

## Prognosis of preoperative positron emission tomography uptake in hepatectomy patients

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**Purpose:** Preoperative F-18-fluoro-2-deoxy-glucose positron emission tomography (18F-FDG PET) imaging results appear to predict tumor recurrence and patient survival. The present study compared outcomes between PET-positive and PET-negative groups with HBV-related hepatocellular carcinoma (HCC) who underwent curative hepatectomy and assessed the prognostic value of positive PET-CT for HCC recurrence and death.

**Methods:** This study included patients who underwent liver resection of solitary HCC between 2007 and 2014 based on preoperative radiological images. There were 133 patients in the PET-positive group and 93 in the PET-negative group.

**Results:** There were no statistically significant differences in baseline, perioperative, or pathologic characteristics between the 2 groups except HBsAg titer, tumor size, and presence of bile duct tumor thrombi. Multivariate analysis showed that tumor size >3.5 cm and HBsAg titer >1,000 cutoff index were predisposing factors of positive PET-CT. Disease-free survival and overall survival rate at 1, 3, and 5 years were 76.3%, 64.4%, 60.3% and 96.8%, 91.1%, 85.1% in the PET-negative group, respectively, compared with 70.7%, 62.2%, 58.9% and 98.5%, 97.0%, 97.0% in the PET-positive group (P = 0.547 and P = 0.046). Multivariate analysis showed that positive PET-CT was closely associated with increased patient survival, but was not related to HCC recurrence.

**Conclusion:** These results suggest that positive PET findings are not a predisposing factor for recurrence of HBV-related HCC patients, but appear to be associated with improved patient survival. Further prospective studies are needed to confirm the prognostic value of 18F-FDG PET in these patients.

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**Key Words:** Hepatocellular carcinoma, Hepatitis B virus, Outcome

### INTRODUCTION

Liver resection is a curative treatment for management of solitary liver cancer; however, tumor recurrence after curative surgery has limited treatment options. Tumor size, intrahepatic metastasis, microvascular invasion, serum AFP, and serum proteins induced by vitamin K antagonist-II (PIVKA-II), CRP, and serum alkaline phosphatase have been reported as risk factors associated with early recurrence [1-4].

The most commonly used method for evaluating oncologic

patients is F-18-fluoro-2-deoxy-glucose positron emission tomography (18F-FDG PET), which is based on glucose metabolism processes that are enhanced in rapidly growing cells and thus cause increased 18F-FDG uptake [5]. PET-CT is increasingly being used in the field of oncology not only for detecting and staging malignant tumors but also for monitoring therapy response and differentiating malignant from benign lesions [5-7]. PET-CT has been used as a predictor of outcomes in various cancers. In addition, PET-CT has been applied for the detection and evaluation of hepatocellular carcinoma (HCC).

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PET-CT is useful for evaluating patients with unexplained increased AFP after locoregional therapy for HCC and in differentiating malignant and benign portal vein thrombosis [8,9]. However, PET-CT is not currently included as an HCC diagnostic method because of its suboptimal sensitivity (<50%) for detection of new HCC. In a series of patients who underwent liver resection for HCC, preoperative positive PET-CT imaging results were associated with poor tumor differentiation and appeared to predict poor outcomes such as tumor recurrence and death [10]. However, there are few studies on the prognostic value of 18F-FDG PET-CT in patients with HBV-related HCC.

The purpose of the present study was to compare the outcomes between PET-positive and PET-negative groups with HBV-related HCC who underwent curative hepatic resection and to assess the prognostic value of positive PET-CT for HCC recurrence and death.

## METHODS

### Patients

This study included patients who underwent surgical resection of solitary HCC based on preoperative radiological images between July 2007 and September 2014. This study was approved by the Institutional Review Board of Samsung Medical Center (SMC-2016-08-161-001). A total of 226 patients with HBV-related HCC underwent curative liver resection in our hospital. HCC was proved based on pathology after hepatectomy.

