Original Article

DOI: 10.5582/bst.2017.01110

Clinical correspondence to hepatocellular carcinoma-related lesions with atypical radiological pattern

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Summary **In patients at risk of hepatocarcinogenesis, tumors are frequently detected with atypical radiological patterns related to hepatocellular carcinoma (HCC) on imaging studies. Despite their high potential for malignancy, whether to resect such lesions immediately is controversial. Based on histological findings, patients with non-enhanced tumors or enhanced tumors without washout were divided into two groups: those with tumors that should be treated containing well, moderately, and poorly differentiated HCC (Group 1), and those that can be observed containing early HCC, hepatocellular adenoma, focal nodular hyperplasia, dysplastic nodules, and regenerative nodules (Group 2), and we elucidated the clinical correspondence to these tumors. Seventy-two patients had a single tumor with atypical radiological pattern: 39 patients had HCC (Group 1), while 33 patients had benign tumors or early HCC (Group 2). Among nine baseline variables, serum α-fetoprotein (AFP) level in Group 1 (median, 13.2 ng/mL; range, 0.6-5881.6) was significantly higher than that in Group 2 (5.6 ng/mL; 0.8-86.3, *P* = 0.003). The cut-off value of AFP was 36.4 ng/mL for prediction of Group 1, and the median overall and recurrence-free survival periods of 23 patients in the high-AFP (≥ 36.4 ng/mL) group (5.3 years; 95%CI, 2.1 – N.A. and 1.6 years; 0.5-2.2) were significantly shorter than those of the 49 patients in the low-AFP (< 36.4) group (7.5 years; 7.5 – N.A., *P* = 0.047, and 2.8 years; 1.9-3.3, *P* = 0.001). Taken together, HCC-related tumors with an atypical radiological pattern could be observed unless serum AFP level is elevated.**

Keywords: α-fetoprotein, atypical radiological pattern, benign liver tumor, hepatocellular carcinoma

1. Introduction

Diagnosis of hepatocellular carcinoma (HCC) is defined by early enhancement in the arterial phase and washout in the portal phase on imaging studies, including computed tomography (CT) and magnetic resonance imaging (MRI) (*1*). On the other hand, non-enhanced lesions in the arterial phase or hypervascular nodules without washout in the portal phase are found during the follow-up period in patients with high risk of hepatocarcinogenesis (*2-4*). The frequency of diagnosis of such nodules has increased since gadoxetic acid-enhanced MRI has become clinically available (*5-7*).

Tumors associated with HCC with an atypical radiological pattern are considered as "dysplastic nodules" or "early HCC", and are known to have substantial malignant potential (*1,8-10*). In contrast, some of these tumors may be poorly differentiated HCC, and grow rapidly during observation. As these lesions are often small and it is difficult to perform a biopsy to confirm malignancy, whether such nodules should be treated immediately is controversial (*11-13*).

Due to the better prognosis after treatment for such lesions with atypical radiological patterns, some authors

Released online in J-STAGE as advance publication June 18, 2017.

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have suggested extensive treatment including ablation for non-enhanced tumors (*9,14,15*). On the other hand, we reported previously that non-enhanced lesions and enhanced lesions without washout coexisting with HCC should be considered as risk factors for new lesions in the remnant liver, and not target lesions for treatment (*16*). Furthermore, it is not necessary to treat hypovascular tumors associated with HCC immediately after diagnosis due to the long lead time and the substantial risk of developing classical HCC in the remnant liver (*17,18*).

In this study, we investigated the risk of malignancy of tumors with atypical radiological patterns on imaging studies and clarified what types of such nodules associated with HCC should be treated immediately.

2. Materials and Methods

2.1. *Patients*

Patients undergoing liver resection for malignant tumors at Nihon University Itabashi Hospital during the period from 2006 to 2014 were included in this study. Among these patients, those diagnosed as having a single non-enhanced tumor or a hypervascular tumor without washout associated with HCC were analyzed.

2.2. *Diagnosis*

Nodules that are hypervascular in arterial phase but become hypovascular in portal phase on contrast CT and/or MRI are defined as classical HCC. On the other hand, other nodules that show hypovascularity in arterial phase and are distinguishable from cysts or hemangiomas are defined as non-enhanced lesions (*1*).

