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C-reactive protein may be a prognostic factor in hepatocellular carcinoma with malignant portal vein invasion

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Abstract

Background: Hepatocellular carcinoma (HCC) has a high predilection for portal vein invasion, and the prognosis of HCC with malignant portal vein invasion is extremely poor. The objective of this study was to investigate the outcomes and the prognostic factor of recurrence in HCC patients with malignant portal vein invasion.

Methods: We retrospectively reviewed the clinicopathologic data and outcomes of 83 HCC patients with malignant portal vein invasion and 1,056 patients without portal vein invasion who underwent liver resection.

Results: Increased serum alkaline phosphatase (ALP) levels, increased maximum tumor size, and intrahepatic metastasis were predisposing factors for malignant portal vein invasion by multivariate analysis. The median disease-free survival and overall survival of HCC patients with malignant portal vein invasion was 4.5 months and 25 months, respectively. The 1-year, 2-year, and 3-year disease-free survival rates were 30.6%, 26.1%, and 21.2%, respectively, and the overall survival rates for HCC patients with malignant portal vein invasion were 68.6%, 54.2%, and 41.6%, respectively. The initial detection site was the lung in HCC patients with portal vein invasion and the liver in HCC patients without portal vein invasion. C-reactive protein (CRP) was a significant independent predictor of tumor recurrence in HCC with malignant portal vein invasion after surgery.

Conclusions: Increased ALP levels, increased maximum tumor size, and intrahepatic metastasis were independent predictors of malignant portal vein invasion in HCC. CRP level was closely associated with the predisposing factor of tumor recurrence in HCC patients with malignant portal vein invasion after a surgical resection, and lung metastasis was common.

Keywords: C-reactive protein, Hepatectomy, Hepatocellular carcinoma, Malignant portal vein invasion, Tumor recurrence

Background

Hepatocellular carcinoma (HCC) is a leading cause of cancer death, and its incidence is particularly high in Asian countries, including Korea. Chronic hepatitis B is endemic in Korea, representing the most important risk factor and constituting approximately 70% of all HCC cases [1].

The prognosis of HCC is very poor as a result of intrahepatic metastasis and recurrence, which are closely

associated with portal vein invasion [2,3]. HCC has a tendency to invade the portal vein causing tumor thrombosis, which has been shown to be an adverse prognostic factor for HCC [4]. The prognosis of HCC with portal vein tumor invasion is extremely poor, with a median survival of 2.7 to 4 months without intervention [5]. However, the characteristics of HCC with malignant portal vein invasion are not well understood.

Although liver transplantation for HCC alters the natural history of this disease, liver resection remains one of the main treatment modalities that can provide a good outcome [6].

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In this study, we retrospectively compared patients with portal vein invasion to patients without portal vein invasion and analyzed the predisposing factors of tumor recurrence in HCC patients with malignant portal vein invasion who underwent liver resection.

Methods

Patients

From January 2006 to June 2010, 1,139 patients who were newly diagnosed with HCC underwent liver resection at Samsung Medical Center. The diagnoses of HCC with malignant portal vein invasion were confirmed by a histologic examination after surgery. We excluded patients who were younger (age <18 years), had pathologically proven mixed hepatocellular carcinoma and cholangiocarcinoma, or who were lost to follow-up after liver resection. The demographic, preoperative laboratory, and pathologic data of all patients were collected from the electronic medical record (EMR) and retrospectively reviewed. The Child-Pugh classification system was used to evaluate liver function.

Surgery and pathology

Selection criteria for the liver resection procedure depended on tumor location and extent, liver function, and future liver remnant volume. Child-Pugh class C, severe co-morbidity, and distant metastasis were considered contraindications for hepatectomy. A standard operative technique for the hepatectomy was used for these tumors. Depending on the part of liver to be resected, adequate mobilization was performed. Selective clamping of the portal vein and hepatic artery was performed when feasible; if not, intermittent the Pringle maneuver was performed. The parenchymal transection was performed using Cavitron Ultrasonic Surgical Aspirator (CUSA) under low central venous pressure. A major hepatectomy was defined as a resection of three or more Couinaud segments, and minor hepatectomy was defined as resection of less than three segments. R₀ resection status was defined as the presence of microscopic tumor >1 mm from the resection margin.