Exclusion criteria were as follows: mixed HCC and cholangiocarcinoma on pathology; age <18 years; history of liver resection, transarterial chemoembolization, radiofrequency ablation (RFA), or percutaneous ethanol injection; history of radiation; concurrent intraoperative RFA; fibrolamellar HCC; lack of PET-CT evaluation in the preoperative period; or loss to follow-up after hepatectomy. Demographic, preoperative laboratory, and pathologic data collected from electronic medical records were retrospectively reviewed.

None of the patients received postoperative adjuvant therapy before recurrence. All patients received antiviral therapy after liver resection. The procedures used for surveillance after liver resection have been described previously [1].

### Surgery and pathology

Surgical and pathological procedures used after liver resection have been described previously [4,11]. Major hepatectomy was defined as resection of 3 or more segments, and minor hepatectomy was defined as resection of fewer than 3 segments. Postoperative histological assessment included maximum tumor size, encapsulation, intrahepatic metastasis, multicentric occurrence, microvascular invasion, serosal involvement, and cirrhosis. Intrahepatic metastasis and multicentric occurrence were defined based on guidelines from the Liver Cancer

Study Group of Japan [12]. The histologic grade of HCC was assigned according to the Edmonson-Steiner system as well differentiated (grade I), moderately differentiated (grade II), or poorly differentiated (grades III, IV) [13].

### FDG PET-CT procedures

The PDF PET-CT procedure in our hospital was previously described [14]. All FDG PET-CT imaging was performed with dedicated PET-CT scanners (Discovery STE, GE Healthcare, Milwaukee, WI, USA) at Samsung Medical Center. All patients fasted for at least 6 hours prior to intravenous administration of FDG. A blood glucose level  $\leq 140$  mg/dL was required before administering FDG. Approximately 5.5 MBq/kg of FDG was administered intravenously for the Discovery STE. Foci of increased metabolic activity were compared between normal surrounding tissues and tumor tissue and visually interpreted using a 2-point grading score of (1) positive and (2) negative.

### Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA). Continuous variables are described as median with range. Categorical variables are expressed as number and percentage of patients. Fisher exact test was conducted to evaluate differences in the frequencies of categorical variables between the groups. Mann-Whitney U analysis was conducted to evaluate differences in continuous variables between the two groups. Binary logistic regression analysis using significant factors ( $P < 0.1$ ) was used to predict positive PET-CT in the preoperative period. The Kaplan-Meier survival method was performed to evaluate differences in patient survival between the 2 groups. Cox regression analysis was performed to identify prognostic factors of patient survival. All tests were 2-sided, and statistical significance was defined as  $P < 0.05$ .

## RESULTS

### Baseline characteristics

The baseline characteristics of the PET-negative and PET-positive groups are summarized in Table 1. The median HBsAg titer was 4,435 cutoff index (COI) (range, 1–9,758 COI) in the PET-positive group and 3,319 COI (range, 1–20,093 COI) in the PET-negative group ( $P = 0.009$ ). There were no statistically significant differences in sex, age, white blood cells, lymphocyte to neutrophil ratio, monocyte to neutrophil ratio, hemoglobin level, platelet count, liver function tests, HBV DNA level, presence of HBeAg, or indocyanine green value between the 2 groups. The median AFP and PIVKA-II levels were 14.1 ng/dL (range, 1.3–50,488.1 ng/dL) and 48 mAU/mL (range, 8–41,631 mAU/mL), respectively, in the PET-negative group compared with 18.3 ng/dL (range, 1.3–200,000 ng/mL) and 56 mAU/mL

