Acta Medica
Okayama

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Original Article

Obstructions of Portal Veins and Tumor Numbers Are Associated with Humped Hepatocellular Carcinoma

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Tumor protrusion in hepatocellular carcinoma (HCC) is one of the risk signs of tumor rupture. Despite curative tumor treatments, HCC recurrences sometimes occur with rapidly growing humped or ruptured HCC in small sized tumors. The aim of this study was to clarify the characteristics of humped HCC clinically and radiologically associated with tumor progression, liver damage, and treatment. The subjects were 179 consecutive HCC patients who underwent angiographic examination. Dynamic studies, using helical computed tomography and magnetic resonance imaging were assessed, and the HCC area were measured. The tumor-node-metastasis (TNM) stage differed significantly between the humped and non-humped HCC groups. Humped HCC was more frequently observed in the right lobe (29.3% of right-lobe HCCs) than in the left (10.1%; $p = 0.003$). Analysis of recurrent HCC revealed that patients with multiple treatments of ≥ 4 sessions had more humped HCC (33.8%) than those with 1–3 sessions (16.7%; $p = 0.042$). Multivariate regression analysis revealed that tumor invasion in the portal vein, rather than large tumor size, was significantly associated with tumor protrusion. HCC recurrence with humped HCC occurs often in patients with multiple treatments. Tumor factors of the TNM classification, especially tumor invasion in the portal vein, might be associated with the mechanisms of tumor protrusion.

Key words: humped HCC, tumor protrusion

H epatocellular carcinoma (HCC) is the fifth most common cancer worldwide, and the incidence is likely to increase [1, 2]. The "hump sign," comprising tumor protrusion out of the liver margin, represents one of the specific characteristics of HCC, and is useful for differential diagnosis [3]. Furthermore, humped HCC is reported to have a high risk of spontaneous rupture that often results in fatal liver failure [4–7]. In the 1980s in Japan, as in Taiwan [6],

because periodic screenings for HCC were not well-established for patients with the hepatitis B virus (HBV) or hepatitis C virus (HCV), numerous HCC patients with large sized tumors suffered from spontaneous ruptures. The patients with HBV or HCV often visited hospitals for abdominal pain from HCC rupture without any regular follow-ups. Recently, the number of spontaneous HCC rupture cases seems to be decreasing, with only several ruptured cases annually at our hospital. Regular follow-ups with periodic surveillance using helical computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound might detect HCC in earlier stages [8], and with

these methods, many patients could receive treatment before tumor rupture.

Several reports studied spontaneous HCC rupture in the natural course [6, 7], and the comparison between ruptured and non-ruptured HCC revealed that tumors often become humped as they grow larger. Large tumor size may be one of the important factors for tumor protrusion. However, once the patients receive HCC treatments, such as trans-catheter arterial chemo-embolization (TACE) or ablation, treatments may modify the characteristics of HCC, such as poor tumor differentiation or sarcomatous changes as previously reported [9, 10]. We occasionally experienced recurrent HCCs that grew humped rapidly with tumor rupture in small sized tumors. Understanding the precise characteristics of humped HCC is crucial for early detection to avoid tumor protrusion or rupture. Therefore, we assessed humped HCC using angiography, CT, and MRI in order to clarify the characteristics of humped HCC associated with tumor progression, liver damage, treatment, and other clinical parameters.

Materials and Methods

Study subjects. The subjects comprised 179 HCC patients who underwent assessment using digital subtraction angiography (DSA) at our hospital for the diagnosis or treatment of HCC. The patient backgrounds are shown in Table 1. The tumor-node-metastasis (TNM) classification, the staging criteria of the Liver Cancer Study Group of Japan, was used for staging tumor progression [11]. In terms of liver function, we evaluated the patients using the Child-Pugh stage [12]. The number of patients in Child-Pugh stage C was much smaller than the numbers in stages A or B, since some patients in Child-Pugh stage C did not receive DSA examinations due to poor liver condition. The study was approved by the institutional ethics committee.