Postoperative histological assessment and reporting included the maximal tumor diameter, capsular formation, capsular invasion, portal vein invasion, bile duct invasion, microvascular invasion, serosal involvement, intrahepatic metastasis, multicentric occurrence of HCC, cirrhosis, resection margin, and others. Histologic grade of HCC was assessed according to the Edmonson-Steiner grade system, and groups as well differentiated (grade I), moderate differentiated (grade II), or poorly differentiated (grades III, IV) [7].

Surveillance after surgical resection

After surgery, the patients with HCC with pathologic portal vein invasion were followed up every 2 to 3 months in the postoperative period. A follow-up included physical examination, serum alpha-fetoprotein (AFP), protein induced by vitamin K antagonist (PIVKA)-II, liver function test, and chest X-ray. An abdominal computed tomography (CT) was performed every 3 months or when intrahepatic recurrence was suspected. Magnetic resonance imaging (MRI) and/or positron emission tomography (PET) scan were performed as CT could not show definitively the evidence of recurrence. Detailed information on patients who were identified to have peritoneal recurrence was recorded. Patients with intrahepatic recurrence were treated with radiofrequency ablation (RFA), transarterial chemoembolization (TACE), or sorafenib according to their liver function reserve and the pattern of recurrence. The follow-up time was defined as the length of time from surgery to last follow-up (December 1, 2011) or death. None of the patients were lost to follow-up or died within 30 days after surgery, and 1,139 patients were included in the survival analysis.

Statistical analysis

All data were analyzed using SPSS statistical software (Ver 19.0; SPSS Inc., Chicago, IL, USA). Continuous variables are presented as the median and range and were compared by Mann-Whitney *U* test. Categorical variables were compared by Fisher's exact test. A multivariate analysis was performed to identify the risk factors of the pathological portal vein invasion using logistic regression analysis. The disease-free survival rates and overall survival rates were calculated with the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed to identify the risk factors of HCC recurrence in HCC with pathologic portal vein invasion using Cox regression model. A *P* value of <0.05 was considered statistically significant.

Results

Demographics of HCC patients with portal vein invasion

The clinicopathologic features of HCC patients with malignant portal vein invasion and HCC patients without malignant portal vein invasion are summarized in Table 1. Of the 83 HCC patients (7.3%) with malignant portal vein invasion, there were 71 men and 12 women, with a median age of 49 years (range, 20–72 years). There were 1,056 (92.7%) HCC patients without portal vein invasion, and their median age was 54 years (range, 19–92 years). The age of HCC patients with malignant portal vein invasion was lower than that of HCC patients without portal vein invasion (*P* <0.001). Most cases of HCC were caused by hepatitis B virus (HBV), and