All patients underwent preoperative multiphase contrast-enhanced CT with/without gadoxetate disodium-enhanced MRI, as described previously (*16*). Briefly, a four-channel multidetector CT scanner was used. After precontrast CT scans, two sets of contrast-enhanced CT scans were performed, with one during the arterial phase and the other during the portal phase. The standard protocol for contrast-enhanced CT required 120-150 mL of nonionic intravenous contrast material (370 mg/mL) administered by a power injector at a rate of 3 mL/s, with a delay of 35 seconds for the arterial phase and 65 seconds for the portal phase. MRI was performed using gadoxetate disodium administered intravenously at a rate of 2 mL/s, with delay times for the arterial and portal phases of 20 and 60 seconds, respectively.

2.3. *Pathology*

Pathological evaluations of resected specimens were performed by two pathologists with more than 10 years of experience in the field of liver pathology as follows (*19-22*):

I) HCC: well-vascularized tumors with wide trabeculae (> 3 cells), prominent acinar pattern, small cell changes, cytological atypia, mitotic activity, vascular invasion, absence of Kupffer cells, and loss of the reticulin network

II) Early HCC: characterized by intratumoral portal tracts, the presence of stromal invasion, increased cell density, and structural atypia.

III) Hepatocellular adenoma: benign hepatocytes arranged in mildly thickened cell plates, with a preserved reticulin network and thin-walled arteries.

IV) Regenerative nodule: local proliferation of hepatocytes surrounded by fibrous septa, and hemosiderin deposition is fairly common.

V) Dysplastic nodule: regenerative nodule containing atypical cells without definite histological features of malignancy.

VI) Focal nodular hyperplasia: presence of ductular reaction with varied intensity at the junction of the fibrous septa with the hepatocellular component.

Based on the pathological findings, non-enhanced tumors or hypervascular tumors without washout were divided into two groups; tumors that should be treated immediately including well, moderately, and poorly differentiated HCC (Group 1) and those that could be followed up by observation consisting of early HCC, hepatocellular adenoma, focal nodular hyperplasia, dysplastic nodule, regenerative nodules, and other benign tumors (Group 2).

2.4. *Statistical analysis*

Variables in each of the groups were analyzed using Fisher's exact test and the Mann-Whitney *U* test. Prognostic factors among the nine parameters (Table 1) for classification for treatment (Group 1) or observation (Group 2) were identified with the logistic regression model. The predictive ability of variables for classification into Group 1 and Group 2 was assessed by receiver operating characteristic (ROC) curve analysis and the corresponding area under the curve (AUC). The optimal cut-off value was set as the value maximizing the sum of sensitivity and specificity. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

3. Results

3.1. *Patients*

Among the total of 1467 patients that underwent curative liver resection under a diagnosis of HCC, 1147 were diagnosed as having a single tumor. Overall, 72 patients underwent liver resection for a tumor with atypical radiological patterns (Figure 1). These patients included 45 (72.0%) men and the median age was 70

Table 1. Patient characteristics

Variables	Group 1 (*n* = 39)	Group 2 (*n* = 33)	*P* value
Age, yr	70 (41-82)	68 (30-81)	0.088
Male, *n* (%)	27 (69.2)	18 (54.5)	0.290
Non-enhanced tumor, *n* (%)	16 (41.0)	23 (69.6)	0.015
Hepatitis, HB/HC/nBnC	5 / 25 / 9	4 / 20 / 9	0.919
Liver, LC/CH/NL	22 /15 /2	7 / 11 / 5	0.357
Size, mm	20 (9-40)	17 (8-32)	0.056
AFP, ng/mL	13.2 (0.6-5881)	5.6 (0.8-86.3)	0.003
DCP, mAU/mL	26 (10-915)	21 (1-18142)*	0.263
Repeated liver resection, *n* (%)	7 (17.9)	2 (6.0)	0.128

*One patient with high DCP level took warfarin before surgery. HB, hepatitis B virus; HC, hepatitis C virus; LC, liver cirrhosis; CH, chronic hepatitis; NL, normal liver; AFP, alpha-fetoprotein; DCP, Des-gamma carboxy prothrombin.

