuperscript{24}

Four subtypes of HCAs are recognized based on genotype-phenotype analyses as H-HCA, b-HCA, I-HCA, and u-HCA.\textsuperscript{4,16} Of them, b-HCAs are known to trigger a potent mitogenic signaling pathway that is prominent in HCC.\textsuperscript{25} The incidence of HCC or borderline malignant tumors in b-HCAs has been reported to be up to 46%, but such a malignant progression was seldom seen in other subtypes.\textsuperscript{26} HCA shows a higher risk of malignant transformation in men.\textsuperscript{27} Hepatitis, underlying glycogen storage disease, or sex steroid hormone abuse are predisposed to
transformation, long-term follow-up is necessary. The low risk of H-HCA degeneration may help to simplify the management of HCAs. Future studies should determine whether different subtypes of HCA carry different profiles of risk for bleeding, tumor recurrence and malignant transformation.

The present study has limits of note. First, this is a retrospective, single-center study with a small number of patients. Thus, multi-center studies are necessary to collect more data on rarely diagnosed cases. Second, the follow-up period was not sufficiently long to reliably evaluate the lifelong risk of tumor recurrence and malignant transformation.

In conclusion, surgery may be indicated if imaging studies show diagnostic ambiguity with HCC, growing tumor, or symptomatic mass with or without bleeding. Because of the risk of tumor recurrence and malignant transformation, long-term follow-up is necessary.

CONFLICT OF INTEREST

None of the authors have any conflicts of interest.

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Conceptualization: SH. Data curation: CSA, KHK, DBM, TYH, GWS, DHJ, GCP. Methodology: SMH. Visualization: SH. Writing - original draft: SMK, SH. Writing - review & editing: SH.

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