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RAPID COMMUNICATION

Des-gamma-carboxy prothrombin as an important prognostic indicator in patients with small hepatocellular carcinoma

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Abstract

AIM: To clarify the effect of a high des-gamma-carboxy prothrombin (DCP) level on the invasiveness and prognosis of small hepatocellular carcinoma.

METHODS: Among 142 consecutive patients with known DCP levels, who underwent hepatectomy because of hepatocellular carcinoma, 85 patients met the criteria for small hepatocellular carcinoma, i.e. one ⩽ 5 cm sized single tumor or no more than three ⩽ 3 cm sized tumors.

RESULTS: The overall survival rate of the 142 patients was 92.1% for 1 year, 69.6% for 3 years, and 56.9% for 5 years. Multivariate analysis showed that microscopic vascular invasion (P = 0.03) and serum DCP ⩾ 400 mAU/mL (P = 0.02) were independent prognostic factors. In the group of patients who met the criteria for small hepatocellular carcinoma, DCP ⩾ 400 mAU/mL was found to be an independent prognostic factor for recurrence-free (P = 0.02) and overall survival (P = 0.0005). In patients who did not meet the criteria, the presence of vascular invasion was an independent factor for recurrence-free (P = 0.02) and overall survivals (P = 0.01). In 75% of patients with small hepatocellular carcinoma and high DCP levels, recurrence occurred extrahepatically.

CONCLUSION: For small hepatocellular carcinoma, a high preoperative DCP level appears indicative for tumor recurrence. Because many patients with a high preoperative DCP level develop extrahepatic recurrence, it is necessary to screen the whole body.

Key words: Small hepatocellular carcinoma; Hepatic resection; Des-gamma-carboxy prothrombin; Vascular invasion; Prognostic factor

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INTRODUCTION

Des-gamma-carboxy prothrombin (DCP) is a tumor marker specific for hepatocellular carcinoma[1]. It is believed that the elevation of the serum DCP level correlates with the presence of vascular invasion or intrahepatic metastases[2-8]. Furthermore, DCP has been reported to be an independent prognostic factor for recurrence and survival after hepatic resection[4,9-13], liver transplantation[6,14], ablation treatment[15-17], and transarterial chemoembolization (TAE) treatment[18]. However, the rate of detectable serum DCP levels in patients with small hepatocellular carcinoma is low[19-24]. Although methods have been improved[25,26], sensitivity is still at about 50% for most small cell carcinoma[27-30]. Thus, almost all reports on the biological nature of DCP and its prognostic value are based on analyses of patients with larger or more advanced tumors with various degrees of hepatic functional reserve. Reports on the relevance of preoperative DCP level as a prognostic marker in small hepatocellular carcinoma patients are rare.

This study thus aimed analysing the predictive value of preoperative serum DCP level on tumor recurrence and prognosis, particularly in hepatocellular carcinoma patients who had undergone liver resection and who met the criteria for small hepatocellular carcinoma[31], i.e. a single

tumor with all dimensions being 5 cm or less, or no more than three tumors with dimensions of 3 cm or less.

MATERIALS AND METHODS

From a total of 172 consecutive patients who had undergone a first curative hepatic resection for hepatocellular carcinoma at the Hirosaki University Hospital from 1990 to 2004, 142 patients whose preoperative DCP level was measured by a highly-sensitive assay were enrolled. Patients who met the criteria of small hepatocellular carcinoma, i.e. a single tumor with the largest dimension being 5 cm or less, or no more than three tumors with the largest dimension being 3 cm or less, were compared to the others. Sixteen clinical parameters were recorded [age, gender, Child-Pugh score, serum total bilirubin level, serum albumin level, prothrombin activity, 15-min retention rate of indocyanine green (ICG R15), status of hepatitis virus infection, the number of tumors, the largest dimension of the tumor, the degree of tumor differentiation, the presence or absence of macroscopic and microscopic vascular invasion, the extent of tumor (stage), DCP, and alpha-fetoprotein (AFP)] and the predictivity for probability of recurrence and prognosis of survival were evaluated.

DCP was measured by the chemiluminescent immunoassay using a sensitive anti-DCP antibody (Eisai Co., Ltd., Tokyo, Japan), and threshold values were set to 40, 100, 200, and 400 mAU/mL for determining the presence or absence of a positive reaction. Moreover, the extent of tumor was classified according to the stage classification by the Liver Cancer Study Group of Japan[32].

Statistical analysis

Comparisons between the two groups were carried out by the Chi-square test for categorical data and Student's *t*-test for continuous data. The continuous variables were reported as the mean ± SD. A Cox proportional hazards model was used to test the significance of 16 parameters as predictors of recurrence-free and overall survivals. Kaplan-Meier method and long rank test were also adapted to compare the effect of these factors on survival. These statistical analyses were performed using the SPSS 11.0 statistical software program. P values < 0.05 were considered to be statistically significant.

RESULTS

In this series, 85 of 142 patients met the criteria of small hepatocellular carcinoma, accounting for 60% of the total. Patients' characteristics are given in Table 1. The mean age was 63.0 ± 10.6 years; that of the patients with small hepatocellular carcinoma was significantly higher than that of the patients with greater tumors. No difference was observed between males and females. Concerning Child-Pugh score, Class B was observed more commonly in patients who did not meet the criteria.