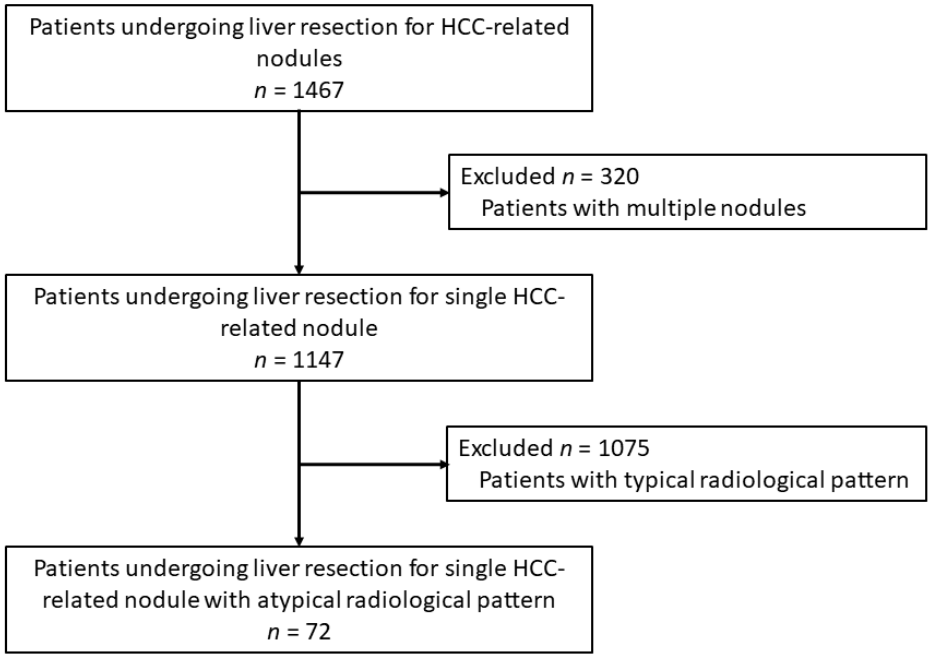

Figure 1. Flow diagram of patient recruitment.

years (range, 30-82 years) (Table 1).

3.2. *Pathology*

Based on the results of histological examination of the resected specimens, 14 patients had well-differentiated, 21 moderately differentiated, and four poorly differentiated HCCs (Group 1, 39 (54.1%) patients). On the other hand, 24 patients were given a diagnosis of early HCC, one with hepatocellular adenoma, two with dysplastic nodules, two with regenerative nodules, and four with focal nodular hyperplasia (Group 2, 33 (45.8%) patients). The median tumor size was 1.8 cm (range, 0.8-4.0 cm). Among the 72 patients, 39 (54.1%) had liver cirrhosis, 26 (36.1%) had chronic hepatitis, and seven (9.7%) had normal livers.

3.3. *Risks of hepatocellular carcinoma*

By univariate analysis, serum α-fetoprotein (AFP) level was significantly higher in Group 1 (median, 13.2 ng/mL; range, 0.6-5881.6) than in Group 2 (5.6 ng/mL; 0.8-86.3, $P = 0.003$). Patients with hypervascular tumors without washout were significantly more frequent in Group 1 (69.7% *vs*. 30.3%, $P = 0.015$). On the other hand, the logistic regression model indicated that serum AFP level was the only independent factor for Group 1 (odds ratio, 0.98; 95%CI, 0.96-0.99, $P = 0.011$), and hypervascular nodules without washout tended to be more frequent in Group 1 ($P = 0.065$) (Table 2).

3.4. *Cut-off value of* α*-fetoprotein level*

The AUC of the ROC was 0.56 ($P = 0.003$) for AFP in relation to the need for treatment of tumors with an atypical radiological pattern. The calculated cut-off value for AFP was 36.4 ng/mL, with sensitivity of 41.0%, specificity of 84.8%, positive predictive value of 76.1%, and negative predictive value of 54.9% for prediction of malignancy (Figure 2).