Assessment of humped HCC. Dynamic studies using helical CT and MRI within 1 month prior to DSA were assessed. All HCCs with diameters >1cm based on CT or MRI images (axial view) were included for this analysis. Humped HCC was defined as a tumor with one-third or more of the area protruding from the liver surface, and severely humped HCC as a protrusion of two-thirds or more of the area. Image analysis was undertaken by measuring the HCC area using a TFS-7000 DICOM Viewer (Toshiba Medical Systems Corporation, Tokyo, Japan). An example of an actual analysis is shown in Fig. 1.

Diagnosis and treatment of HCC. When HCCs were diagnosed with helical CT, MRI, or ultrasound, the patients received DSA examinations to confirm blood supplies to the HCC. When blood supply to HCC through the hepatic arteries was scarce, we also examined blood supply through extrahepatic vessels (ExHV), as previously reported [13]. All tumors were treated with TACE, and additionally

Table 1 Clinical characteristics of the patients at the time of diagnosis

Characteristics	All patients (N = 179)	Humped (n = 51)	Non-humped (n = 128)	p
Age (years)	71 (53–89)[‡]	72 (55–89)[‡]	71 (53–83)[‡]	0.95
Gender (female/male)	37/142	16/35	21/107	0.026
Virus (HBV/HCV/none)	20/139/20	10/35/6	10/104/14	0.071
TNM stage (1/2/3/4)	20/27/91/41	1/1/28/21	19/26/63/20	<0.001
Child-Pugh (A/B/C)	108/62/9	27/23/1	81/39/8	0.12
Treatment (0/1–3/4–)[†]	44/63/72	13/13/25	31/50/47	0.19
AST (IU/L)	49 (16–250)[‡]	51 (22–155)[‡]	48 (16–250)[‡]	0.44
ALT (IU/L)	41 (11–156)[‡]	35 (11–156)[‡]	44 (12–131)[‡]	0.64
Platelet (10^4/μL)	11 (2–38)[‡]	10 (2–38)[‡]	11 (2–30)[‡]	0.13
AFP (ng/mL)	24 ($2–2×10^5$)[‡]	62 ($2–2×10^5$)[‡]	21 ($2–2×10^4$)[‡]	0.013
DCP (mAU/mL)	126 ($10–6×10^3$)[‡]	217 ($11–6×10^3$)[‡]	126 ($10–6×10^3$)[‡]	0.006

TNM, Tumor-node-metastasis stage according to the Liver Cancer Study Group of Japan; Treatment, Treatment times over the lifetime; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, Alpha fetoprotein; DCP, des-gamma-carboxy prothrombin; [†]: Sessions; [‡]: Median (maximum-minimum).
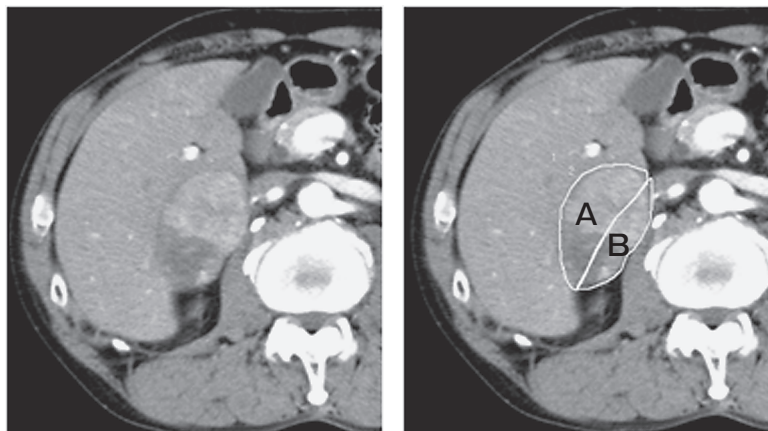
Fig. 1   Measurement of humped HCC. Image analysis was undertaken by measuring the HCC area using a TFS-7000 DICOM Viewer (Toshiba Medical Systems Corporation, Tokyo, Japan). Humped and non-humped areas of the tumor were traced on the screen. The program calculated the traced area automatically. This figure shows an example of an actual analysis. Area **A** is 1,429 mm^2, while area **B** is 770 mm^2. The humped area (area B) is greater than one-third of the HCC (total of areas **A** and **B**).

with percutaneous ablation in case of tumor number ≤ 3 and tumor size ≤ 3 cm in diameter. Single tumors of ≤ 3 cm in diameter were resected if the patients were tolerant to the resection. When the patients received several treatments such as TACE, percutaneous ablation and resection within a 1-month interval, successive treatments were counted as 1 session of treatment for the analysis.