Other liver function tests as serum total bilirubin level, albumin level, platelet counts, or ICG R15 were also found to be lower in patients with small hepatocellular carcinoma. A positive status for hepatitis virus, either hepatitis B or C virus, was more frequent in small hepatocellular carcinoma patients. The largest dimension of the tumor was 2.9 ± 1.2 cm in patients who met the criteria for small hepatocellular carcinoma; it was 7.6 ± 4.6 cm in patients who did not meet the criteria, and lesions > 5 cm in size accounted for more than 70% of the cases in the latter group. Ninety percent of the patients who met the criteria for small hepatocellular carcinoma had a solitary lesion, whereas a significantly larger number of patients outside the criteria had multiple lesions. Pathological evaluation of tumor specimens revealed a significantly higher rate of poorly differentiated tumor cells and a more frequent presence of microscopic vascular invasion in patients who did not meet the criteria for small hepatocellular carcinoma compared to those who did. According to the TNM-Staging by the Liver Cancer Study Group of Japan, approximately 90% of the patients who met the criteria were classified as being in Stage Ⅰ or Ⅱ, whereas two-thirds of the patients outside the criteria were classified as being in Stage Ⅲ or higher. Serum AFP level were not found to be different between the two groups, when threshold was set to 40 ng/mL. However, when a threshold of ⩾ 200 ng/mL was chosen, the positive rate among patients outside the criteria was high. On the other hand, the serum DCP showed a lower positive rate among patients who met the criteria for small hepatocellular carcinoma compared to those who did not independently on the threshold value.

The recurrence-free survival and the overall survival of the whole group of patients was 60.3% for 1 year, 29.5% for 3 years, and 13.9% for 5 years, and 92.1% for 1 year, 69.6% for 3 years, and 56.9% for 5 years, respectively. The recurrence-free survival of the patients who met the criteria was 66.2% for 1 year, 34.1% for 3 years, and 16.6% for 5 years, with the overall survival of 97.5% for 1 year, 82.5% for 3 years, and 67.9% for 5 years, which compared particularly well to the recurrence-free survival of patients who did not meet the criteria as 49.9% for 1 year, 20.1% for 3 years, and 7.5% for 5 years ($P = 0.0195$), and the overall survival being 82.8% for 1 year, 46.8% for 3 years, and 36.5% for 5 years ($P < 0.0001$).

An univariate analysis, including all patients revealed the number of tumors, the degree of tissue differentiation, vascular invasion, tumor stage, any of the DCP thresholds, and AFP ⩾ 20 ng/mL, as significant prognostic factors for recurrence. Concerning overall survival, the tumor diameter was also a significant prognostic factor (Table 2). Consequently, a multivariate analysis indicated that microscopic vascular invasions ($P = 0.03$) and DCP ⩾ 400 mAU/mL ($P = 0.02$) were independent prognostic factors for survival prognosis (Table 3). There was no independent factor reflecting the recurrence-free survival.

The univariate analysis of the 85 patients with small hepatocellular carcinoma showed that DCP of various cut-off values was the most significant prognostic factor (Table 4), and a multivariate analysis showed that DCP ⩾ 400 mAU/mL was the only independent prognostic factor for recurrence-free survival (Hazard ratio (HR): 3.32; 95% confidence interval (CI): 1.20-9.17, $P = 0.02$) and overall survival (HR: 1.20; 95% CI: 2.98-50.00, $P = 0.0005$) (Table 5).

On the other hand, a multivariate analysis of the 57 patients outside the criteria showed that microscopic

Table 1 Comparison of demographic and clinical data

Factor		Conforming to the criteria (n = 85)	Outside the criteria (n = 57)	P value
Age (yr)		65.0 ± 8.4	60.1 ± 12.7	0.007
Gender	Male	62 (73%)	44 (77%)	0.57
	Female	23 (27%)	13 (23%)	
Child-Pugh score	Class A	71 (84%)	54 (95%)	0.04
	Class B	14 (16%)	3 (5%)	
	Class C	0	0	
Total bilirubin (mg/dL)		0.90 ± 0.55	0.74 ± 0.32	0.04
	< 1	42 (49%)	41 (72%)	0.008
	⩾ 1	43 (51%)	16 (28%)	
Albumin (g/dL)		3.7 ± 0.5	3.8 ± 0.50	0.04
	⩽ 3.5	39 (46%)	14 (25%)	0.01
	>3.5	46 (54%)	43 (75%)	
Prothrombin time (%)		83.0 ± 15.2	85.9 ± 17.6	0.30
	⩽ 80	35 (41%)	25 (44%)	0.75
	> 80	50 (59%)	32 (56%)	
Platelet count (× 10^4/mm^3)		11.8 ± 6.3	17.5 ± 8.6	< 0.0001
	< 10	35 (41%)	13 (23%)	0.02
	⩾ 10	50 (59%)	44 (77%)	
ICG R15 (%)		19.8 ± 9.9	14.1 ± 1.2	0.0005
	< 15	26 (31%)	35 (61%)	0.0003
	⩾ 15	59 (69%)	22 (39%)	
Hepatitis virus	C positive	68 (80%)	26 (46%)	< 0.0001
	B positive	8 (10%)	15 (26%)	0.008
Tumor number	Single	77 (91%)	29 (51%)	< 0.0001
	Multiple	8 (9%)	28 (49%)	
Tumor size (cm)		2.9 ± 1.2	7.6 ± 4.6	< 0.0001
	⩽ 3	52 (61%)	5 (9%)	< 0.0001
	3-5	33 (39%)	11 (19%)	
	> 5	0	41 (72%)	
Histology	Well or moderately differentiated	68 (87%)	39 (71%)	0.02
	Poorly differentiated	10 (13%)	16 (29%)	
Vascular invasion	Macroscopically positive	0	5 (8.8%)	0.005
	Microscopically positive	8 (10%)	18 (32%)	0.0008
TNM Staging by the LCSGJ[1]	Ⅰ / Ⅱ / Ⅲ / Ⅳ-A	25/51/8/1	2/17/25/13	< 0.0001
	Ⅰ + Ⅱ	76 (89%)	19 (33%)	< 0.0001
	Ⅲ + Ⅳ-A	9 (11%)	38 (67%)	
AFP (ng/mL)		933 ± 6610	31473 ± 192949	0.15
	AFP ⩾ 20	52 (61%)	35 (61%)	0.98
	AFP ⩾ 100	28 (33%)	26 (46%)	0.13
	AFP ⩾ 200	16 (19%)	24 (42%)	0.003
	AFP ⩾ 400	11 (13%)	23 (40 %)	0.0002
DCP (mAU/mL)		780 ± 4129	8168 ± 28247	0.02
	DCP ⩾ 40	45 (53%)	43 (75%)	0.007
	DCP ⩾ 100	26 (31%)	36 (63%)	0.0001
	DCP ⩾ 200	16 (19%)	30 (53%)	< 0.0001
	DCP ⩾ 400	11 (13%)	27 (47%)	< 0.0001