**Table 1.** Baseline, perioperative and pathologic characteristics

Characteristic	Negative PET CT (n = 93)	Positive PET CT (n = 133)	P-value
<b>Baseline characteristics</b>			
Male sex	69 (74.2)	104 (78.2)	0.525
Age (yr)	53 (28–76)	55 (32–76)	0.053
White blood cells (/μL)	5,370 (2,070–13,610)	5,260 (1,370–11,970)	0.855
LNR	0.631 (0.051–1.458)	0.649 (0.136–1.737)	0.320
MNR	0.133 (0.026–0.283)	0.135 (0.014–0.325)	0.900
Hemoglobin (g/dL)	14.2 (10.0–17.2)	14.7 (8.2–17.9)	0.161
Platelet (/μL)	151,000 (44,000–380,000)	162,000 (60,000–324,000)	0.707
Total bilirubin (mg/dL)	0.6 (0.2–2.3)	0.6 (0.2–2.2)	0.291
AST (U/L)	31 (15–177)	29 (13–244)	0.408
ALT (U/L)	31 (5–158)	30 (8–302)	0.248
ALP (U/L)	76 (35–287)	71 (41–245)	0.175
INR	1.05 (0.91–1.34)	1.04 (0.90–1.60)	0.059
Albumin (g/dL)	4.3 (3.2–5.2)	4.4 (3.3–5.1)	0.167
Creatinine (mg/dL)	0.86 (0.40–5.64)	0.85 (0.50–3.50)	0.958
ICG-R15 (%)	10.1 (1.2–24.8)	10.0 (1.4–21.4)	0.479
HBV DNA (IU/mL)	153 (12–43,075,048)	232 (12–200,000,000)	0.527
HBeAg (COI)	26 (28.0)	47 (35.3)	0.252
AFP >200 ng/mL	18 (20.7)	42 (31.6)	0.089
PIVKA-II >40 mAU/mL	49 (52.7)	71 (53.4)	0.974
HBsAg titer >1,000 COI	58 (62.4)	101 (75.9)	<0.001
<b>Perioperative and pathologic characteristics</b>			
Laparoscopic approach	15 (16.1)	22 (16.5)	0.856
Extent of operation, major	37 (39.8)	51 (38.3)	0.890
Tumor size >3.5 cm	34 (36.6)	64 (48.1)	0.172
Grades 3 and 4	12 (12.9)	19 (14.3)	0.846
Necrosis	35 (37.6)	64 (48.1)	0.164
Hemorrhage	44 (47.8)	67 (50.4)	0.786
Encapsulation	81 (87.1)	122 (91.7)	0.272
Microvascular invasion	45 (48.4)	74 (55.6)	0.343
PVTT	6 (6.5)	11 (8.3)	0.799
BDTT	6 (6.5)	1 (0.8)	0.020
Serosal involvement	1 (1.1)	5 (3.8)	0.405
Intrahepatic metastasis	11 (11.8)	12 (9.0)	0.510
Multicentric occurrence	6 (6.5)	3 (2.3)	0.166
Cirrhosis	47 (50.5)	56 (42.1)	0.224
Free resection margin (mm)	10.5 (2–70)	12.0 (2–65)	0.734

Values are presented as number (%) or median (range).

LNR, lymphocyte-neutrophil ratio; MNR, monocyte-neutrophil ratio; INR, international normalized ratio; ICG, indocyanine green; PIVKA-II, proteins induced by vitamin K antagonist-II; COI, cutoff index; PVTT, portal vein tumor thrombosis; BDTT, bile duct tumor thrombi.

(range, 12–67,612 mAU/mL) in the PET-positive group. AFP and PIVKA-II levels were not significantly different between the groups.

### Perioperative and pathologic characteristics

The incidence of laparoscopic resection and major liver resection was not significantly different between PET-positive and PET-negative groups. Median tumor size was 3.3 cm (range, 1.0–16.5) in the PET-positive group and 2.8 cm (range, 0.3–16.0) in the PET-negative group (P = 0.036). There were no statistically significant differences in tumor grade, necrosis, encapsulation,

microvascular invasion, portal vein tumor thrombosis, serosal involvement, intrahepatic metastasis, multicentric occurrence, or cirrhosis between the 2 groups. The incidence of bile duct tumor thrombi was 6.5% in the PET-negative group and 0.8% in the PET-positive group (P = 0.020). Tumor size > 3.5 cm (odds ratio [OR], 2.291; 95% confidence interval [CI], 1.130–4.645; P = 0.0022) and HBsAg titer > 1,000 COI (OR, 4.354; 95% CI, 1.932–9.813; P < 0.001) were predisposing factors of positive PET-CT in multivariate analysis (Table 2).