Table 2. Uni- and multivariate analysis

Variables	Univariate Analysis		Multivariate Analysis*	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age	70 (41-82)	0.290	68 (30-81)	0.359
Gender	27 (69.2)	0.088	18 (54.5)	0.731
Vascularity	16 (41.0)	0.015	23 (69.6)	0.065
Hepatitis	5 / 25 / 9	0.919	4 / 20 / 9	0.693
Liver**	22 /15 /2	0.357	7 / 11 / 5	0.885
Size	20 (9-40)	0.056	17 (8-32)	0.094
AFP	13.2 (0.6-5881)	0.003	5.6 (0.8-86.3)	0.014
DCP	26 (10-915)	0.263	21 (1-18142)*	0.172
Repeated liver resection	7 (17.9)	0.128	2 (6.0)	0.129

*Logistic regression model. ** Diagnosis by imaging studies containing liver cirrhosis, chronic hepatitis, and normal liver. AFP, α-fetoprotein; DCP, Des-gamma carboxy prothrombin.

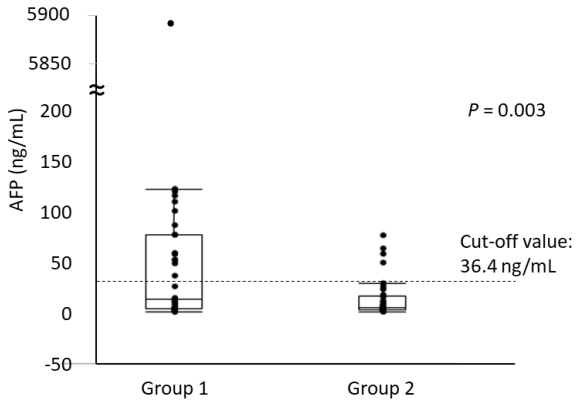

Figure 2. Distribution of serum AFP level and tumor pathology as shown by box plots. There was a significant correlation between AFP and pathology ($P = 0.003$).

3.5. *Survival*

We defined patients with AFP level ≥ 36.4 ng/mL as the high-AFP group and those with AFP level < 36.4 ng/mL as low-AFP group, and compared survival rates between the patients in these groups.

After a median follow-up of 3.9 years (range, 0.6-9.0 years), 14 (63.6%) and 21 (42.0%) patients had recurrence in the high- and low-AFP groups, respectively. A total of 33 patients (94.2%) had recurrence in the remnant liver, and recurrence occurred in distant sites in two patients (5.7%). There were no significant differences in recurrence site ($P = 0.152$) or treatments for recurrent HCC ($P = 0.749$) between the two groups.

The median overall and recurrence-free survival periods were 5.3 (95% CI, 2.1 to N.A.) years and 1.6 (0.5-2.2) years in the high-AFP group and 7.5 years (95% CI, 7.5 to N.A., $P = 0.047$) and 2.8 years (1.9-3.3, $P = 0.001$) in the low-AFP group, respectively. The 5-year overall survival rates were 61.7% and 76.8%, and the recurrence-free survival rates at the end of 5 years were 0% and 57.2% in the two groups, respectively (Figure 3).