   Statistical analysis.   The Student t-test was used for comparing the patient backgrounds between the humped HCC and non-humped HCC group. The Kruskal-Wallis test was utilized for the analysis of the associations between tumor size and location, and the association of tumor protrusion with TNM stage and Child-Pugh stage. The frequencies of humped HCC among the treatment groups were evaluated with the Kruskal-Wallis test. The Fisher exact probability test, x^2 test, and Student t-test were also used to compare the frequency of humped HCC between the two treatment groups. The logistic regression analysis was utilized to determine factors that strongly affect tumor protrusion. P values of less than 0.05 were defined as statistically significant.

Results

   Humped HCC was identified on 51 CT or MRI, and confirmed with DSA examinations, including 4 cases with double humped HCCs. As a result, a total of 55 humped HCCs were studied. Eighteen HCCs

were severely humped. Ten HCCs occupied over 2 segments according to the Couinaud classification. Table 1 shows the patient backgrounds. In comparing the humped HCC and non-humped HCC group, the high prevalence in the female patients, advanced TNM stages, high alpha-fetoprotein (AFP) levels and high des-gamma-carboxy prothrombin (DCP) levels were significantly observed in the humped HCC groups.

   Table 2 shows the number of humped and non-humped HCCs. HCC was defined as belonging to the segment where the tumor was mainly located. The frequency of humped HCC was calculated for each lobe and each segment. The right lobe had twice as many HCCs as the left lobe, and humped HCCs were more frequently observed in the right lobe (27.4% of all HCCs in the right lobe) than in the left (10.1%; $p = 0.003$, the x^2 test). Furthermore, humped HCCs were most often located in Segment 7 (20.2%). Similar results were observed in the severely humped HCC group. As shown in Fig. 2, mean tumor size was 2,942 mm^2 (range, 125–21,150 mm^2). Twelve humped HCCs were large in size (> 4 cm in diameter), while 18 were small tumors ≤ 2 cm in diameter. Severely humped HCCs were not always large tumors. Tumor size was not significantly associated with tumor location ($p = 0.097$, the Kruskal-Wallis test).

   Fig. 3 shows the association of tumor protrusion with TNM stage and Child-Pugh stage. Most patients with humped HCC were at TNM stage 3 (54.9%) or stage 4 (41.2%), ($p < 0.001$, the Kruskal-Wallis test).

Table 2   Humped HCC was more frequently observed in the right lobe

	All HCCs	Humped (%)	S-Humped (%)
Left lobe	89	9 (10.1)	4 (4.5)
Segment 1	56	2 (3.6)	1 (1.8)
2	58	1 (1.7)	1 (1.7)
3	62	2 (3.2)	1 (1.6)
4	73	4 (5.5)	1 (1.4)
Right lobe	157	46 (29.3)	14 (8.9)
Segment 5	88	4 (4.5)	0 (0)
6	97	9 (9.3)	5 (5.2)
7	99	20 (20.2)	8 (8.1)
8	103	13 (12.6)	1 (1.0)