**Table 2.** Risk factors of hepatocellular carcinoma recurrence

Variable	OR	95% CI	P-value
<b>Univariate</b>			
Female sex	0.884	0.526–1.489	0.644
NLR	0.673	0.320–1.414	0.295
MNR	0.405	0.008–20.275	0.651
HBsAg titer >1,000 COI	0.957	0.548–1.671	0.878
HBeAg	1.491	0.961–2.313	0.075
HBV DNA	1.000	1.000–1.000	0.445
Positive PET CT	1.143	0.740–1.766	0.547
AFP >200	1.004	0.612–1.647	0.987
PIVKA-II >40	1.953	1.223–3.119	0.005
Laparoscopic approach	0.642	0.332–1.242	0.188
Extent of operation, major	1.149	0.742–1.780	0.534
Tumor size >3.5 cm	2.398	1.550–3.710	<0.001
Grade 3 and 4	2.741	1.656–4.214	<0.001
Tumor necrosis	1.811	1.179–2.782	0.007
Tumor hemorrhage	0.829	0.539–1.274	0.391
Encapsulation	0.502	0.278–0.907	0.022
Microvascular invasion	2.314	1.471–3.641	<0.001
PVTT	3.659	1.979–6.763	<0.001
BDTT	1.144	0.361–3.628	0.819
Serosal involvement	3.372	1.364–8.336	0.008
Intrahepatic metastasis	3.012	1.743–5.203	<0.001
Multicentric occurrence	2.392	1.103–5.190	0.027
Free resection margin	0.989	0.972–1.007	0.244
Cirrhosis	1.137	0.743–1.741	0.553
<b>Multivariate</b>			
Serosal involvement	5.067	1.213–21.159	0.026
Intrahepatic metastasis	3.265	1.270–8.394	0.014

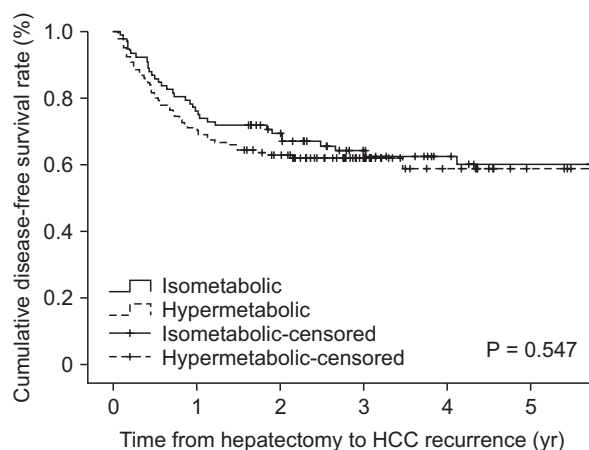
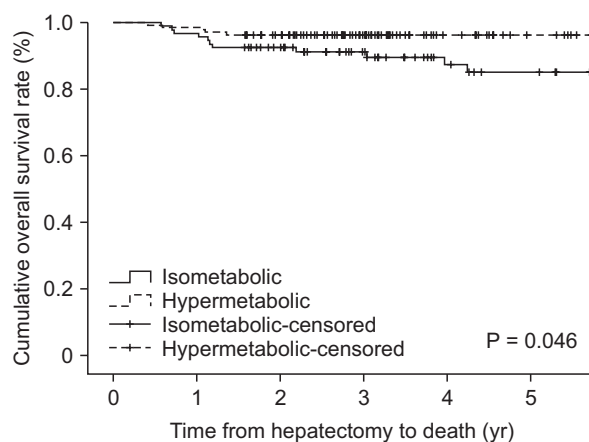
OR, odds ratio; CI, confidence interval; LNR, lymphocyte-neutrophil ratio; MNR, monocyte-neutrophil ratio; PIVKA-II, proteins induced by vitamin K antagonist-II; PVTT, portal vein tumor thrombosis; BDTT, bile duct tumor thrombi.

### HCC recurrence

The median follow-up duration was 42.5 months (range, 7–103 months) in the PET-negative group and 36.4 months (range, 5–70 months) in the PET-positive group ( $P = 0.008$ ). The disease-free survival rate at 1, 3, and 5 years was 76.3%, 64.4% and 60.3% in the PET-negative group, respectively, and 70.7%, 62.2%, and 58.9% in the PET-positive group (Fig. 1) ( $P = 0.547$ ). The most common site of recurrence for both groups was an intrahepatic site (82.4% in the PET-negative group compared with 78.4% in the PET-positive group;  $P = 0.904$ ). Multivariate analysis showed that serosal involvement and intrahepatic metastasis were closely associated with HCC recurrence (Table 2).