[1]Liver Cancer Study Group of Japan.

vascular invasion was the only independent prognostic factor for recurrence-free survival (HR: 2.97; 95% CI: 1.17-7.58, P = 0.02) and overall survival (HR: 3.92; 95% CI: 1.38-11.24, P = 0.01) (Table 6).

By performing a Kaplan-Meier analysis of small hepatocellular carcinoma patients, the period of recurrence-free survival was found to be significantly shorter in the group of patients with DCP levels ⩾ 400 mAU/mL (P = 0.02), and more than 70% of the patients experienced some recurrence within 1 year (Figure 1A). Tumor recurrence after surgery occurred within the liver in 95% of patients with DCP levels < 400 mAU/mL, but extrahepatically in 75% of patients with DCP levels ⩾ 400 mAU/mL (P < 0.0001). At the time of tumor recurrence, an elevation of DCP levels was observed among all patients. Most of the patients with tumor recurrence received TAE, local ablation therapy, or a second hepatectomy, but the overall survival also significantly decreased for the group of DCP ⩾ 400 mAU/mL (P < 0.0001) (Figure 1B).

DISCUSSION

In this series, a high preoperative level of DCP was the only prognostic indicator for recurrence and poor prognosis in patients who underwent hepatectomy for a small hepatocellular carcinoma. Presence of microscopic vascular invasion, on the other hand, was the independent predictor of poor prognosis of both recurrence-free and overall survivals in more advanced hepatic carcinomas. Thus, different results were obtained for the prognostic factors, depending on disease progression.

There are reports that a high DCP level correlates

Table 2 Univariate analysis for recurrence-free and overall survivals in 142 patients undergoing hepatectomy for hepatocellular carcinoma

Factor	Covariate (*n*)	Reference (*n*)	Recurrence-free survival			Overall survival		
			HR	95% CI	*P*	HR	95% CI	*P*
Gender	Female (36)	Male (106)	1.00	0.63-1.58	0.99	1.26	0.73-2.18	0.42
Child-Pugh score	B (17)	A (125)	0.77	0.42-1.42	0.4	0.87	0.42-1.84	0.72
Total bilirubin (mg/dL)	≥ 1 (59)	< 1 (83)	1.14	0.76-1.70	0.53	1.13	0.68-1.87	0.64
Albumin (g/dL)	≤ 3.5 (53)	> 3.5 (89)	0.93	0.62-1.40	0.74	1.13	0.69-1.86	0.62
Prothrombin time (%)	≤ 80 (60)	> 80 (82)	1.34	0.89-2.01	0.16	1.31	0.79-2.16	0.30
Platelet (× 10^4/mm^3)	< 10 (48)	≥ 10 (94)	0.92	0.61-1.40	0.71	0.82	0.49-1.39	0.47
ICG R15	≥ 15% (81)	< 15% (61)	0.94	0.63-1.40	0.76	0.79	0.48-1.31	0.36
Hepatitis C virus	Positive (94)	Negative (48)	1.24	0.80-1.93	0.33	0.87	0.52-1.48	0.62
Hepatitis B virus	Positive (23)	Negative (118)	0.99	0.58-1.70	0.97	1.39	0.74-2.62	0.30
Number of tumor	Multiple (36)	Single (106)	1.70	1.07-2.71	0.02	2.08	1.22-3.54	0.007
Size of tumor (cm)	> 5 (85)	≤ 5 (57)	1.37	0.86-2.17	0.18	2.00	1.08-3.70	0.03
Histology	Poor[1] (26)	Well-mod[2] (107)	1.70	1.01-2.85	0.04	1.81	0.90-3.65	0.10
Vascular invasion	Present (20)	Absent (113)	1.96	1.19-3.23	0.008	2.36	1.32-4.20	0.004
Stage by LCSGJ[3]	Ⅲ + Ⅳ (47)	Ⅰ + Ⅱ (85)	1.99	1.29-3.06	0.001	2.86	1.71-4.76	< 0.0001
AFP (ng/mL)	≥ 20 (87)	< 20 (55)	1.71	1.11-2.62	0.01	1.90	1.09-3.33	0.02
	≥ 100 (54)	< 100 (88)	1.19	0.79-1.80	0.41	1.43	0.86-2.39	0.16
	≥ 200 (40)	< 200 (102)	1.06	0.68-1.66	0.07	1.25	0.73-2.16	0.41
	≥ 400 (34)	< 400 (108)	1.24	0.78-1.96	0.36	1.59	0.91-2.79	0.10
DCP (mAU/mL)	≥ 40 (88)	< 40 (54)	1.75	1.14-2.70	0.01	1.70	1.00-2.90	0.05
	≥ 100 (62)	< 100 (80)	1.86	1.23-2.80	0.003	1.82	1.10-3.00	0.02
	≥ 200 (46)	< 200 (96)	1.75	1.14-2.70	0.01	3.03	1.79-5.15	< 0.0001
	≥ 400 (38)	< 400 (104)	1.84	1.17-2.89	0.008	2.98	1.73-5.13	< 0.0001

n: Number of patients; HR: Hazard ratio; CI: Confidence interval. [1]Poorly differentiated; [2]Well or moderately differentiated hepatocellular carcinoma; [3]LCSGJ: Liver Cancer Study Group of Japan.