S-Humped HCC, Severely humped HCC.
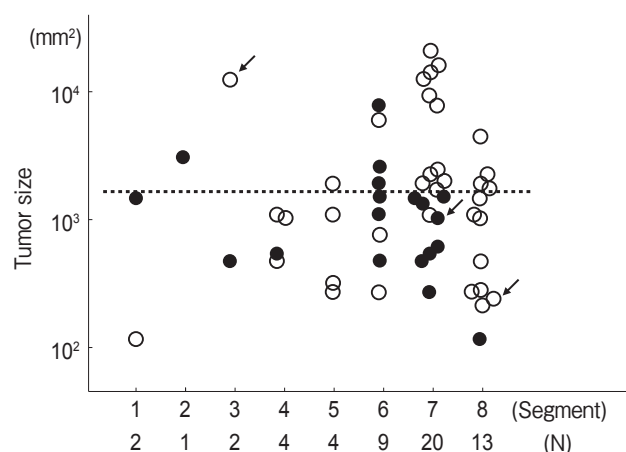
Fig. 2   Humped HCC is frequently observed in the right lobe. A total of 51 DSA images showed humped HCC. This figure shows the distribution and size of humped HCCs. The vertical axis shows tumor size, and the horizontal axis shows Couinaud segments. The mean tumor size was 2,042 mm^2 (range, 125–21,150 mm^2). Open circles are humped HCC, and closed circles are severely humped HCC. The circles with arrows indicated ruptured HCC. No significant associations were noted with humped HCC in terms of distribution and tumor size ($p = 0.097$, the Kruskal-Wallis test).

Conversely, no significant correlations were noted between tumor protrusion and Child-Pugh stage ($p = 0.12$). Interestingly, among the patients in Child-Pugh stage A, 9 of the 15 HBV-infected patients had humped HCC (60%) compared to 15 of 82 HCV-infected patients (18.3%, $p < 0.001$, the x^2 test).

Next, we studied the relationships between humped HCC and HCC treatment. When patients received several treatments such as TACE, percutaneous ablation and resection within a 1-month interval, successive treatments were counted as 1 session of treat-

ment. There was no statistical difference in the frequency of humped HCC among the treatment groups (Table 1; $p = 0.19$, the Kruskal-Wallis test). However, as shown in Fig. 4, large humped tumors (> 4 cm in diameter) were more frequently observed among treatment-naïve patients (38.5%) compared with patients with recurrent HCC (5.9%; $p = 0.012$, the Fisher exact probability test). In patients with recurrent HCC who did not have humped HCC initially, patients with multiple treatments of ≥ 4 sessions had more humped HCC (33.8%) than those with 1–3 sessions of treatments (16.7%; $p = 0.042$, the x^2 test). Interestingly, the humped HCC group had a significantly longer duration after initial HCC diagnosis (58.6 ± 37.2 months) than the non-humped HCC group (38.2 ± 28.0 months; $p = 0.0014$, the Student t-test). Tumor invasion in the portal vein was frequently recognized among humped tumors in the right lobe (38.1%) rather than in the left (22.2%), although this difference was not statistically significant ($p = 0.31$, the Fisher exact probability test).