### Patient survival

The overall survival rate at 1, 3, and 5 years was 96.8%, 91.1%, and 85.1% in the PET-negative group, respectively, and 98.5%, 97.0%, and 97.0% in the PET-positive group (Fig. 2). The overall survival curve for the PET-positive group was higher than that

**Fig. 1.** Disease-free survival.**Fig. 2.** Overall survival.

for the PET-negative group ( $P = 0.046$ ). Multivariate analysis showed that tumor size > 3.5 cm and positive preoperative PET-CT were closely associated with patient survival (Table 3).

## DISCUSSION

FDG PET-CT is not used in the early evaluation of HCC patients because of high costs and low sensitivity. As metabolic activity in tumor cells can be higher than that in normal hepatocytes, PET-CT can be used for malignant characterization of tumors by assessing metabolic activity. Many studies have suggested that a positive FDG PET-CT finding is a powerful predictor of prognosis in HCC patients [5,15,16]. One of the major goals in the surgical treatment of HCC is minimizing the risk of tumor recurrence, which is strongly associated with patient survival.

However, the present study failed to prove a correlation between PET results and patient outcomes after liver resection. Our data showed that baseline, perioperative, and pathologic characteristics in the PET-negative group were not different

**Table 3.** Risk factors of mortality

Variable	OR	95% CI	P-value
Univariate			
Female sex	1.552	0.539–4.467	0.415
NLR	0.168	0.025–1.130	0.067
MNR	0.001	0.000–14.741	0.156
HBsAg titer >1,000 COI	0.933	0.298–2.928	0.906
HBeAg	0.982	0.341–2.826	0.973
HBV DNA	1.000	1.000–1.000	0.626
Positive PET CT	0.353	0.121–1.026	0.056
AFP > 200	1.439	0.491–4.216	0.506
PIVKA-II > 40	4.825	1.079–21.573	0.039
Laparoscopic approach	0.037	0.000–12.273	0.266
Extent of operation, major	2.056	0.765–5.526	0.153
Tumor size >3.5 cm	5.805	1.654–20.376	0.006
Grades 3 and 4	8.434	3.125–22.761	<0.001
Tumor necrosis	4.181	1.347–12.974	0.013
Tumor hemorrhage	1.266	0.471–3.404	0.640
Encapsulation	0.328	0.106–1.018	0.054
Microvascular invasion	6.551	1.489–28.829	0.013
PVTT	3.239	0.919–11.421	0.068
BDTT	3.666	0.820–16.401	0.089
Serosal involvement	2.678	0.353–20.310	0.341
Intrahepatic metastasis	2.682	0.863–8.334	0.088
Multicentric occurrence	3.241	0.733–14.330	0.121
Free resection margin	1.013	0.979–1.048	0.460
Cirrhosis	0.908	0.338–2.440	0.849
Multivariate			
Positive PET CT	0.284	0.085–0.949	0.041
Microvascular invasion	8.196	1.020–65.847	0.048

OR, odds ratio; CI, confidence interval; LNR, lymphocyte-neutrophil ratio; MNR, monocyte-neutrophil ratio; PIVKA-II, proteins induced by vitamin K antagonist-II; PVTT, portal vein tumor thrombosis; BDTT, bile duct tumor thrombi.

from those in the PET-positive group with the exception of HBsAg titer, tumor size, and the presence of bile duct tumor thrombi. The disease-free survival rates for the PET-positive group were not significantly different from those in the PET-negative group; however, the overall patient survival rates in the PET-positive group were better than those in the PET-negative group ( $P = 0.046$ ). In addition, multivariate analysis showed that negative PET-CT finding was an important predictor of poor patient survival.