Table 3 Multivariate analysis for recurrence-free and overall survivals in 142 patients undergoing hepatectomy for hepatocellular carcinoma

Factor	Covariate (*n*)	Reference (*n*)	Recurrence-free survival			Overall survival		
			HR	95%CI	*P*	HR	95% CI	*P*
Number of tumor	Multiple (36)	Single (106)	0.93	0.39-2.23	0.87	0.82	0.29-2.35	0.71
Size of tumor (cm)	> 5 (85)	≤ 5 (57)	0.93	0.51-1.82	0.82	1.00	0.41-2.42	1.00
Histology	Poor[1] (26)	Well-mod[2] (107)	1.14	0.63-2.05	0.67	0.73	0.33-1.61	0.44
Vascular invasion	Present (20)	Absent (113)	1.68	0.99-2.86	0.05	2.02	1.07-3.83	0.03
Stage by LCSGJ[3]	Ⅲ+Ⅳ (47)	Ⅰ + Ⅱ (85)	1.72	0.73-2.69	0.22	2.24	0.78-6.45	0.13
AFP (ng/mL)	≥ 20 (87)	< 20 (55)	1.36	0.83-2.22	0.23	1.55	0.81-2.97	0.18
DCP (mAU/mL)	≥ 400 (38)	< 400 (104)	1.45	0.78-2.69	0.24	2.44	1.15-5.21	0.02

n: Number of patients; HR: Hazard ratio; CI; Confidence interval. [1]Poorly differentiated; [2]Well or moderately differentiated hepatocellular carcinoma; [3]LCSGJ: Liver Cancer Study Group of Japan.

with invasiveness and the metastasizing property of carcinoma[2-8]. Shirabe *et al*[8] reported that the preoperative DCP level, tumor diameter, and histologic differentiation correlated with the presence or absence of microscopic vascular invasion in a study on 218 patients who had undergone hepatic resection. Sakon *et al*[2], Suehiro *et al*[4], Grazi *et al*[3], Sugimoto *et al*[5], and Nanashima *et al*[13] also reported that a high preoperative DCP level correlated with the presence of microscopic vascular invasion in patients undergoing hepatectomy. Shimada *et al*[6] reported in a study on 40 patients who had undergone a living donor liver transplantation DCP levels ≥ 300 mAU/mL to be correlated with the presence of microscopic vascular invasion and DCP thus to be a poor prognostic factor.

However, the above reports regarding the invasive character of carcinoma among patients with a high level of DCP were based on the analyses of those with various cancer stages, including more advanced tumors and those with various degrees of liver cirrhosis. There are only a few reports on patients who had undergone a resection for small hepatocellular carcinoma, because vascular invasion or intrahepatic metastases are seldom seen in this group with earlier stage.

It has been reported that the rate of detectable levels of DCP is higher in patients with larger tumors[19]. On the other hand, the positive rate of DCP detectability is low for small hepatocellular carcinoma[19-24]. Okuda *et al*[24] reported that it was 81.3% with a tumor diameter of ≥ 3 cm, while it was 30.4% for ≤ 2 cm. Sassa *et al*[27] reported that it was 44.3% for ≤ 2 cm. An assay that employs higher DCP diagnostic sensitivity has been introduced[25,26], but the diagnostic sensitivity for small hepatocellular carcinoma still remains at about 50%[27-30]. Thus, most reports on biological properties of DCP positive hepatic

Table 4 Univariate analysis for recurrence-free and overall survivals in 85 patients who met the criteria

Factor	Covariate (*n*)	Reference (*n*)	Recurrence-free survival			Overall survival		
			HR	95% CI	*P*	HR	95% CI	*P*
Gender	Female (23)	Male (62)	0.81	0.44-1.48	0.48	0.91	0.43-1.94	0.81
Child-Pugh score	B (14)	A (71)	0.83	0.43-1.61	0.58	1.06	0.46-2.43	0.89
Total bilirubin (mg/dL)	≥ 1 (43)	< 1 (42)	1.37	0.82-2.30	0.23	1.77	0.83-3.79	0.14
Albumin (mg/dL)	≤ 3.5 (39)	> 3.5 (46)	0.92	0.55-1.52	0.74	0.56	0.28-1.09	0.09
Prothrombin time (%)	≤ 80 (35)	> 80 (50)	1.25	0.75-2.08	0.40	0.82	0.42-1.61	0.56
Platelet (× 10^4/mm^3)	< 10 (35)	≥ 10 (50)	1.05	0.63-1.76	0.84	0.98	0.50-1.92	0.95
ICG R15	≥ 15% (59)	< 15% (26)	1.37	0.79-2.38	0.27	1.51	0.70-3.26	0.29
Hepatitis C virus	Positive (68)	Negative (17)	1.42	0.75-2.70	0.28	1.46	0.60-3.52	0.40
Hepatitis B virus	Positive (8)	Negative (76)	0.63	0.25-1.57	0.32	0.56	0.13-2.34	0.43
Number of tumor	Multiple (8)	Single (77)	1.12	0.48-2.61	0.79	1.29	0.50-3.36	0.60
Size of tumor (cm)	> 3 (33)	≤ 3 (52)	1.08	0.64-1.81	0.78	1.27	0.63-2.56	0.50
Histology	Poor[1] (10)	Well-mod[2] (68)	1.32	0.56-3.11	0.53	3.03	0.89-10.29	0.08
Vascular invasion	Present (8)	Absent (75)	0.96	0.38-2.06	0.77	0.88	0.31-2.54	0.82
Stage by LCSGJ[3]	Ⅲ + Ⅳ (9)	Ⅰ + Ⅱ (76)	1.41	0.64-3.12	0.39	1.80	0.74-4.35	0.20
AFP (ng/mL)	≥ 20 (52)	< 20 (33)	1.47	0.87-2.49	0.15	1.50	0.75-3.02	0.25
	≥ 100 (28)	< 100 (57)	0.77	0.42-1.39	0.39	0.80	0.36-1.75	0.57
	≥ 200 (16)	< 200 (69)	0.53	0.25-1.13	0.10	0.50	0.18-1.42	0.20
	≥ 400 (11)	< 400 (74)	0.57	0.23-1.43	0.23	0.53	0.13-2.21	0.38
DCP (mAU/mL)	≥ 40 (45)	< 40 (40)	1.73	1.03-2.92	0.04	1.46	0.75-2.82	0.27
	≥ 100 (26)	<100 (59)	1.67	0.96-2.91	0.07	1.71	0.83-3.50	0.14
	≥ 200 (16)	< 200 (69)	1.69	0.84-3.40	0.14	5.81	2.56-13.16	< 0.0001
	≥ 400 (11)	< 400 (74)	2.41	1.12-5.18	0.02	5.71	2.38-13.70	< 0.0001