HCC sometimes acquires blood supply through ExHV. It is unclear whether HCCs fed through ExHV are more often humped. Thirty-three HCCs, including humped or non-humped tumors, were supplied through ExHV in this study. ExHV included the right inferior phrenic artery (n = 20), cystic artery (n = 8), right adrenal artery (n = 2), gastro-duodenal artery (n = 1), left gastric artery (n = 1), and left inferior phrenic artery (n = 1). The frequency of humped HCCs supplied through ExHV was 27.3%, which was similar to that through hepatic arteries (28.8%). Tumor size of the humped HCCs did not differ statistically between the groups ($p = 0.82$, the
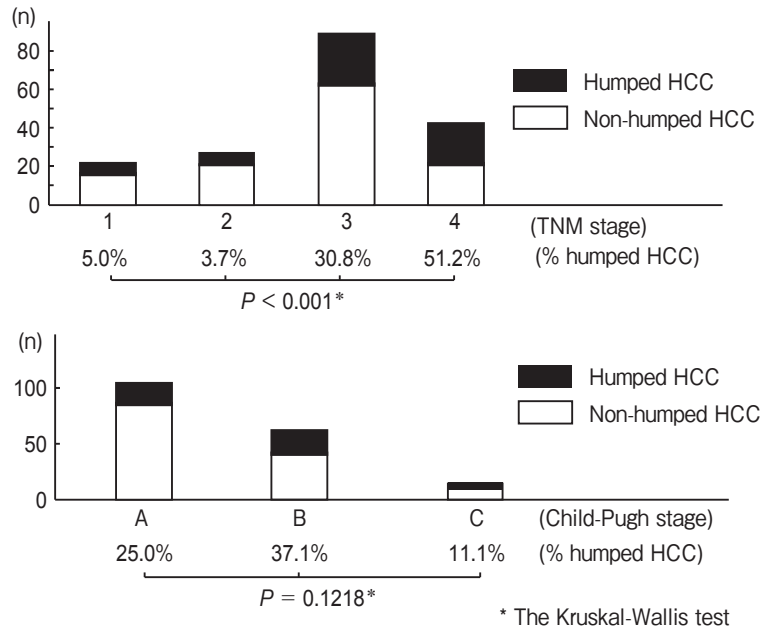
Fig. 3   Tumor protrusion is associated with TNM stage, but not Child-Pugh stage. The upper half of the figure shows the frequency of humped and non-humped HCC at each stage based on tumor progression (TNM stage). Humped HCC was significantly more common at stage 3 (30.8%) or 4 (51.2%) than at stage 1 or 2 ($p < 0.001$, the Kruskal-Wallis test). The lower half of the figure shows the frequency of humped and non-humped HCC at each stage of liver damage (Child-Pugh stage). No significant association was noted between tumor protrusion and Child-Pugh stage ($p = 0.122$, the Kruskal-Wallis test).
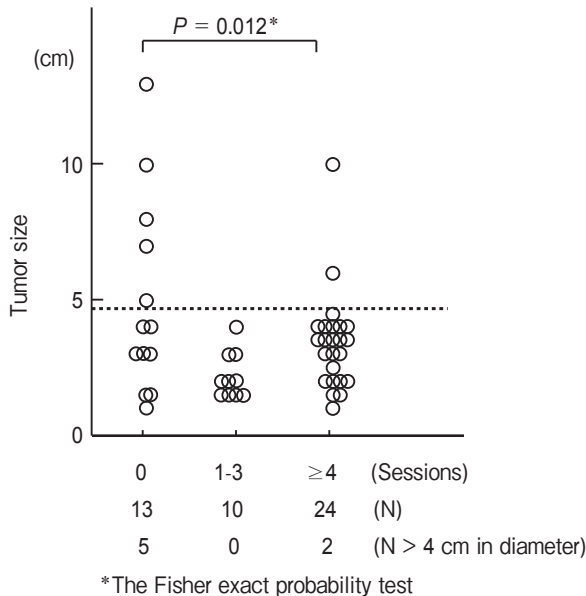
Fig. 4   Tumor protrusion is associated with the time of treatment. The figure shows the association between tumor size and the time of HCC treatment. Large-sized humped tumors (> 4 cm in diameter) were more frequently observed among treatment-naïve patients (38.5%), compared with patients with recurrent HCC (5.9%; $p = 0.012$, the Fisher exact probability test).

x^2 test). HCCs fed through ExHV were often observed in patients who underwent multiple treatments of ≥ 4 sessions; however, they were not identified in any treatment-naive patients, revealing that blood-supply through ExHV is associated with the time of HCC treatment, but not with tumor protrusion.

In order to determine factors that strongly affect tumor protrusion, we assessed individual factors of TNM classification (tumor number, tumor size, tumor invasion in the portal vein, lymph node metastasis, and distant metastasis) in univariate regression analysis (Table 3). All 3 factors for tumor staging exhibited strong associations with tumor protrusion. Distant metastasis showed high correlations with tumor protrusion, although the number of patients with distant metastasis was small (n = 7). Multivariate regression analysis indicated that tumor invasion in the portal vein and tumor number, rather than tumor size, were important factors for tumor protrusion. Tumor invasion in the portal vein was seen in 35.3% of patients with humped tumors, compared to 14.1% of patients with non-humped ones ($p = 0.0028$, the x^2 test).