A previous study showed that PET-positive HCC was significantly associated with AFP >200 ng/mL and microvascular invasion [17]. Another study reported that preoperative 18F-FDG uptake was closely associated with metabolic activity and tumor grade. Therefore, there was a difference in uptake of 18F-FDG according to degree of tumor differentiation of HCC [18]; the uptake of 18F-FDG in well- and well-to-moderately differentiated HCC was similar to that in normal liver, whereas moderate-to-poorly and poorly differentiated HCC demonstrated

increased uptake [19]. However, our results did not confirm this.

The present study revealed that positive PET CT was closely associated with tumor size >3.5 cm and HBsAg titer > 1,000 COI in patients with HBV-related HCC who underwent curative hepatectomy. It has been reported that quantification of HBsAg is associated with the level of intrahepatic covalently closed circular DNA (cccDNA), which reflects the number of HBV-infected hepatocytes [20]. Intrahepatic cccDNA level in the tumor tissue was higher than that in the nontumor tissue of HBsAg-positive patients with HCC [21]. Our results suggest that a positive PET-CT findings reflected cccDNA level based on the relationship between positive PET-CT finding and high HBsAg titer.

A previous study reported a correlation between PET-CT findings and prognosis in HCC patients [22]. Another study showed a good correlation among 18F-FDG uptake, tumor volume doubling time, and prognosis [16]. Many studies reported similar results and strengthened the correlation between 18F-FDG uptake and HCC prognosis regardless of tumor stage or treatment strategy [5,6,15,16,23]. However, the present study did not find similar outcomes in hepatectomy patients. HCC recurrence was not different between PET-positive and PET-negative groups, and patient survival was better for the PET-positive group compared with the PET-negative group. Tumor recurrences in most gastrointestinal cancers involve not only local recurrence, but also remote metastases. Most cases of recurrent HCC after hepatectomy in patients with HBV-related HCC involved development of intrahepatic metastasis or *de novo* recurrence. Since tumor recurrence patterns are different between HCC and other gastrointestinal cancers, PET-CT does not seem to predict the exact prognosis after curative surgical resection in HCC patients.

Underestimation of 18F-FDG uptake by malignant lesions that contributes to PET false-negative findings can occur because of physiological movements of the liver during emission scans [16]. The degree of this underestimation is variable, particularly in the case of subcentimeter lesions, and might even lead to nonvisualization of the lesion [24]. However, no information is available in the literature on prognosis after liver resection, during which PET can give false-negative results.

In 2 studies, PET-CT in liver transplantation patients predicted HCC recurrence [17,25]. However, those studies included many patients with various etiologies who received several locoregional therapies. The present study focused on patients with solitary HBV-related HCC with preoperative locoregional therapies who underwent curative hepatic resection. PET-CT scans in patients undergoing liver transplant or hepatectomy as treatment for HCC are considered to have different value in terms of tumor biology worsening during multiple locoregional therapies [26].

This study has several limitations. First, the study is retrospective. Second, selection bias can occur due to the inclusion of hepatectomy patients with preoperative radiologically solitary tumor and well-preserved liver function. Third, we did not measure standardized uptake value (SUV) in the tumor and non-tumor lesions. SUV in the liver, including normal liver and tumor, was heterogeneous and therefore dependent on the arbitrary selected points. In addition, the SUV ratio varies according to the examiner. We compared PET CT-positive and PET CT-negative groups because positive and negative findings in the PET CT were clearly seen. Fourth, intrahepatic cccDNA level in the resected liver specimen was not measured; therefore, we could not demonstrate the relationship between serum HBsAg level and intrahepatic cccDNA level in HBV-related HCC. In addition, regular assessment of HBsAg level was not performed during the follow-up after resection. Consequently, the correlation between HBsAg level and PET-CT findings was not investigated when HCC recurrence was detected in patients

undergoing resection.

In conclusion, the present study showed that large tumor size and increased HBsAg titer are associated with positive PET-CT findings in patients with HBV-related HCC. Preoperative 18F-FDG PET CT is not an independent prognostic factor for survival in these patients undergoing curative treatment; however, positive PET-CT appears to be associated with better patient survival. These results suggest that 18F-FDG PET-CT scans do not have a dominant predictive role in HCC recurrence of HBV-related HCC patients. Our study emphasizes that further prospective studies are needed in order to assess the potential prognostic role of 18F-FDG PET-CT in patients undergoing hepatectomy.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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