n: Number of patients; HR: Hazard ratio; CI: Confidence interval. [1]Poorly differentiated; [2]Well or moderately differentiated hepatocellular carcinoma; [3]LCSGJ: Liver Cancer Study Group of Japan.

Table 5 Multivariate analysis for recurrence-free and overall survivals in 85 patients who met the criteria

Factor	Covariate (*n*)	Reference (*n*)	Recurrence-free survival			Overall survival		
			HR	95% CI	*P*	HR	95% CI	*P*
Number of tumor	Multiple (8)	Single (77)	0.66	0.06-7.45	0.74	0.46	0.006-35.08	0.72
Histology	Poor[1] (10)	Well-mod[2] (68)	0.70	0.24-2.01	0.51	0.37	0.07-2.12	0.27
Vascular invasion	Present (8)	Absent (75)	1.04	0.44-2.46	0.93	0.96	0.31-2.99	0.95
Stage by LCSGJ[3]	Ⅲ + Ⅳ (9)	Ⅰ + Ⅱ (76)	1.90	0.17-21.28	0.60	3.97	0.05-333.33	0.53
AFP (ng/mL)	≥ 20 (52)	< 20 (33)	1.28	0.71-2.29	0.41	1.20	0.54-2.66	0.66
DCP (mAU/mL)	≥ 400 (11)	< 400 (74)	3.32	1.20-9.17	0.02	1.20	2.98-50.00	0.0005

n: Number of patients; HR: Hazard ratio; CI: Confidence interval. [1]Poorly differentiated; [2]Well or moderately differentiated hepatocellular carcinoma; [3]LCSGJ: Liver Cancer Study Group of Japan.

Table 6 Multivariate analysis for recurrence-free and overall survivals in 57 patients who did not meet the criteria

Factor	Covariate (*n*)	Reference (*n*)	Recurrence-free survival			Overall survival		
			HR	95% CI	*P*	HR	95% CI	*P*
Gender	Female (13)	Male (44)	1.35	0.56-3.25	0.50	2.35	0.90-6.17	0.08
Number of tumor	Multiple (28)	Single (29)	0.84	0.32-2.25	0.73	0.72	0.24-2.20	0.57
Histology	Poor[1] (16)	Well-mod[2] (39)	1.14	0.47-2.76	0.76	0.61	0.21-1.73	0.35
Vascular invasion	Present (18)	Absent (38)	2.97	1.17-7.58	0.02	3.92	1.38-11.24	0.01
Stage by LCSGJ[3]	Ⅲ + Ⅳ (38)	Ⅰ + Ⅱ (19)	1.65	0.57-4.78	0.36	1.92	0.52-7.09	0.33
AFP (ng/mL)	≥ 20 (35)	< 20 (22)	1.58	0.59-4.22	0.36	1.85	0.52-6.54	0.34
DCP (mAU/mL)	≥ 400 (27)	< 400 (30)	0.79	0.35-1.79	0.58	2.29	0.35-2.29	0.83

n: Number of patients; HR: Hazard ratio; CI: Confidence interval. [1]Poorly differentiated; [2]Well or moderately differentiated hepatocellular carcinoma; [3]LCSGJ: Liver Cancer Study Group of Japan.

carcinoma are based on more advanced diseases[7].

Many reports state high DCP levels to be of poor prognostic value. It has been shown that patients with high DCP and high AFP levels show poor prognostic factors[4,6,10-12,14-18]. Thus, a prognostic staging system in which DCP has been incorporated is being suggested. From an analysis of 141 patients Kawakita *et al*[15] concluded DCP ≥ 100 mAU/mL to be a prognostic factor, and the authors suggested a stage classification in which DCP ≥ 100 mAU/mL should be incorporated into

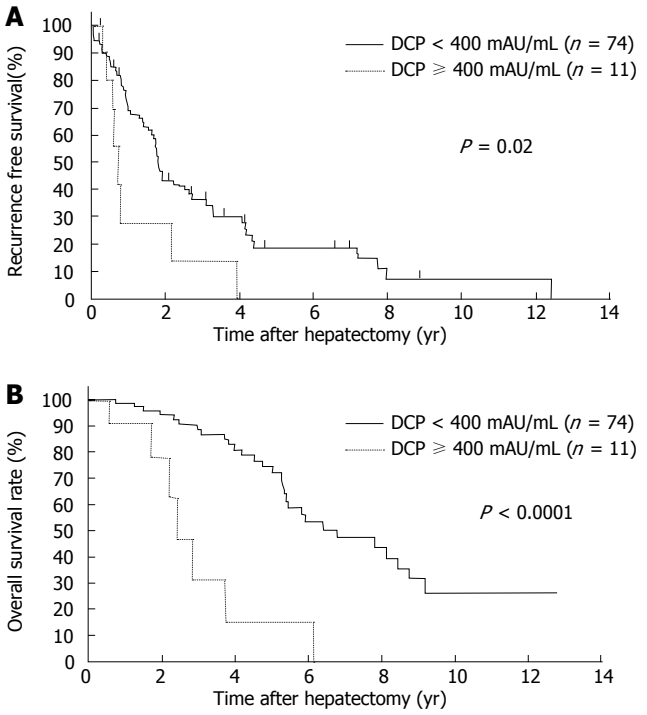

Figure 1 Postoperative recurrence-free (**A**) and overall (**B**) survival of patients with small hepatocellular carcinoma. In 85 patients who met the criteria for small hepatocellular carcinoma, the period of recurrence-free survival was significantly shorter in patients with DCP ⩾ 400 mAU/mL than in those with DCP < 400 mAU/mL (P = 0.02). More than 70% of recurrences occurred within a year (**A**). Overall survival was also significantly shorter in patients with DCP ⩾ 400 mAU/mL (**B**).