Table 3   Univariate and multivariate regression analysis for humped HCC

Factors	Univariate analysis		Multivariate analysis	
	Odds ratio (Range[†])	p	Odds ratio (Range[†])	p
TNM stage[‡]	0.32 (0.19–0.53)	<0.001		
Tumor	2.87 (1.76–4.69)	<0.001		
Node	1.17 (0.10–13.1)	0.90		
Metastasis	9.19 (1.84–45.8)	0.007		
Tumor number (not single)	3.00 (1.91–22.3)	0.003	3.70 (1.02–13.4)	0.047
Tumor size (≥ 2 cm)	5.78 (1.69–19.8)	0.005	3.03 (0.83–11.1)	0.095
VP	3.49 (1.66–7.33)	0.001	2.47 (1.15–5.31)	0.020

Tumor, Tumor stage in TNM classification; Node, Lymph node metastasis; Metastasis, Distant metastasis; VP, Tumor invasion in the portal vein; [†]: 95% confidence interval; [‡]: Tumor-node-metastasis stage according to the Liver Cancer Study Group of Japan.

Discussion

Recent progress in HCC treatment has contributed to improvement of patient survival [1, 2]. However, HCC recurrence occasionally occurs with humped or ruptured HCC. No prospective randomized control trials or comparative studies have examined tumor protrusion. Only a few reports [14, 15] studied the resected tissues of humped or ruptured HCC and discussed successful treatments. This is a retrospective study with consecutive HCC cases, focusing on the characteristics of humped HCC with clinical and radiological analysis. We compared clinical and radiological factors between humped HCC and severely humped HCC, and suggested they might be similar in their essential characters. Our results revealed that humped HCC is often observed in patients at advanced TNM stages with multiple treatments. Furthermore, tumor invasion in the portal vein, rather than tumor size, might play important roles in the mechanisms of tumor protrusion.

The frequency of humped HCC was previously reported at 7.8%, which is close to that of severely humped HCC (10.1%) in our results [14]. Distribution of bleeding or the humped site remains controversial [6, 7, 14–17]. Chen et al. reported more ruptured tumors in the left [7], while no difference in the distribution was reported by Kanematsu et al. [6]. A recent study by Battula et al. showed more ruptured tumors in the right [17], similar to our results of humped HCC. As for the distribution of humped tumors, we doubted the associations of ExHAs, because ExHAs supplies blood for tumors from outside the liver. Therefore, we evaluated ExHAs with regard to tumor protrusion, and revealed that ExHAs are not significantly associated with tumor protrusion. When comparing humped HCC in the right lobe and those in the left, no significant difference was identified in the patient background or tumor size, or the frequency of tumor invasion in the portal vein. Tumors might be difficult to expand out of liver surface if they face to diaphragm, both in the right lobe and in the left.

Our analysis for the mechanisms of tumor protrusion showed that tumor invasion in the portal vein, independently from tumor size, might be significantly associated with tumor protrusion. Ong et al. reported that when portal veins are peripherally obstructed, tumors cannot be drained by the portal veins, causing high pressure in the tumors [18]. High pressure in the tumor might result in tumor protrusion if the tumor is located on the liver surface. Nakashima et al. precisely studied portal vein invasion of HCC with resected HCC tissues and revealed that 33.4% of tumors as small as 2 cm in diameters obstructed the portal vein [14]. Obstructions of the peripheral portal veins might occur on some occasions associated with treatments. When the tumors were treated with ablation, the peripheral portal veins adjacent to the tumors might be injured. Segmental TACE might cause an overflow of iodized oil to segmental portal veins [19–21]. Atrophic changes of the liver parenchyma surrounding the HCC might be associated with tumor protrusion. Patients who receive multiple treatments might consequently be at more risk of peripheral portal obstructions, as shown in the results. The incidence of protrusion might be presumed to be mainly associated with the location of the

tumor and with tumor size. The present study analyzed the location of the tumor, and tumor size as for tumor protrusion, and revealed that large size tumors in poor control cause portal thrombus in some cases, while humped HCCs sometimes occur in small sized tumors, even when HCC control is good. We also revealed that portal vein thrombus is an independent factor for protrusion in multivariate analysis, suggesting that portal vein thrombus is not just a concomitant phenomenon, but one of major factors for tumor protrusion.

In conclusion, humped HCC is often observed in patients at advanced TNM stages regardless of Child-Pugh stage. HCC recurrence with humped HCC might occur more frequently after multiple treatments. Tumor factors of TNM classification, especially tumor invasion in the portal vein, might be associated with tumor protrusion.

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