Table 1 Characteristics of HCC patients with and without portal vein invasion

Variables	HCC with PV invasion (n=83, 7.3%)	HCC without PV invasion (n=1056, 92.7%)	P value
<i>Gender</i>			0.252
Male	71 (85.5%)	842 (79.7%)	
Female	12 (14.5%)	214 (20.3%)	
Age (years)	49 (20–72)	54 (19–82)	<0.001
<i>Etiology</i>			0.447
HBV	63 (75.9%)	816 (77.6%)	
HCV	4 (4.8%)	54 (5.1%)	
Alcohol	4 (4.8%)	19 (1.8%)	
Non-B, non-C	10 (12.0%)	142 (13.5%)	
Others	2 (2.4%)	20 (1.9%)	
<i>Locoregional therapy</i>			0.070
None	64 (77.1%)	907 (85.9%)	
TACE	18 (21.7%)	127 (12.0%)	
RFA	1 (1.2%)	13 (1.2%)	
TACE and RFA	0 (0%)	9 (0.9%)	
White blood cells (/uL)	5,730 (2,520–10,530)	5,460 (1,270–16,530)	0.103
Hemoglobin (g/dL)	14.3 (9.8–17.0)	14.2 (8.1–16.8)	0.360
Platelet counts (/uL)	174,000 (80,000–627,000)	160,000 (19,000–708,000)	0.125
INR	1.09 (0.93–1.32)	1.08 (0.84–1.59)	0.901
Albumin (g/dL)	4.1 (2.9–5.0)	4.1 (2.1–5.3)	0.423
Total bilirubin (mg/dL)	0.7 (0.2–3.5)	0.7 (0.2–4.3)	0.310
AST (U/L)	43 (23–283)	35 (14–353)	<0.001
ALT (U/L)	44 (17–288)	35 (13–385)	0.002
ALP (U/L)	93 (38–233)	79 (32–562)	<0.001
GGT (U/L)	105 (17–1,442)	49 (8–1,322)	<0.001
Creatinine (mg/dL)	0.86 (0.44–1.27)	0.88 (0.42–5.87)	0.586
Estimated GFR (mL/min)	98.6 (72.2–149.2)	89.4 (5.7–189.0)	0.003
CRP (mg/dL)	0.27 (0.04–28.62)	0.13 (0.01–22.24)	0.048
AFP (ng/mL)	813.2 (1.8–200,000)	26.4 (1.0–2,121,720)	<0.001
PIVKA-II (mAU/mL)	482.0 (12–1,200)	42.0 (2–2,000)	<0.001
<i>Operation</i>			<0.001
Anatomical	61 (73.5%)	540 (51.1%)	
Non-anatomical	22 (26.5%)	516 (48.9%)	
<i>Hepatectomy</i>			<0.001
Major	50 (60.2%)	274 (25.9%)	
Minor	33 (39.8%)	782 (74.1%)	
<i>Resection</i>			0.035
R ₀	77 (93.9%)	1029 (98.0%)	
R ₁	5 (6.1%)	21 (2.0%)	
Margin (mm)	10 (1–53)	10 (1–80)	0.331
Maximum tumor size (mm)	6.0 (1.4–17.5)	3.3 (0.2–21.0)	<0.001

Table 1 Characteristics of HCC patients with and without portal vein invasion (Continued)

Grade			0.001
1 and 2	67 (80.7%)	976 (92.4%)	
3 and 4	16 (19.3%)	80 (7.6%)	
Cirrhosis	40 (48.2%)	468 (44.3%)	0.494
Capsule formation			<0.001
None	33 (39.8%)	69 (6.6%)	
Complete	35 (42.2%)	875 (83.2%)	
Partial	15 (18.1%)	108 (10.3%)	
Bile duct invasion	7 (8.4%)	24 (2.3%)	0.005
Serosa involvement	2 (2.4%)	12 (1.1%)	0.272
Intrahepatic metastasis	41 (49.4%)	112 (10.6%)	<0.001
Multicentric occurrence	1 (1.2%)	57 (5.4%)	0.118
Hospitalization	9 (5–53)	9 (3–102)	0.932
Duration of Follow-up (months)	18 (5–68)	32 (3–82)	<0.001

AFP, Alpha-fetoprotein; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CRP, C-reactive protein; GFR, Estimated glomerular filtration rate; GGT, Gamma-glutamyl transferase; HBV, Hepatitis B virus; HCV, Hepatitis C virus; INR, International normalized ratio; PIVKA-II, Protein induced by vitamin K antagonist-II; PV, Portal vein; RFA, Radiofrequency ablation; TACE, Transarterial chemoembolization.