the CLIP score. Nanashima *et al*[13] concluded that DCP ⩾ 400 mAU/mL was a poor prognostic factor and suggested modified CLIP scoring. Moreover, Omagari *et al*[16] suggested the SLiDe score combined with stages and liver damage, and Toyoda *et al*[17] suggested the BALAD score that can predict the prognosis only by measuring bilirubin, albumin, AFP-L3, AFP, and DCP using preoperative serum samples, according to an analysis of 2600 patients.

In this study, we used the criteria of small hepatocellular carcinoma "a 5-cm single tumor or no more than three 3-cm tumors" as suggested by Mazzaferro *et al*[31]. These criteria are internationally accepted as inclusion criteria for liver transplantation for unresectable small hepatocellular carcinoma, because they reflect a restriction of the tumor to the liver[33].

The univariate analyses of 16 clinical parameters in all patients indicated that the number of tumors, the tumor diameter, the degree of histologic differentiation, vascular invasion, the tumor staging, serum AFP level, and DCP level to be significant prognostic factors. These results are in accordance with previous reports[3,8,10,12,15-19,34-36]. However, limiting this to small hepatocellular carcinoma, DCP alone is the independent prognostic factor for both tumor recurrence and patients' survival, while presence of microscopic vascular invasion is a prognostic factor in patients outside the criteria. Regarding the mechanism of these different results, we assume the following. "Specifically, a high DCP level constitutes a risk factor of microscopic vascular invasion and in small hepatocellular carcinoma, DCP shows positive before the development of microscopic vascular invasion and becomes an independent prognostic factor. As a tumor becomes larger, the frequency of the detection of microscopic vascular invasion increases and the independence of DCP disappears, thus showing a stronger correlation with the prognosis than does DCP."

DCP is an abnormal prothrombin that is produced by under-carboxylation of normal prothrombin[37]. Suzuki *et al*[38] reported that DCP exerts a mitogenic effect on hepatocellular carcinoma cells *via* a Met-Janus kinase 1-STAT3 signaling pathway. On the other hand, it has been demonstrated that the antiproliferative effect of vitamin K on hepatic carcinoma is not due to a depressed production of DCP, but rather caused by protein kinase A[39]. Regarding the above, the mechanism of the antiproliferative effect of DCP on hepatic carcinoma is still unknown. However, in this study, it was clarified that a high DCP level is an important prognostic factor for recurrence, even in a condition in which small hepatocellular carcinoma before the histological invasion of carcinoma such as vascular invasion becomes obvious. This result corresponds to reports by Koike *et al*[40] and Hagiwara *et al*[34] showing that patients who have a high DCP level can expect the expression of future vascular invasion. Moreover, in many of our patients tumor recurred extrahepatically early after resection. Regarding the precise mechanism of DCP on hepatic carcinoma development, it would be necessary to study its effect on the initiation of vascular invasion and on proliferative activity.

COMMENTS

Background

Des-gamma-carboxy prothrombin (DCP) is a marker specific for hepatocellular carcinoma, which has been reported to correlate with the presence of vascular invasion. These reports, however, are based mostly on analyses on advanced carcinoma.

Research frontiers

In this study, the authors retrospectively reviewed the prognostic factors in patients undergoing a first hepatectomy for hepatocellular carcinoma, with special reference to the effect of a high DCP level on the prognosis of small hepatocellular carcinoma.

Innovations and breakthroughs

Preoperative DCP was found to have a different prognostic impact in small hepatocellular carcinoma compared to more advanced tumors. DCP ⩾ 400 mAU/mL was an independent prognostic factor for recurrence-free and overall survivals in patients with small hepatocellular carcinoma.

Applications

Preoperative DCP could be integrated into the prognostic scoring, staging and inclusion criteria for hepatectomy, and liver transplantation in patients with small hepatocellular carcinoma.

Peer review

The paper with its scientific and innovative contents as well as readability reflects the advanced level of the clinical research in gastroenterology both at home and abroad.