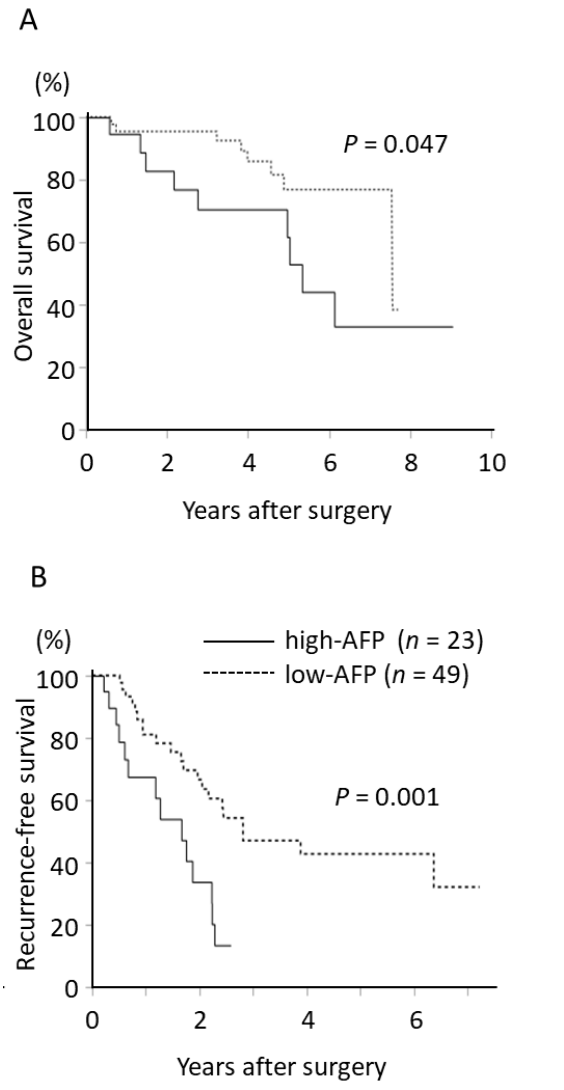

Figure 3. Survival outcomes after liver resection. There were significant differences between the two groups in both overall **(A)** and recurrence-free **(B)** survival rates for patients after liver resection.

4. Discussion

We found that tumors associated with HCC with an atypical radiological pattern have a high risk of

malignancy if serum AFP level is high, especially in patients with non-enhanced nodules at arterial phase.

Through the development of carcinogenesis, HCC gains vascularity and washout at the portal phase (*2,23*), and non-enhanced and hypervascular nodules without washout could be precancerous lesions, including early HCC (*8,10*). Nearly half of such tumors that were suspected to be HCC could have been placed under observation in this series. With improvements in diagnostic modalities, including gadoxetic acid-enhanced MRI and contrast ultrasound, more lesions that are not definitively HCC are discovered (*5-7*).

Whether non-enhanced nodules should be treated immediately after diagnosis remains controversial. Treatment of these marginal lesions with high malignant potential is inconclusive, as some authors have suggested that these lesions should be strictly monitored or ablated (*14*). On the other hand, a study using a statistical model to estimate the long-term survival benefit of radiofrequency ablation of high-grade dysplastic nodules indicated no additional time benefit compared to regular follow-up and timely treatment (*24*).

In our previous report, survival rates from diagnosis of hypovascular liver tumors were similar between patients that underwent liver resection immediately and those treated after vascularization (*18*). Furthermore, the tumors associated with HCC with atypical radiological pattern that coexisted with classical HCC were not necessarily removed, because new classical HCC lesions, which should be treated immediately, often appear prior to the malignant transformation of non-enhanced lesions or hypervascular tumors without washout due to multicentric hepatocarcinogenesis (*16,17*).

These findings were attributed to the fact that treatment of early HCC does not contribute to patient survivals due to the long lead time from early to classical HCC (*25*). That is, the survival benefit of patients undergoing liver resection for early HCC is too marginal to justify the procedure. Therefore, similar to the premalignant lesions such as hepatocellular adenoma or dysplastic nodules which are not necessary to be treated immediately, it was appropriate for early HCC to be classified into Group 2 in this study.

Serum AFP level was the only independent factor and hypervascular nodules without washout tended to be HCC compared with non-enhanced tumors in this study. We decided a cut-off value of AFP based on the AUC of the ROC, and the survival periods of patients in the high-AFP group were significantly shorter than those in the low-AFP group. Therefore, patients with HCC-related tumors with atypical radiological pattern and high serum AFP level should be candidates for treatment rather than observation.

The approach for tumors with an atypical radiological pattern depends on the clinical features of the nodules. Non-enhanced nodules > 2 cm in diameter had high malignant potential (*26*), and 41-62% of HCC smaller than 2 cm showed an atypical radiological pattern (*1,10*). In contrast, the majority of nodules in the cirrhotic liver < 1 cm are benign (*8*). On the other hand, our data showed that high serum AFP level was the only independent factor for malignancy and the tumor size was not significantly larger in tumors of Group 1 compared to Group 2, and these clinical features tended to be dominant in patients with hypervascular nodules without washout. In addition, the sensitivity according to the cut-off value of serum AFP in this study is not so high and therefore, vascularity and tumor size as well as AFP level should be taken into account in decision-making regarding resection for such tumors.

In conclusion, non-enhanced nodules or enhanced tumors without washout associated with HCC could be observed unless serum AFP levels are not elevated. In particular, large hypervascular tumors without washout should be followed-up carefully because of the high potential for malignancy.

Acknowledgements

This work was mainly supported by a Grant-in-Aid for Scientific Research (C) 15K10152 (Y.M.) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

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(Received May 10, 2017; Revised June 7, 2017; Accepted June 9, 2017)