patients with malignant portal vein invasion did not receive radiation in the preoperative period. There were no differences in gender, cause, and type of locoregional therapy between the two groups. As for laboratory data before the operation, the HCC patients with malignant portal vein invasion had higher serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), estimated glomerular filtration rate (GFR), and C-reactive protein (CRP) levels compared with HCC patients without portal vein invasion ($P < 0.05$). However, white blood cell (WBC) count, hemoglobin, platelet count, INR, albumin, total bilirubin, direct bilirubin, and creatinine were similar in both groups. The median of AFP and PIVKA-II in HCC patients with malignant portal vein invasion was 813.2 ng/mL (range, 1.8–200,000 ng/mL) and 482.0 mAU/mL (range, 12–1,200 mAU/mL), respectively, but the median in HCC patients without portal vein invasion was 26.4 ng/mL (range, 1.0–2,121,720 ng/mL) and 42.0 mAU/mL (range, 2–2,000 mAU/mL), respectively ($P < 0.001$ and $P < 0.001$, respectively).

The surgery and pathologic results in HCC patients with malignant portal vein invasion

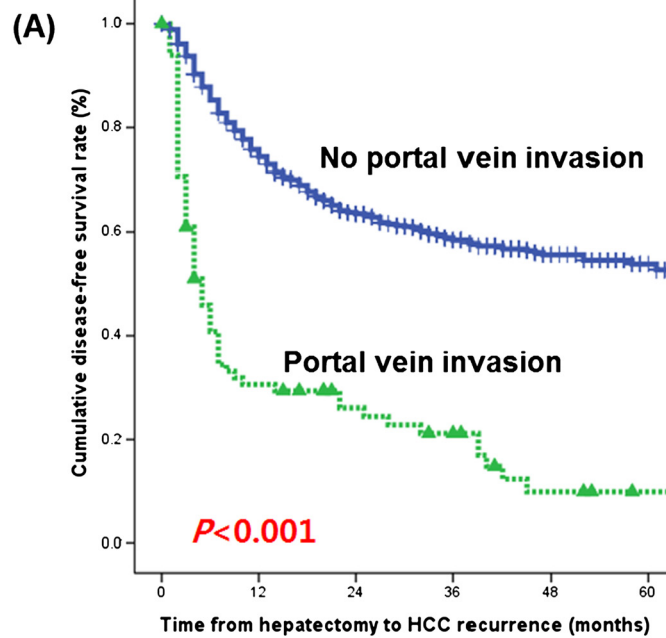
The proportion of anatomical resection and major hepatectomy in HCC patients with malignant portal vein invasions was higher than that in HCC patients without portal vein invasion ($P < 0.001$ and $P < 0.001$, respectively). Postoperative mortality was not occurred in the patients with malignant portal vein invasion. Pathologically proven malignant portal vein invasion consisted of segmental portal vein invasion ($n=57$) and left or right main portal vein invasion ($n=26$). Left or right main

portal vein invasion was detected in the preoperative radiology, but segmental portal vein invasion was not diagnosed in the preoperative radiology. The median tumor size was 6 cm (range, 1.4–17.5 cm) in HCC with malignant portal vein invasion and 3.3 cm (range, 0.2–21.0 cm) in HCC without portal vein invasion ($P < 0.001$). The proportion of R₁ resection in HCC patients with malignant portal vein invasion was 6.1%, which was higher than that in HCC patients without portal vein invasion ($P=0.035$). None of the studied patients had distant metastasis and there was no patient with R₂ resection in this study. There were 16 cases (19.3%) of grade 3 or 4 HCC with malignant portal vein invasion and 80 (7.6%) cases of HCC without portal vein invasion. The grade in HCC with malignant portal vein invasion was poorer than that in HCC without portal vein invasion ($P=0.001$). Bile duct invasion, intrahepatic metastasis, and the absence of capsular formation were more prevalent in HCC with portal vein invasion than in HCC without portal vein invasion ($P < 0.05$). However, no significant difference was found in serosa involvement and multicentric occurrence between the two groups. The median hospitalization in both groups was 9 days and the duration of follow-up in HCC patients with