REFERENCES

1 **Liebman HA**, Furie BC, Tong MJ, Blanchard RA, Lo KJ, Lee

SD, Coleman MS, Furie B. Des-gamma-carboxy (abnormal) prothrombin as a serum marker of primary hepatocellular carcinoma. *N Engl J Med* 1984; **310**: 1427-1431
2 **Sakon M**, Monden M, Gotoh M, Kanai T, Umeshita K, Nakano Y, Mori T, Sakurai M, Wakasa K. Relationship between pathologic prognostic factors and abnormal levels of des-gamma-carboxy prothrombin and alpha-fetoprotein in hepatocellular carcinoma. *Am J Surg* 1992; **163**: 251-256
3 **Grazi GL**, Mazziotti A, Legnani C, Jovine E, Miniero R, Gallucci A, Palareti G, Gozzetti G. The role of tumor markers in the diagnosis of hepatocellular carcinoma, with special reference to the des-gamma-carboxy prothrombin. *Liver Transpl Surg* 1995; **1**: 249-255
4 Suehiro T, Matsumata T, Itasaka H, Taketomi A, Yamamoto K, Sugimachi K. Des-gamma-carboxy prothrombin and proliferative activity of hepatocellular carcinoma. *Surgery* 1995; **117**: 682-691
5 **Sugimoto H**, Takeda S, Inoue S, Kaneko T, Watanabe K, Nakao A. Des-gamma-carboxy prothrombin (DCP) ratio, a novel parameter measured by monoclonal antibodies MU-3 and 19B7, as a new prognostic indicator for hepatocellular carcinoma. *Liver Int* 2003; **23**: 38-44
6 **Shimada M**, Yonemura Y, Ijichi H, Harada N, Shiotani S, Ninomiya M, Terashi T, Yoshizumi T, Soejima Y, Maehara Y. Living donor liver transplantation for hepatocellular carcinoma: a special reference to a preoperative des-gamma-carboxy prothrombin value. *Transplant Proc* 2005; **37**: 1177-1179
7 **Carr BI**, Kanke F, Wise M, Satomura S. Clinical evaluation of lens culinaris agglutinin-reactive alpha-fetoprotein and des-gamma-carboxy prothrombin in histologically proven hepatocellular carcinoma in the United States. *Dig Dis Sci* 2007; **52**: 776-782
8 **Shirabe K**, Itoh S, Yoshizumi T, Soejima Y, Taketomi A, Aishima S, Maehara Y. The predictors of microvascular invasion in candidates for liver transplantation with hepatocellular carcinoma-with special reference to the serum levels of des-gamma-carboxy prothrombin. *J Surg Oncol* 2007; **95**: 235-240
9 **Shimada M**, Takenaka K, Fujiwara Y, Gion T, Kajiyama K, Maeda T, Shirabe K, Sugimachi K. Des-gamma-carboxy prothrombin and alpha-fetoprotein positive status as a new prognostic indicator after hepatic resection for hepatocellular carcinoma. *Cancer* 1996; **78**: 2094-2100
10 **Imamura H**, Matsuyama Y, Miyagawa Y, Ishida K, Shimada R, Miyagawa S, Makuuchi M, Kawasaki S. Prognostic significance of anatomical resection and des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma. *Br J Surg* 1999; **86**: 1032-1038
11 **Utsunomiya T**, Shimada M, Shirabe K, Kajiyama K, Gion T, Takenaka K, Sugimachi K. Clinicopathological characteristics of patients with extrahepatic recurrence following a hepatectomy for hepatocellular carcinoma. *Hepatogastroenterology* 2001; **48**: 1088-1093
12 **Kaibori M**, Matsui Y, Yanagida H, Yokoigawa N, Kwon AH, Kamiyama Y. Positive status of alpha-fetoprotein and des-gamma-carboxy prothrombin: important prognostic factor for recurrent hepatocellular carcinoma. *World J Surg* 2004; **28**: 702-707
13 **Nanashima A**, Morino S, Yamaguchi H, Tanaka K, Shibasaki S, Tsuji T, Hidaka S, Sawai T, Yasutake T, Nakagoe T. Modified CLIP using PIVKA-II for evaluating prognosis after hepatectomy for hepatocellular carcinoma. *Eur J Surg Oncol* 2003; **29**: 735-742
14 **Soejima Y**, Taketomi A, Yoshizumi T, Uchiyama H, Aishima S, Terashi T, Shimada M, Maehara Y. Extended indication for living donor liver transplantation in patients with hepatocellular carcinoma. *Transplantation* 2007; **83**: 893-899
15 **Kawakita T**, Shiraki K, Yamanaka Y, Yamaguchi Y, Saitou Y, Enokimura N, Yamamoto N, Okano H, Sugimoto K, Murata K, Yamakado K, Takeda K, Nakano T. A new prognostic scoring system involving des-gamma-carboxy prothrombin as a useful marker for predicting prognosis in patients with hepatocellular carcinoma. *Int J Oncol* 2003; **23**: 1115-1120
16 **Omagari K**, Honda S, Kadokawa Y, Isomoto H, Takeshima F, Hayashida K, Mizuta Y, Murata I, Kohno S. Preliminary analysis of a newly proposed prognostic scoring system (SLiDe score) for hepatocellular carcinoma. *J Gastroenterol Hepatol* 2004; **19**: 805-811
17 **Toyoda H**, Kumada T, Osaki Y, Oka H, Urano F, Kudo M, Matsunaga T. Staging hepatocellular carcinoma by a novel scoring system (BALAD score) based on serum markers. *Clin Gastroenterol Hepatol* 2006; **4**: 1528-1536
18 **Maeda S**, Fujiyama S, Tanaka M, Ashihara H, Hirata R, Tomita K. Survival and local recurrence rates of hepatocellular carcinoma patients treated by transarterial chemolipiodolization with and without embolization. *Hepatol Res* 2002; **23**: 202-210
19 **Nakamura S**, Nouso K, Sakaguchi K, Ito YM, Ohashi Y, Kobayashi Y, Toshikuni N, Tanaka H, Miyake Y, Matsumoto E, Shiratori Y. Sensitivity and specificity of des-gamma-carboxy prothrombin for diagnosis of patients with hepatocellular carcinomas varies according to tumor size. *Am J Gastroenterol* 2006; **101**: 2038-2043
20 **Kasahara A**, Hayashi N, Fusamoto H, Kawada Y, Imai Y, Yamamoto H, Hayashi E, Ogihara T, Kamada T. Clinical evaluation of plasma des-gamma-carboxy prothrombin as a marker protein of hepatocellular carcinoma in patients with tumors of various sizes. *Dig Dis Sci* 1993; **38**: 2170-2176
21 **Chan CY**, Lee SD, Wu JC, Lin HC, Huang YS, Lo GH, Lee FY, Tsai YT, Lo KJ. The diagnostic value of the assay of des-gamma-carboxy prothrombin in the detection of small hepatocellular carcinoma. *J Hepatol* 1991; **13**: 21-24
22 **Weitz IC**, Liebman HA. Des-gamma-carboxy (abnormal) prothrombin and hepatocellular carcinoma: a critical review. *Hepatology* 1993; **18**: 990-997
23 **Nomura F**, Ishijima M, Kuwa K, Tanaka N, Nakai T, Ohnishi K. Serum des-gamma-carboxy prothrombin levels determined by a new generation of sensitive immunoassays in patients with small-sized hepatocellular carcinoma. *Am J Gastroenterol* 1999; **94**: 650-654
24 **Okuda H**, Nakanishi T, Takatsu K, Saito A, Hayashi N, Takasaki K, Takenami K, Yamamoto M, Nakano M. Serum levels of des-gamma-carboxy prothrombin measured using the revised enzyme immunoassay kit with increased sensitivity in relation to clinicopathologic features of solitary hepatocellular carcinoma. *Cancer* 2000; **88**: 544-549
25 **Ikoma J**, Kaito M, Ishihara T, Nakagawa N, Kamei A, Fujita N, Iwasa M, Tamaki S, Watanabe S, Adachi Y. Early diagnosis of hepatocellular carcinoma using a sensitive assay for serum des-gamma-carboxy prothrombin: a prospective study. *Hepatogastroenterology* 2002; **49**: 235-238
26 **Ando E**, Tanaka M, Yamashita F, Kuromatsu R, Takada A, Fukumori K, Yano Y, Sumie S, Okuda K, Kumashiro R, Sata M. Diagnostic clues for recurrent hepatocellular carcinoma: comparison of tumour markers and imaging studies. *Eur J Gastroenterol Hepatol* 2003; **15**: 641-648
27 **Sassa T**, Kumada T, Nakano S, Uematsu T. Clinical utility of simultaneous measurement of serum high-sensitivity des-gamma-carboxy prothrombin and Lens culinaris agglutinin A-reactive alpha-fetoprotein in patients with small hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 1999; **11**: 1387-1392
28 **Shimauchi Y**, Tanaka M, Kuromatsu R, Ogata R, Tateishi Y, Itano S, Ono N, Yutani S, Nagamatsu H, Matsugaki S, Yamasaki S, Tanikawa K, Sata M. A simultaneous monitoring of Lens culinaris agglutinin A-reactive alpha-fetoprotein and des-gamma-carboxy prothrombin as an early diagnosis of hepatocellular carcinoma in the follow-up of cirrhotic patients. *Oncol Rep* 2000; **7**: 249-256
29 **Toyoda H**, Kumada T, Kiriyama S, Sone Y, Tanikawa M, Hisanaga Y, Yamaguchi A, Isogai M, Kaneoka Y, Washizu J. Prognostic significance of simultaneous measurement of three tumor markers in patients with hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2006; **4**: 111-117
30 **Mita Y**, Aoyagi Y, Yanagi M, Suda T, Suzuki Y, Asakura H. The usefulness of determining des-gamma-carboxy prothrombin by sensitive enzyme immunoassay in the early diagnosis of patients with hepatocellular carcinoma. *Cancer* 1998; **82**:

1643-1648
31 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699
32 **Liver Cancer Study Group of Japan**. Classification of Primary Liver Cancer. 1st ed. Tokyo: Kanehara, 1997: 2-22
33 **Furukawa H**, Shimamura T, Suzuki T, Taniguchi M, Yamashita K, Kamiyama T, Matsushita M, Todo S. Living-donor liver transplantation for hepatocellular carcinoma. *J Hepatobiliary Pancreat Surg* 2006; **13**: 393-397
34 **Hagiwara S**, Kudo M, Kawasaki T, Nagashima M, Minami Y, Chung H, Fukunaga T, Kitano M, Nakatani T. Prognostic factors for portal venous invasion in patients with hepatocellular carcinoma. *J Gastroenterol* 2006; **41**: 1214-1219
35 **Hamamura K**, Shiratori Y, Shiina S, Imamura M, Obi S, Sato S, Yoshida H, Omata M. Unique clinical characteristics of patients with hepatocellular carcinoma who present with high plasma des-gamma-carboxy prothrombin and low serum alpha-fetoprotein. *Cancer* 2000; **88**: 1557-1564
36 **Tateishi R**, Shiina S, Yoshida H, Teratani T, Obi S, Yamashiki N, Yoshida H, Akamatsu M, Kawabe T, Omata M. Prediction of recurrence of hepatocellular carcinoma after curative ablation using three tumor markers. *Hepatology* 2006; **44**: 1518-1527
37 **Naraki T**, Kohno N, Saito H, Fujimoto Y, Ohhira M, Morita T, Kohgo Y. gamma-Carboxyglutamic acid content of hepatocellular carcinoma-associated des-gamma-carboxy prothrombin. *Biochim Biophys Acta* 2002; **1586**: 287-298
38 **Suzuki M**, Shiraha H, Fujikawa T, Takaoka N, Ueda N, Nakanishi Y, Koike K, Takaki A, Shiratori Y. Des-gamma-carboxy prothrombin is a potential autologous growth factor for hepatocellular carcinoma. *J Biol Chem* 2005; **280**: 6409-6415
39 **Otsuka M**, Kato N, Shao RX, Hoshida Y, Ijichi H, Koike Y, Taniguchi H, Moriyama M, Shiratori Y, Kawabe T, Omata M. Vitamin K2 inhibits the growth and invasiveness of hepatocellular carcinoma cells via protein kinase A activation. *Hepatology* 2004; **40**: 243-251
40 **Koike Y**, Shiratori Y, Sato S, Obi S, Teratani T, Imamura M, Yoshida H, Shiina S, Omata M. Des-gamma-carboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma: a prospective analysis of 227 patients. *Cancer* 2001; **91**: 561-569

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