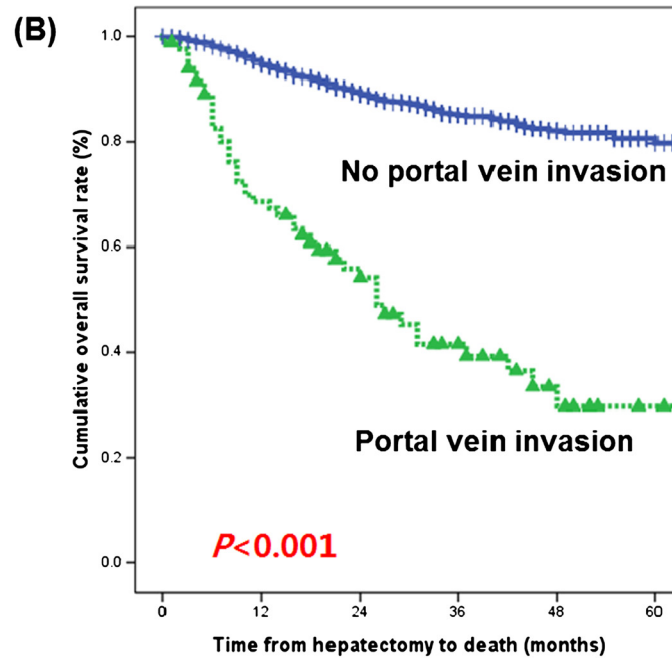
Table 2 Risk factors for portal vein invasion in HCC by multivariate analysis

Variables	Hazard ratio	95% confidence interval	P value
ALP	1.017	1.005–1.030	0.007
Maximum tumor size	1.025	1.010–1.040	0.001
Intrahepatic metastasis	6.064	1.553–23.673	0.009

ALP, Alkaline phosphatase.



No portal vein invasion	1056	770	489	289	134	54
Portal vein invasion	83	24	16	12	4	1



No portal vein invasion	1056	970	714	450	219	88
Portal vein invasion	83	54	33	19	9	2

Figure 1 (A) Disease-free survival rate and (B) overall survival rate in HCC patients according to portal vein invasion. The disease-free survival curve and overall survival curve in HCC patients with malignant portal invasion were inferior to those in HCC patients without portal vein invasion.

Table 3 Initial detection site for recurrence after surgical resection

Sites	Recurrence		P value
	HCC with PV invasion (n=67)	HCC without PV invasion (n=410)	
Liver	18 (26.9%)	254 (62.0%)	<0.001
Lung	34 (50.7%)	95 (23.2%)	<0.001
Bone	7 (10.4%)	22 (5.4%)	0.161
Brain	0 (0%)	5 (1.2%)	0.364
Peritoneum	8 (11.9%)	34 (8.3%)	0.351

malignant portal vein invasion was 18 months (range, 5-68 months), and that in HCC with portal vein invasion was 32 months (range, 3-82 months). The duration of follow-up in HCC patients with malignant portal vein invasion was shorter than that in HCC patients without portal vein invasion because HCC patients died due to tumor recurrence in the early period after surgery.

Risk factors for malignant portal vein invasion in HCC patients

To identify risk factors for malignant portal vein invasion in HCC, we performed a multivariate analysis on all variables that were significantly associated with malignant portal vein invasion on univariate analysis. Increased serum ALP levels, increased maximum tumor size, and intrahepatic metastasis were the predisposing factors of malignant portal vein invasion by multivariate analysis (Table 2).

Survival rate after surgery

For the HCC patients with malignant portal vein invasion who underwent liver resection, the median disease-free survival was 4.5 months and the overall survival was 25 months. The 1-year, 2-year, and 3-year disease-free survival rates and overall survival rates in HCC patients with malignant portal vein invasion were 30.6%, 26.1%, and 21.2%, and 68.6%, 54.2%, and 41.6%, respectively, but those in HCC patients without portal vein invasion

Table 4 Treatments for HCC recurrence

Treatments on recurrence	Recurrence		P value
	HCC with PV invasion (n=67)	HCC without PV invasion (n=410)	
Liver resection	0 (0%)	18 (4.4%)	0.091
Liver transplantation	3 (4.5%)	7 (1.7%)	0.154
RFA	6 (9.0%)	125 (30.5%)	<0.001
TACE	39 (58.2%)	242 (59.0%)	0.894
Sorafenib	12 (17.9%)	67 (16.3%)	0.725
Radiation	9 (13.4%)	42 (10.2%)	0.400
Chemotherapy	5 (7.5%)	23 (5.6%)	0.573

RFA, Radiofrequency ablation; TACE, Transarterial chemoembolization.

were 74.4%, 63.5%, and 58.5%, and 95.5%, 89.6%, and 85.1%, respectively ($P < 0.001$ and $P < 0.001$, respectively) (Figure 1).

Recurrence after surgical resection

The incidence of tumor recurrence was 80.7% (67/83) in HCC patients with malignant portal vein invasion and 38.8% (410/1056) in HCC without portal vein invasion. The initial detection site was lung (50.7%) in HCC patients with malignant portal vein invasion and liver

Table 5 Risk factors for tumor recurrence in HCC patients with portal vein invasion by univariate analysis

Variables	Hazard ratio	95% confidence interval	P value
Gender - Female	0.657	0.313-1.376	0.265
Age	0.973	0.946-1.000	0.052
AFP	1.000	1.000-1.000	0.005
PIVKA-II	1.001	1.000-1.001	0.128
Locoregional therapy	1.495	0.848-2.634	0.165
White blood cells	0.961	0.835-1.107	0.582
Hemoglobin	1.010	0.853-1.195	0.909
Platelet counts	1.000	0.998-1.003	0.821
INR	6.056	0.254-144.219	0.266
Albumin	0.533	0.290-0.980	0.043
Total bilirubin	1.047	0.654-1.676	0.849
AST	1.005	0.999-1.011	0.103
ALT	1.002	0.996-1.008	0.565
ALP	1.002	0.995-1.008	0.643
Creatinine	0.427	0.091-2.004	0.281
Estimated GFR	1.015	0.997-1.033	0.102
GGT	1.000	0.998-1.001	0.739
CRP	1.133	1.028-1.249	0.012
Operation (non-anatomical)	1.473	0.863-2.515	0.156
Hepatectomy (minor)	0.922	0.367-2.315	0.863
Maximum tumor size	1.003	0.997-1.010	0.282
Grade (3 and 4)	0.627	0.311-1.267	0.194
Cirrhosis	1.426	0.879-2.314	0.150
Capsule formation	1.020	0.353-2.941	0.971
Capsular invasion	0.715	0.439-1.165	0.178
Bile duct invasion	0.752	0.302-1.873	0.540
Serosa involvement	5.863	1.372-25.058	0.017
Intrahepatic metastasis	1.787	1.098-2.910	0.020
Multicentric occurrence	0.048	0.00-195.191	0.474
Margin (mm)	1.006	0.986-1.026	0.566

AFP, Alpha-fetoprotein; ALP, Alkaline phosphate; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CRP, C-reactive protein; GFR, Estimated glomerular filtration rate; GGT, Gamma-glutamyl transferase; INR, International normalized ratio; PIVKA-II, Protein induced by vitamin K antagonist-II.

(62.0%) in HCC patients without portal vein invasion. There was a difference in liver or lung as the initial detection site of tumor recurrence between the two groups ($P < 0.001$ and $P < 0.001$, respectively) (Table 3). However, no significant difference was found in the recurrence in bone, brain, and peritoneum between the two groups.

Radiofrequency ablation (RFA) in HCC patients without portal vein invasion was used more often because of high incidence of recurrence in liver, compared with HCC patients with malignant portal vein invasion ($P < 0.001$). No HCC patients with portal vein invasion were treated with liver resection due to recurrence. Liver transplantation, TACE, sorafenib, radiation, and chemotherapy as treatments for tumor recurrence were similar in both groups (Table 4).

Prognostic factors for recurrence in HCC with malignant portal vein invasion after surgery

Univariate analysis showed that increased AFP level, decreased serum albumin level, serosa involvement, and intrahepatic metastasis were closely associated with tumor recurrence after liver resection (Table 5). On multivariate analysis of the prognostic factors for disease-free survival in HCC patients with malignant portal vein invasion, only the CRP level (hazard ratio, 1.133; 95% confidence interval, 1.028–1.249; $P = 0.012$) was a significant independent predictor of tumor recurrence after liver resection.

Discussion

The prognosis for patients who have HCC with malignant portal vein invasion remained extremely poor in this study, even though a few long-term survivors were observed. Several studies have shown that tumor size, high grade, the presence of fibrous capsule, and platelet counts are strongly associated with portal vein invasion [8-10]. In the present study, increased ALP levels, increased maximum tumor size, and intrahepatic metastasis were independent predictors of malignant portal vein invasion in HCC by multivariate logistic regression analysis. Therefore, these factors may be helpful in predicting malignant portal vein invasion before surgery for HCC.

Many studies reported that an increase in the serum CRP level was associated with a shorter survival in patients with various malignancies, including multiple myeloma [11], ovarian cancer [12], colorectal [13], and esophageal cancer [14]. For the serum CRP levels associated with HCC, high CRP was linked to the diffuse type of HCC and elevated preoperative CRP levels in patients with HCC associated with tumor size and portal vein invasion, and predicted recurrence after curative resection and a poor surgical outcome [15,16].

The basis for the relationship between elevated CRP and poor prognosis is unclear and there are several possible explanations. An elevated CRP level may reflect a

non-specific inflammatory response to tumor necrosis or local tissue damage, which may be indicative of a favorable environment for the establishment and growth of tumor. The serum level of vascular endothelial growth factor (VEGF), an angiogenic factor, is increased in the presence of raised CRP concentration [17]. Angiogenesis plays an important role in tumor growth and is associated with a poor outcome [18]. This creates a microenvironment that favors tumor angiogenesis, proliferation, growth, and metastases.

Tumor invasion in the remnant liver after surgery is common in HCC patients with malignant portal vein invasion [19]. However, our study revealed that lung metastasis was common in HCC patients with malignant portal vein invasion after surgery, while liver metastasis was common in HCC patients without portal vein invasion.

Although intrahepatic recurrence predominates, probably because of the early spread of neoplasm and metachronous multicentric carcinogenesis, several effective therapeutic modalities can control recurrent disease (such as repeated hepatectomy, TACE, percutaneous ethanol injection therapy, microwave coagulation therapy, and RFA) [16,20]. Compared with frequent intrahepatic recurrence, the incidence of distant metastasis is relatively low in HCC [21]. However, extrahepatic metastasis, such as lung, was higher than intrahepatic metastasis in HCC with portal vein invasion. The poor prognosis for patients with extrahepatic metastasis of HCC occurs because it is an indicator of an aggressive primary HCC [22].

Our study revealed that chest CT must be regularly performed in HCC patients with malignant portal vein invasion after surgical resection. In addition, patients who had preoperatively elevated CRP levels, should be closely monitored after hepatectomy because of a poor prognostic factor of tumor recurrence.

Conclusion

In conclusion, our study reveals that increased ALP levels, increased maximum tumor size, and intrahepatic metastasis were independent predictors of malignant portal vein invasion in HCC. CRP levels are closely associated with the predisposing factor of tumor recurrence in HCC patients with malignant portal vein invasion after surgical resection, and lung metastasis is common.

Competing interests

The authors declare no conflicts of interest.

Authors' contribution

JMK: data collection, analysis, and interpretation, manuscript writing; JWJ and SWP: data design and interpretation; CHDK, JSK: data collection and analysis; JBP, JHL, SJK, and CKP: data collection. All authors read and approved the final manuscript.

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